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Committee for Medicinal Products for Human Use (CHMP)

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

International non-proprietary name:TERIFLUNOMIDE

Procedure No. EMEA/H/C/PSUSA/00010135/201503

Period covered by the PSUR: 13 September 2014 to 12 March 2015

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Scientific conclusions

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

Severe skin reactions

There have been two (2) cases of Stevens-Johnson syndrome and two (2) cases reported with skin exfoliation reported during the period under review, and seven (7) cases of Stevens-Johnson syndrome and 27 cases reporting skin exfoliation cumulatively. Upon review of post-marketing cases with severe skin disorders (potentially Stevens-Johnson syndrome), it was observed that teriflunomide could not be excluded from potential causality in cases where time to onset, de-challenge/re-challenge information, and discontinuation from teriflunomide were available.

Pancreatitis

There have been eight (8) cases of pancreatitis reported during the period under review, and 18 cases cumulatively. Upon review of post-marketing cases with pancreatitis, as well as the review of clinical trial data, statistical signals, and epidemiology, the PRAC considered that teriflunomide could not be excluded from potential causality in cases where time to onset, de-challenge/ rechallenge information, and discontinuation from teriflunomide were available.

Hypersensitivity reactions

Post-marketing cases with hypersensitivity reactions (immediate or delayed) some of which were severe, such as anaphylaxis and angioedema, were reported. The PRAC observed that teriflunomide could not be excluded from potential causal association in cases where time to onset, de-challenge/rechallenge information and discontinuation were available. Two (2) patients underwent reportedly the rapid elimination procedure; however, the outcome was unknown for both patients.

Headache

There have been cumulatively 2179 Adverse Drug Reactions (ADR) reports from post-marketing sources. Upon review of post-marketing cases for headache, as well as the review of clinical trial data (placebo-controlled studies), the PRAC considered that there is a trend towards a causal association with teriflunomide for headache.

Blood creatine phosphokinase (CPK) increased

The reported cases together with the higher number of CPK increase cases or associated events in pooled clinical trials (7 mg /14 mg) show a clear trend towards a causal association. CPK increase is labelled as a common ADR in section 4.8 of the SmPC of leflunomide (Arava). Upon review of post-marketing cases for CPK increase, as well as the review of clinical trial data (placebo-controlled studies), the PRAC considered that there is a trend towards a causal association with teriflunomide.

Arthralgia

Clinical trial data shows a trend towards more events in the pooled teriflunomide group (7mg /14 mg) compared to placebo group. The reported cases together with the higher number of arthralgia cases or associated events in clinical trials show a clear trend towards a causal association. Upon review of clinical trial data, the PRAC considered that there is a trend towards a causal association with teriflunomide.

Palpitations

In placebo-controlled studies palpitations were reported >1% more often in the teriflunomide 7 mg group (but not in the teriflunomide 14 mg group) when compared to placebo. Upon review of clinical trial data, the PRAC considered that there is a trend towards a causal association with teriflunomide.

Sepsis

Cumulatively, there have been a total of 24 case reports (all were assessed as serious) referring to 22 events of sepsis (one wound sepsis and one urosepsis), of which five were with fatal outcome and one life-threatening sepsis. The 5 patients who died due to sepsis (4 due to urinary tract infection and 1 secondary to decubitus ulcers), all had advanced Multiple Sclerosis disease and multiple drug therapy. The PRAC is of the opinion that there is enough evidence leading to the conclusion that severe infections during teriflunomide treatment can result to sepsis.

Peripheral neuropathy

In placebo-controlled studies, in total there have been 17 cases of peripheral neuropathy that were confirmed by nerve conduction studies, out of 898 patients treated. Of these 17 patients, there were 5 patients who discontinued treatment.

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

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

Grounds for the variation to the terms of the Marketing Authorisation

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 favourable subject to the proposed changes to the product information

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