25 March 2021
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): sacubitril / valsartan

Procedure No. EMEA/H/C/PSUSA/00010438/202007

Period covered by the PSUR: 01/08/2019 To: 31/07/2020

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Scientific conclusions

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

Psychiatric disorders
In view of available data on psychosis and psychotic disorders from the literature, spontaneous reports including in multiple cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC Rapporteur considers a causal relationship between sacubitril/valsartan and hallucinations, sleep disorder and paranoia are at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing sacubitril/valsartan should be amended accordingly.

Update of section 4.4 and 4.8 of the SmPC to add hallucinations, sleep disorder and paranoia with a frequency 'rare' for hallucinations and sleep disorder and frequency 'very rare' for paranoia. The package leaflet is updated accordingly.

Tablet splitting
In view of available data on 'tablet splitting' from the literature and spontaneous reports including the following risk of dose modification (underdose/overdose), changes in pharmacokinetics and potentially gastrointestinal tract disturbances, the PRAC Rapporteur considers that the product information of products containing sacubitril/valsartan should be amended accordingly.

Update of section 4.2 of the SmPC to add information on correct use of the medicine, with a recommendation not to split/cut/crush the tablet. The package leaflet is updated accordingly.

Lithium drug-drug interaction and toxicity
In view of available data on lithium drug-drug interaction and toxicity from spontaneous reports including in one case a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC Rapporteur considers a causal relationship between sacubitril/valsartan and lithium drug-drug interaction and toxicity is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing sacubitril/valsartan should be amended accordingly.

Update of section 4.5 of the SmPC to amend the lithium drug-drug interaction and toxicity. No updates to the package leaflet are considered 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 sacubitril / valsartan the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing sacubitril / valsartan 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.