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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/00010301/201611

Period covered by the PSUR: 13 May 2016 to 12 November 2016

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Scientific conclusions

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

Hepatitis B reactivation

In the context of this PSUR, the MAH has performed a cumulative review of all cases of hepatitis B reactivation. On a total population of 1741 patients enrolled in clinical trials, HBV reactivation was reported in only 2 subjects. However, it is noted that candidate subjects for clinical trials had been screened for signs of prior or acute hepatitis infection (hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody) and that patients who resulted positive for hepatitis B core antibody or hepatitis B surface antigen were required to have a negative polymerase chain reaction (PCR) to be eligible for enrolment in clinical trial. With regards to individual case safety reports, 8 cases of hepatitis B reactivation (including one fatal case) were reported, in which the treating physician/investigator considered the role of ibrutinib as probable/possible (7 cases) or related.

Given the evidence reported in post-marketing settings, the HBV pre-screening of patients to be enrolled in clinical trials operated by the MAH and the impossibility to exclude a causative role played by ibrutinib in cases of hepatitis b reactivation, this safety concern should be listed in section 4.8 of the SmPC with frequency 'uncommon'. In addition, the PRAC considered that healthcare professionals should be informed about the risk of viral reactivation and that a warning should be introduced in the product information.

Ventricular tachyarrhythmia

52 cases of ventricular tachyarrhythmia were reported in post-marketing settings of which the role of ibrutinib could not be ruled out in 2 cases. Also a recent study by Lampson and colleagues (2016) reports 11 cases of Ventricular tachycardia/ ventricular fibrillation and 6 cases of sudden cardiac death in patients exposed to ibrutinib. In 12 of the total 17 cases, the events above occurred without any evidence of prior cardiac history. Finally, atrial fibrillation is included as an important identified risk- and 'cardiac arrhythmia (excluding cardiac fibrillation)' as an important potential risk in the RMP. Atrial fibrillation is also reported in section 4.4 of the SmPC and listed as 'common' in section 4.8 of the SmPC. Therefore, although the biological mechanism is still not clear, it cannot be excluded that ibrutinib might have general pro-arrhythmogenic properties. Based on this outcome, update of section 4.4 and 4.8 of the Summary of product characteristic to include the risk of ventricular tachyarrhythmia is recommended.

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.