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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): levetiracetam

Procedure No. EMEA/H/C/PSUSA/00001846/201511

Period covered by the PSUR: 01 December 2012-30 November 2015

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Scientific conclusions

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

Acute kidney injury

Following the review of the signal assessment report (SSAR), the Innovator MAH confirmed the possible association between levetiracetam and acute kidney injury. Therefore the undesirable effect “Acute kidney injury” should be added under the MedDRA System Organ Class (SOC) Renal and urinary disorders (frequency ‘rare’) as well as a warning in the Product Information of all levetiracetam-containing products.

Rhabdomyolysis/Blood creatine phosphokinase increased

Four case reports (2 published) with very suggestive causal association were issued during the reporting period regarding rhabdomyolysis in association with levetiracetam use. The statistical analysis in Eudravigilance based in proportional reporting ratio (PRR) was significant for a signal. Therefore, the MAHs should add the undesirable effect “Rhabdomyolysis” under the SOC Musculoskeletal and connective tissue disorders (frequency ‘rare’) in the Product Information of all levetiracetam-containing products. Moreover, as it is associated with rhabdomyolysis, the undesirable effect “Blood creatine phosphokinase increased” should also be added to the Product Information under the SOC Musculoskeletal and connective tissue disorders (frequency ‘rare’).

Encephalopathy

The safety report prepared by the Innovator MAH contained several cases very suggestive of a causal association between levetiracetam and encephalopathy. The statistical disproportionality analysis performed by the Innovator MAH in its own database was suggestive of a safety signal for ‘encephalopathy’ associated with levetiracetam. This statistical signal was also confirmed in Eudravigilance, based on PRR analysis. Based on the above, it is considered justified to document that cases of “encephalopathy” have been observed rarely in the Product Information of all levetiracetam-containing products.

Therefore in view of the data presented in the PSURs the PRAC considers that changes to the product Information of medicinal products containing levetiracetam 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 levetiracetam the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing levetiracetam 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.