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Committee for Medicinal Products for Human Use (CHMP)

# Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

International non-proprietary name:canagliflozin, metformin

Procedure No. EMEA/H/C/PSUSA/00010077/201411

Period covered by the PSUR: 16 May 2014 – 15 November 2014

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## Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for canagliflozin and cangaliflozin/metformin, the scientific conclusions of CHMP are as follows:

During the reporting period the Marketing Authorisation Holder (MAH) identified 105 serious cases of hypersensitivity and 379 non-serious cases. Out of these, a total of 65 cases reported 77 events relating to 'swelling of the facial region'. Of the 25 cases which included a case narrative latency was not reported or not assessable in 11 cases. In the remaining 14 cases, latency of the event ranged from several hours to 6 months including 4 cases with latency of < 1 day and 2 with 1-2 days. Twelve (12) cases reported a positive dechallenge with one case of positive re-challenge. Given the available evidence the PRAC agreed that the term "angioedema" should be added to section 4.8 of the SmPC with a frequency of unknown under the SOC Skin and subcutaneous tissue disorders.

During the reporting period there were 123 confirmed cases of urinary tract infections, 2 cases with positive re-challenge. There were 6 serious events of urosepsis and 7 serious events of pyelonephritis. In view of the fact that urinary tract infections are an identified risk for canagliflozin and pyelonephritis and urosepsis are already included in section 4.8 of the SmPC in a footnote, the PRAC considered that few cases of pyelonephritis and urosepsis with a positive dechallenge or no confounding factors seen postmarketing are considered enough evidence for a more prominent presentation to alert physicians that a common urinary tract infection might ascend and become a pyelonephritis.

Postmarketing data also revealed the occurrence of recurrent infections leading to the deletion of wording in section 4.8 of the SmPC which stated that the incidence of recurrent infections was not increased with canagliflozin.

Therefore, in view of available data regarding angioedema, pyelonephritis and urosepsis, the PRAC considered that changes to the product information were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC however requested that the product information be further amended to provide additional clarity to prescribers on the proposed changes. The additional changes relate to:

- The addition of a footnote in section 4.8 stating that the frequency of angioedema is "Based on postmarketing experience with canagliflozin". The package leaflet is updated accordingly.
- And deletion of footnote "g" ("Urinary tract infection includes the terms urinary tract infection, cystitis, kidney infection, and urosepsis. There was no imbalance among canagliflozin 100 mg, canagliflozin 300 mg, and placebo for kidney infection or urosepsis") as available data from clinical trials indicate there seem to be more events of pyelonephritis and urosepsis with the medicinal product than with the active comparators or placebo treatment. Additionally the information that urinary tract infections do not only concern the lower parts of the urinary tract like urethra or bladder but also the kidney already is now included in the table of adverse drug reactions and therefore need not be repeated in a footnote.

## Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for canagliflozin and canagliflozin/metformin, the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing canagliflozin and canagliflozin/metformin is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisations should be varied.