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Committee for Medicinal Products for Human Use (CHMP)

Gilenya

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

International non-proprietary name: fingolimod

Procedure No. EMEA/H/C/002202/PSUV/0023

Period covered by the PSUR: 01.09.2012 - 28.02.2013

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Gilenya, the scientific conclusions of PRAC are as follows:

The adverse event profile in this Periodic Safety Update Report (PSUR) is consistent with the known safety profile of Gilenya to date. However new safety information emerged from this PSUR period in relation to disseminated herpes infection, interaction with carbamazepine and strong CYP450 inducers, cases of overdose:

- A detailed review of cases of cutaneous Varicella Zoster Virus (VZV) dissemination and VZV reactivation with central nervous system involvement resulted in identification of 35 cases of disseminated herpes viral infections as of October 2012. According to literature, the risk of herpes viral infections increases with altered cell-mediated immune responses. From the PRAC viewpoint, the risk of viral infection should be considered with fingolimod treatment due to its mechanism of action. These disseminated herpes viral infections cases included: 1 case with visceral involvement (pulmonary), 3 cases with brain or spinal cord involvement and 31 cutaneous dissemination (13 cases multidermatomal, 3 cases with bilateral lesions, 10 cases unilateral and 5 cases unspecified). An additional case of varicella disseminated infection leading to death was recently reported and occurred 6 months after fingolimod initiation. This case is still under evaluation and should be discussed in the next PSUR. Furthermore, the PRAC also noted the recent follow up received after the Data Lock Point of this PSUR regarding the autopsy of the patient who died following an Haemophagocytic syndrome was compatible with a possible origin of disseminated herpes infection. Overall, the PRAC considered that the Summary of Product Characteristics (SmPC) should be amended to reflect that some cases of disseminated herpes infection, including fatal cases, have been reported in post-marketing and clinical trials even at the 0.5 mg dose.

- In healthy volunteers, concomitant treatment of carbamazepine, at the maximal dose of 600 mg twice daily, decreases the exposure of fingolimod and fingolimod-P by approximately 40%. No conclusions can be drawn on which nuclear receptors are mostly activated or which enzymes are specifically impacted in this interaction. Whilst the mechanism causing such reduction in exposure of fingolimod remains to be elucidated, the results of this study question the real role of CYP3A4 in fingolimod metabolism. On this basis, the PRAC recommended a revision of the SmPC information regarding concomitant administration of CYP450 inducers and to include a specific warning on possible reduced efficacy of fingolimod when combined to CYP450-inducing stronger agents (i.e. rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, St John's wort).

- Cases of overdose have been reported. Thus, the PRAC also recommended deletion of the following sentence in section 4.9 of the SmPC: "No cases of overdose have been reported."

Therefore, in view of available data regarding disseminated herpes infection, interaction with carbamazepine and strong CYP450 inducers and cases of overdose, the PRAC considered that changes to the Product Information were warranted.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Gilenya, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance FINGOLIMOD is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.