19 September 2019
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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): carfilzomib

Procedure No. EMEA/H/C/PSUSA/00010448/201901

Period covered by the PSUR: 19 January 2018 – 19 January 2019

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Scientific conclusions

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

Based on a number of angioedema cases reported in relation to carfilzomib monotherapy or combination therapy, 5 of which with positive dechallenge, and the plausible mechanism considering possible class effect (bortezomib has angioedema included in section 4.8 of SmPC), as well as presented cases which suggest causal role of carfilzomib, the PRAC considers that the product information (PI) should be updated to include this adverse reaction.

A number of cases of Hepatitis B reactivation have been identified in relation to carfilzomib treatment. These included 1 well-documented serious case of hepatitis B reactivation with a likely association with carfilzomib and no substantial confounders, and 1 case of hepatitis B reactivation suggestive of a causal association which developed with the addition of carfilzomib to an ongoing regimen of lenalidomide plus dexamethasone, as well as 20 other serious cases which had, at minimum, a plausible temporal association with carfilzomib. Based on high number of cases, plausible mechanism and seriousness of the risk, hepatitis B reactivation is proposed to be added as an adverse drug reaction in the SmPC and PL. A relevant warning should also be included.

Cardiac disorders are known adverse drug reactions of carfilzomib. Based on the number of relevant cases reported cumulatively, including 16 events with a fatal outcome during the reporting period, the existing warning on cardiac disorders should be updated to recommend that patients should be evaluated for cardiovascular risk factors before treatment with carfilzomib, that a comprehensive cardiological assessment should be considered for patients at high-risk for cardiovascular disease and that hypertension should be controlled during treatment, as a history of hypertension was frequently reported in patients presenting with cardiac disorders.

There is biological plausibility for carfilzomib induced PML (lymphopenia and opportunistic infections are expected ADRs). PML is known safety issue of bortezomib, which belongs to the same class as carfilzomib. In addition and according to the agreed case definition by Mentzer et al., two cases of level 1, one case of level 2 and one case of level 3 were identified. In line with the labelling and risk minimisation activities proposed by Segec et al, inclusion of a warning on PML in section 4.4 of the SmPC is warranted. The PL is updated 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 carfilzomib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing carfilzomib 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.