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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): idelalisib

Procedure No. EMEA/H/C/PSUSA/00010303/201701

Period covered by the PSUR: 23 July 2016 - 22 January 2017

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(s) for idelalisib, the scientific conclusions of CHMP are as follows:

The MAH provided a cumulative review of cases of hepatocellular injury. Out of a total of 159 cases, 14 cases met the criteria for inclusion in the final analysis, i.e. had clinical and diagnostic findings consistent with hepatocellular injury that was not already described in the Company Core Data Sheet (CCDS), a plausible association with idelalisib, and met the case definition for the MAH's review.

Following the PRAC review of the 14 cases it was found that 7 of these were supportive of an association of idelalisib and the described hepatic event. Events reported in these cases included hepatic failure (3), hepatitis (1), hepatocellular injury (1), and hepatotoxicity (3). One case included a positive re-challenge, one case a positive de-challenge, once case a negative re-challenge at a lower dose. Overall, the conclusion on a role for idelalisib in the described events was based on compatible time to onset, exclusion of other aetiologies, e.g. viral infection or alcohol abuse, and further improvement of the adverse event with steroid treatment in one of the 7 cases. Furthermore, if patients were concomitantly treated with hepatotoxic co-medication these drugs were initiated considerably earlier than idelalisib.

Following clinical trial data in CLL patients who were treated with idelalisib first in line, Lampson et al observed a higher rate of hepatotoxicity in primarily younger patients. Immunoglobulin heavy chain variable (IGHV) mutation status was found as a second risk factor for ≥grade 3 transaminitis. The authors proposed that idelalisib may induce autoimmune hepatotoxicity by way of reducing the number of regulatory T cells (TREGs) and subsequent effects on the immune system. This hypothesis is supported by a number of pre-clinical and clinical findings and provides a possible explanation of the aetiology of the cases that were found supportive of an association between idelalisib and hepatotoxicity of the MAH's review where sufficient details of liver enzyme tests were available.

Amongst the 14 cases included in the review only one case had biopsy data available; no conclusions could be drawn from those with regards to a possible mechanism leading to the adverse event. The MAH confirmed a statistically significant association between younger age and ≥grade 3 transaminitis as found by Lampson et al. The MAH's data on IGHV mutation status were too scarce to provide meaningful information. Overall, the data provided by the MAH were considered supportive of an association between idelalisib and hepatotoxicity.

Following a cumulative review of cases of lymphocytosis the update of section 4.8 and 5.1 of SmPC is warranted. The MAH concluded that that there is a causal association between Zydelig and lymphocytosis due to pharmacodynamic effect in common with other B-cell receptor pathways inhibitors with effects on the B-cell receptor mediated lymphocyte trafficking being a likely mechanism.

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