20 September 2018
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): fingolimod

Procedure No. EMEA/H/C/PSUSA/00001393/201802

Period covered by the PSUR: 01-Mar-2017 - 28-Feb-2018

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Scientific conclusions

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

A cumulative review of the post-marketing cases identified five cases reporting events of interest [myalgia (n=3) and arthralgia (n=3)], which were considered noteworthy. Three of these five cases were reported with positive re-challenge for the events of interest and the other two cases were reported with positive de-challenge without any plausible alternative explanation for the event of interest. Additionally, 38 cases, reporting 41 events of interest [myalgia (n=15) and arthralgia (n=26)], were reported with positive de-challenge; however, there was limited information about medical history and/or concomitant medication in these 38 cases. Based on the noteworthy cases identified in post-marketing, 'myalgia' and 'arthralgia' will be added to the section of the adverse drug reactions in the SmPC and in the Package leaflet.

Regarding malignant neoplasms including skin and malignant lymphoma, there is a trend for an increased incidence rate (3.3% for the first period then 4.04% for the current period). Lymphoma represented 9.3% (cumulative data) to 10.6% (current period). Lymphomas are heterogeneous but, the number of mycosis fungoides increased during the reporting interval (5 cases). At least 2 published cases of T cell lymphoma reported regression of the cutaneous lesions after fingolimod discontinuation, suggesting strong fingolimod causality and immunosuppressant effect. Based on the increasing frequency of mycosis fungoides, the event will be added under the description on lymphomas in section 4.8 of the SmPC.

In a search for 'HPV and related cancers' a total of 414 cases (464 events) were identified cumulatively with a stable incidence rate over time. The majority of cases reported HPV infection, papilloma, dysplasia and warts. There were 68 neoplasms reported (59 cervix and 9 anal). Underreporting is highly probable for these events and evaluation of causality is consequently hard to define. Nevertheless, reported noteworthy cases suggest temporal relation. More than transformation onto malignant neoplasm following HPV infection, reactivation is a more relevant event suggestive of immunological modifications. Given the pharmacological properties of fingolimod on immunity and cases of reactivation (in some cases after several years of latency) with close temporal association with fingolimod, these data strongly support possible HPV infection reactivation upon fingolimod treatment. These data support the change proposed for the SmPC and in the Package leaflet.

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 fingolimod the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fingolimod 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.