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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): teriflunomide

Procedure No. EMEA/H/C/PSUSA/00010135/201609

Period covered by the PSUR: 13 March 2015 to 12 September 2016

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Scientific conclusions

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

Cumulatively, a total of 39 unique case reports of potential Interstitial lung disease (ILD) were retrieved, of which 3 cases with a possible causal relationship with teriflunomide. Since ILD can be a serious event, possibly fatal, it should be included in section 4.4 of the SmPC as reported in the post-marketing setting and not just as reported for the parent compound leflunomide. Due to the long half-life of the compound recommendation for initiation of an accelerated elimination procedure in case of pulmonary symptoms should also be included. ILD should also be moved from “very rare” to “not known” without a reference to leflunomide in the table in section 4.8.

In the post-marketing setting, 121 hepatic disorders events (26 % of the total) were assessed as associated with teriflunomide. An increase of ALT ($\geqslant$3 x ULN) in combination with an increase of total bilirubin (>2 x ULN) indicates drug induced liver injury showing that teriflunomide is not only associated with non-serious elevations of liver enzymes, but also with serious hepatic events, like “acute hepatitis” which should be included in the SmPC section 4.8 with a frequency unknown. In addition, the adverse reactions “Alanine aminotransferase (ALT) increase”, “Gamma-glutamyl transferase (GGT) increase” and “Aspartate aminotransferase increase” should be moved from the system organ class (SOC) term “Investigations” to the SOC “Hepatobiliary disorders”.

Based on the very high number of reported post-marketing cases of asthenia (cumulatively 5873 cases) and considering that asthenia is also listed in the SmPC for the parent compound leflunomide, it should be included as possible adverse reaction for teriflunomide in the table in SmPC section 4.8 with a frequency of unknown.

Ten post-marketing cases of nail disorders reported a possible causality with teriflunomide and 6 of them resulted positive for de-challenge. It is also noted that nail loss and other nail disorders were often reported together with hair loss or hair thinning, suggesting a possible shared pathophysiologic mechanism; and alopecia is a known side effect of teriflunomide. Therefore, “nail disorders” should be included in the table in SmPC section 4.8 as possible adverse reaction with a frequency of unknown.

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