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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/00010303/201707

Period covered by the PSUR: 23 January 2017 to 22 July 2017

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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 Progressive Multifocal Leukoencephalopathy (PML) as per PRAC request. Sixteen (16) cases were identified in the MAH's Drug Safety & Public Health (DSPH) global safety database following a search using the broad SMQ Demyelination. Eleven (11) cases were consistent with a diagnosis of PML.

The MAH assessed the diagnostic certainty according to a set of criteria outlined in the papers by Mentzer et al (2012) and Segec et al (2015) and concluded that four of the 11 cases fulfilled the definition of the criteria for certainty level 1 and four cases fulfilled the criteria of level 2 (level 1 (highest certainty) to 5 (lowest certainty)). The remaining three (3) cases fulfilled the criteria for certainty level 4.

Based on the assessment, a possible association could not be excluded in 4 cases. Two (2) of these cases were assessed as certainty level 1 and two (2) as certainty level 2. A possible contribution of idelalisib was based on these cases reporting discontinuation of other suspect drugs several months prior to the events of PML whilst idelalisib was continued up until the event. whilst it is acknowledged that the time to onset of PML or time to diagnosis may be several months and may be variable, it is notable that in one of the 4 cases, other suspect drugs were stopped 14 months prior to the event whilst idelalisib was continued. Two (2) of the 4 cases where a contributory role for idelalisib could not be excluded were fatal. The evidence was assessed as proposed by Segec et al (2015) 'Strategy in Regulatory Decision-Making for Management of Progressive Multifocal Leukoencephalopathy'. Based on a total of 19.270 patients (18.467 patients in the US and 803 patients in the EU) exposed cumulatively to idelalisib post-marketing as presented in the current PSUR and 8 cases that met the certainty level 1 and 2 according to Mentzer et al (2012) this equals a reporting rate of 42 cases/ 100.000 patients. We consider one case as moderate evidence (2014-0111037) and 3 further cases as supportive evidence (2015-0172653, 2017-0256330 and 2015-0160573). Based on this information, we concluded that the overall strength of the evidence is moderate and that that labelling PML in section 4.4 but not in section 4.8 of the SmPC may be adequate to mitigate the potential risk of this serious event.

Since one of the indications for idelalisib is indicated in combination with rituximab it will remain a challenge to clearly differentiate possible contributory roles of the two drugs to events of PML. However, idelalisib's mechanism of action of interference in B-cell trafficking and its immunosuppressive effects as evidenced by the occurrence of other serious and fatal infections (eg PJP and CMV infections) are plausible in the context of PML.

PML is a serious clinical event which benefits from early diagnosis and intervention physicians prescribing idelalisib would benefit from a warning that PML has been reported with idelalisib. It is therefore recommended that section 4.4 of the SmPC should be updated to reflect the potential for this risk. This is consistent with similar recommendations regarding the risk of PML adopted by PRAC in December 2016 for ibrutinib, which is indicated for treatment of mantle cell lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma and Waldenstrom's macroglobulinaemia.

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.