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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): ibrutinib

Procedure No. EMEA/H/C/PSUSA/00010301/201911

Period covered by the PSUR: 12 November 2018 to 12 November 2019

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Scientific conclusions

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

In view of the available data on splenic rupture following discontinuation of ibrutinib treatment and considering the seriousness of this condition, a plausible temporal relationship and mechanism of action, the prescribers should be warned about the possibility of splenic rupture occurrence after ibrutinib discontinuation.

Considering the large number of cases reporting events related to cardiac failure/decreased LVEF - total of 839 cases, of which 2 cases with positive dechallenge and rechallenge and 14 cases of positive dechallenge in which heart failure resolved or improved after ibrutinib withdrawal or decreasing the dose as well as literature findings (two literature case reports of cardiac failure which reported positive dechallenge to ibrutinib and one literature case of cardiac failure possibly related to ibrutinib) and plausible mechanism of action, a causal relationship between ibrutinib and cardiac failure is at least a reasonable possibility. The PRAC concluded that the product information of ibrutinib should be amended accordingly.

Based on plausible mechanism of action, the absence of neutrophilic dermatoses events with the comparator in the RCT and 7 cases identified from the MAH's global safety database with positive dechallenge including one also with positive rechallenge; of which 4 were biopsy confirmed and had no alternate explanation for the events, a causal relationship between ibrutinib and the events of neutrophilic dermatosis, acute febrile neutrophilic dermatosis and pyoderma gangrenosum is a reasonable possibility. The PRAC concluded that the product information of ibrutinib should be amended in order to add these 3 events under the grouped term, neutrophilic dermatoses, as a new ADR in the product information.

Twenty five cases were identified in MAH's safety database coded to PTs Haemophagocytic lymphohistiocytosis (HLH) or Macrophage activation, of which 2 cases were identified as cases of interest in which patients had classic symptoms and laboratory findings consistent with HLH and had fatal outcome, one report of HLH of clinical trial database in ibrutinib pool and publication in scientific literature in which a plausible biological mechanism is proposed. Considering the seriousness of this condition with often fatal outcome, there is a need to warn clinicians and patients. The PRAC concluded that the product information of product ibrutinib should be amended accordingly.

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 containing ibrutinib is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation should be varied.