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): nintedanib (oncology indications)

Procedure No. EMEA/H/C/PSUSA/00010318/201710

Period covered by the PSUR: 22 Nov 2016 to 15 Oct 2017

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Scientific conclusions

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

Following a request from the previous PSUR (PSUSA/00010318/201611) and the assessment of the present PSUR, the MAH provided case summaries of 15 post-marketing reported cases of gastrointestinal perforations. Gastrointestinal perforation is a known adverse drug reaction and important identified risk of Vargatef. In total 14 cases were serious and 5 cases had a fatal outcome (in which the role of nintedanib could not be excluded). The outcome of the remaining 10 events was almost evenly distributed among not recovered/not resolved, recovered/resolved and unknown. 3 new cases were reported during the covering period of this PSUR. 6 cases had a positive de-challenge. Cumulatively the overall causality was assessed as related in 6 cases and as not related in 4 cases. Based on the available evidence, the PRAC concluded that section 4.4 of the SmPC should be updated to amend the current warning on gastrointestinal perforations to include that some fatal cases of gastrointestinal perforations have been reported in the post-marketing period.

Following the re-opening by the MAH of the signal of renal failure and following the assessment of the present PSUR, the MAH provided summaries of all the cases under the SMQ ‘acute renal failure’. A total of 15 cases were retrieved. In 8 cases diarrhoea was associated with renal failure. Taking into consideration that only half the reported cases included diarrhoea as a factor provoking renal impairment, another mechanism (e.g. direct effect of nintedanib on kidney through inhibition of PDGFR and VEGFR) cannot be excluded. Also, other risk factors have been identified by the MAH. Although in these confounded cases there was no case indicating direct nephrotoxicity attributable to nintedanib, its role cannot be excluded. Based on the available evidence, the PRAC concluded that renal failure should be added as a new warning in section 4.4. of the SmPC and as a new adverse drug reaction with a frequency ‘uncommon’ in section 4.8 of the SmPC.

Following the assessment of the present PSUR, the MAH provided case summaries of arterial thromboembolism cases. A total of 8 cases under the narrow SMQ 'Embolim and thrombotic events' were retrieved including 4 cases of myocardial infarction in which the role of Vargatef cannot be excluded. In all 4 cases some alternartive etiologies and contributing factors were identified. Based on the available evidence and considering that the PRAC already concluded as part of Ofev LEG 014 that myocardial infarction should be labelled in the Ofev SmPC, the PRAC concluded that myocardial infarction should be added as a new adverse drug reaction with a frequency 'uncommon' in section 4.8 of the SmPC.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing nintedanib (oncology indication) were warranted.

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 nintedanib (oncology indication) the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing nintedanib (oncology indication) is unchanged subject to the proposed changes to the product information

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