14 December 2017
EMA/CHMP/608212/2019
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): ibrutinib

Procedure No. EMEA/H/C/PSUSA/00010301/201705

Period covered by the PSUR: 13 November 2016 – 12 May 2017

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Scientific conclusions

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

During the assessment of the previous PSUR (#4), the MAH provided a cumulative review of all cases of panniculitis and of erythema nodosum (a type of panniculitis). During the review, the MAH identified a total of 26 cases: 17 cases of erythema nodosum and 11 cases of panniculitis. Five of these cases had been reported from a publication (Fabbro S. et al 2015). Briefly, the authors identified 5 patients who reported nodular rashes primarily on the extremities while receiving ibrutinib for CLL. Histopathologic analysis demonstrated a lobular and septal panniculitis. Treatment with prednisone was started in 3 patients and this proved effective in reducing symptoms which returned upon discontinuation of corticosteroids. The authors considered the cases causally related to ibrutinib.
During the period covered by the current PSUR (#5) the MAH reported 3 initial cases of panniculitis of which 2 serious and 1 non-serious. Of the 3 cases, one was excluded from the review as related to 'multiple patients'. Of the remaining two cases, one reports that the treating physician discontinued treatment with ibrutinib and the other is a literature case study reporting positive de-challenge and re-challenge (Hammel J. et al, 2017).
With regards to the cases reported cumulatively by the MAH and assessed during the last PSUR, in one case the investigator believed that a causal association with ibrutinib was possible. In three cases the MAH reported that ibrutinib was discontinued at the onset of symptoms suggesting that the investigator might have considered a correlation as possible. Twelve cases did not report causality assessment but the clinical narrative could not exclude a causative role played by ibrutinib.
Considering the cases reported cumulatively at the time of the previous PSUR in addition to the cases reported during the current interval, these comprised: 1 case of positive de- and re-challenge, 1 case considered possibly related to ibrutinib by the investigator, 4 cases of ibrutinib discontinuation by the treating physician suggesting that a correlation with ibrutinib was considered possible and 12 cases lacking a causality assessment but reporting a clinical narrative that cannot exclude a causative role played by ibrutinib.
The re-assessment of the cumulative data reported in the previous PSUR and in the one under current review, including the case of positive de-challenge and re-challenge reported during this PSUR and the lack of plausible alternative explanation, suggests that the role of ibrutinib in cases of panniculitis cannot be excluded and the above ADR should therefore be listed in section 4.8 of the SmPC.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing ibrutinib were warranted.

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