EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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): nivolumab

Procedure No. EMEA/H/C/PSUSA/00010379/201807

Period covered by the PSUR: 4 January 2018 – 3 July 2018

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Scientific conclusions

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

Immune-related neurologic events including meningitis are rare AEs in the treatment populations. The assessment of individual cases from the MAH's safety database for the interval period did not provide a sufficient number of clearly defined cases of aseptic meningitis to identify a new safety signal. In addition, the MGPS disproportionality analysis identified a marginal EB05 score for meningitis aseptic for nivolumab but may have been affected by cases that included ipilimumab and nivolumab combination therapy. Based on this review of currently available data, it cannot be definitively ascertained whether aseptic meningitis is an ADR for nivolumab. Nevertheless, aseptic meningitis should be added as an ADR of both nivolumab monotherapy and nivolumab/ipilimumab combination therapy in section 4.8 of the SmPC with a frequency 'Not known'.

A cumulative search retrieved 50 cases of sarcoidosis (27 with nivolumab, 21 with nivolumab+ipilimumab and 2 with nivolumab in combination with other agents). The 50 cases were reported from the following sources: 15 spontaneous, 12 literature post marketing, 11 clinical trial Phase 1-3, 5 literature phase IV and 7 phase IV/solicited cases. The 50 cases reported the following 51 AEs (50 serious and 1 non-serious events): sarcoidosis (31), pulmonary sarcoidosis (11), cutaneous sarcoidosis (8), and neurosarcoidosis (1). The time to onset from the first dose of nivolumab ranged from 1 to 1055 days (n = 19; median onset = 230 days). Event outcomes were reported as unknown (n=21), recovered/resolved (n=13), not recovered/ not resolved (n=9), and recovering/resolving (n=8). Based on the data for sarcoidosis discussed within this PSUR, the term should be added to the ADRs list of nivolumab monotherapy with a frequency "Not known".

Anaemia is reported as a very common adverse reaction for both nivolumab monotherapy and nivolumab in combination with ipilimumab in Table 4 of the EU SmPC. Haemolytic anemia is caused by antibodies and based on the immunostimulatory properties of nivolumab, it is plausible that they could be related. As a result, it should be clarified that the term anaemia in section 4.8 of the SmPC also includes haemolytic and autoimmune anaemia.

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