EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): empagliflozin

Procedure No. EMEA/H/C/PSUSA/00010388/201610

Period covered by the PSUR: 18 April 2016 to 17 October 2016

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for empagliflozin, empagliflozin / metformin, the scientific conclusions of CHMP are as follows:

Hypersensitivity reactions have been noted in association with empagliflozin use in post-marketing experience. Cumulative review of post-marketing data up to 17 October 2016 revealed that a total of 320 cases with 362 hypersensitivity adverse drug reactions (ADRs) have been spontaneously reported for empagliflozin and 7 non-serious cases for empagliflozin+metformin. Of the 362 hypersensitivity ADRs for empagliflozin, in 92 times, time to onset was within 1 month and in 153 de-challenge was positive. In addition, there were 6 re-challenge cases and 3 of them were cases of rash.

Furthermore, an increase in angioedema ADRs was observed. Up to 17 October 2016, a total of 12 ADRs (1 serious) have been spontaneously reported according to the summary tabulation of ADRs from post-marketing data submitted by the Marketing Authorisation Holder (MAH). Of these 12 ADRs, 6 were received during the Periodic Safety Update Report (PSUR) reporting period.

The other medicinal products of the same class either list a range of hypersensitivity reactions in their Summary of Product Characteristics (SmPC) (canagliflozin) or this is currently under assessment (dapagliflozin).

During the assessment, the MAH presented a review of Standardised MedDRA query (SMQ) 'Angioedema' including a specific review on urticaria and angioedema. There has been urticaria events reported in clinical trials (37, 0.44%) as well as urticaria ADRs in post-marketing (61 up to 15 March 2017).

Overall, in view of the data presented in the reviewed PSUR, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there is sufficient evidence to suspect a causal relationship between rash, angioedema and urticaria and empagliflozin treatment. Therefore, changes to the product information of medicinal products containing empagliflozin are warranted with consequential changes in the packaged leaflet.

On the other hand, cumulatively seven fatal cases of Diabetic Ketoacidosis (DKA) were presented by the Marketing Authorisation Holder. In line with other Sodium-glucose co-transporter 2 (SGLT2) inhibitors indicated in the treatment of type 2 diabetes, the PRAC considered it necessary to update the existing warning of diabetic ketoacidosis (DKA) on the occurrence of fatal cases.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing empagliflozin were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for empagliflozin, empagliflozin / metformin the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing empagliflozin, empagliflozin / metformin is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.