25 April 2014
EMA/405985/2014
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/0027

Period covered by the PSUR: 1 March 2013 – 31 August 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 hypersensitivity and rash, cancers (cervix and brain):

- Following the results of the safety analysis requested by the PRAC on hypersensitivity, no cases of toxic epidermal necrolysis, Stevens Johnson syndrome or anaphylaxis were reported from clinical trials. Two non-serious cases of erythema multiform in the fingolimod 0.5mg group were reported. The incidence rate of hypersensitivity reactions in clinical trials was not significantly different from placebo. However, cumulatively, 802 cases describing “hypersensitivity” were reported. Among these cases, 784 cases were excluded from further analysis by the Marketing Authorisation Holder (MAH) because these cases were not considered “noteworthy” according to the following criteria: 1) did not have positive dechallenge/rechallenge, 2) had reported confounders, 3) did not require intervention, and/or 4) were not documented. Based on these criteria, the PRAC considered that a causal relationship with Gilenya could not be totally ruled out, especially for the non-documented cases. Considering that a clear causal relationship was established for the remaining 18 cases (all positive dechallenges or positive rechallenges) and taking into account the number of reported cases (including one bullous erythema multiforme coded as Stevens-Johnson syndrome), the PRAC concluded that “hypersensitivity” and “rash” should be added as new adverse reactions of Gilenya.

Therefore, in view of available data regarding hypersensitivity, the PRAC considered that changes to the product information were warranted.

- Regarding the review of other malignant neoplasms (potential risk), 15 cases of cervix cancer and 7 cases of brain cancer have been reported cumulatively (6 were reported during the present PSUR period). Limited information has been presented in this PSUR, particularly for four of the cases of brain cancers, thus not allowing a proper causality assessment between Gilenya and the reported cases. The MAH is requested to improve the quality of data regarding cervix cancer and brain cancer in the next PSUR. A comprehensive clinical assessment of all cervix cancer (taking into account epidemiological data in multiple sclerosis patients and general population) and all brain cancer cases should be provided in the next PSUR (covering PSUR period and cumulatively).

In addition, the PRAC noted the following:

- Regarding infections (identified risk), 1250 cases of infections have been reported during the reporting period (the proportion of infection among all the reported cases in this current period is around 13.1%). Due to the seriousness of the infections reported with fingolimod, these events should be closely monitored.

- Twelve cases of Progressive Multifocal Leukoencephalopathy (PML) were reported including 5 during the current period. In the last PSUR, 10 cases were reported cumulatively. Taking into account the case reported in the late breaking information, there are at least 13 cases reported cumulatively. These events should be closely monitored and a thorough review of all PML cases should be provided in the next PSUR.

- Thrombocytopenia (including immune thrombocytopenic purpura) and pancytopenia were signals under review by the MAH. A safety review was performed by the MAH and reported 115 cases of thrombocytopenia. Moreover 7 cases of immune thrombocytopenic purpura were reported. Since 11 cases of thrombocytopenia had positive dechallenges including one patient with a positive

rechallenge, a potential causal relationship between Gilenya and thrompocytopenia could not be excluded. Regarding pancytopenia, 33 cases were cumulatively reported. The majority of these cases did not have sufficient information to allow a proper causality assessment. However, one case had a positive dechallenge. Based on these data, the PRAC considered necessary to keep these signals under evaluation in the next PSUR for further characterisation.

- Regarding the review of leukopenia/lymphopenia (identified risk), the percentage of cases reporting concomitantly leukopenia and lymphopenia (any) was found higher for more serious types of infections (sepsis) when compared with the percentage of infections overall. Based on this finding, the MAH should discuss whether an update of the Summary of Product Characteristics (e.g additional warning for the prescribers on the higher risk of serious infections) should be considered in the next PSUR.

- The number of skin cancer (potential risk) to date and the duration of follow-up, remain relatively limited and do not permit to draw definitive conclusions on any potential long-term risk for this type of malignancy with fingolimod in particular for exposure greater than 2 years. The risk for basal cell carcinoma (BCC) increases with age. According to some published data, the incidence of BCC in the age group 30-59 years is rather low compared to older population. In addition, based on the available PSUR data, the majority of the patients diagnosed with melanoma were in the age group 30-49 years. In order to further characterise this potential risk, the MAH is requested to provide cumulative information in which age groups skin cancer occurred and match this to the general multiple sclerosis population in the next PSUR.

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. As requested by the MAH, the PRAC agreed that the frequency of the PSUR submission should thereafter be revised to a yearly cycle.

The PRAC considered that the Risk Management Plan (RMP) is acceptable. In addition, revisions (e.g upgrade of hypersensitivity from potential to identified risk) were recommended to be taken into account at the next RMP update.

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.