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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): ipilimumab

Procedure No. EMEA/H/C/PSUSA/00009200/201703

Period covered by the PSUR: 25 March 2016 - 24 March 2017

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for ipilimumab, the scientific conclusions of CHMP are as follows:

Based on 4 reported cases of pemphigoid (3 literature cases and one case from a study), the PRAC considered it reasonably possible that pemphigoid is associated with ipilimumab therapy, in view of the immune related effects of the drug and its possible impact on the skin. Furthermore, the PRAC noted that both nivolumab and pembrolizumab have pemphigoid listed in section 4.8 of their respective SmPCs – both drugs, belonging to the same pharmacotherapeutic class, also have immune modulating effects with immune-related adverse drug reactions of the skin. Based on the available evidence the PRAC concluded that 'pemhigoid' should be added as a new adverse drug reaction with a frequency 'not known' in section 4.8 of the SmPC and section 4 of the Package Leaflet.

Following a request from the PRAC, the MAH provided a cumulative review of all cases concerning histiocytosis haematophagic associated with ipilimumab. 17 cases were identified. In the majority of the cases, the patient was receiving concurrent treatment with ipilimumab and nivolumab. Both PD-1 and CTLA4 have been associated with deregulation of T-cell activity; therefore, a possible influence of nivolumab on the occurrence of histiocytosis haematophagic cannot be excluded. In the majority of the reported cases, a likely causal association with ipilimumab treatment was considered likely. The relatively short time to unset, with in some cases the event being just reported days after starting ipilimumab treatment, supports a potential causal association. The reported events mostly responded well to corticosteroids. Furthermore, the enhancement of T-cell responses and cytokine production as well as the activation of an uncontrolled proliferation of T lymphocytes and well-differentiated macrophages leading to, or increasing the risk of, histiocytosis haematophagic is a plausible mechanism of action. Based on the available evidence, the PRAC concluded that 'histiocytosis haematophagic' should be added as a new warning in section 4.4 of the SmPC and as a new adverse drug reaction with a frequency 'not known' in section 4.8 of the SmPC and in sections 2 and 4 of the Package Leaflet.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation

On the basis of the scientific conclusions for ipilimumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing ipilimumab is unchanged subject to the proposed changes to the product information.

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