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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 (respiratory indication)

Procedure No. EMEA/H/C/PSUSA/00010319/201710

Period covered by the PSUR: 16 Apr 2017 to 15 Oct 2017

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Scientific conclusions

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

Following a request from the previous PSUR (PSUSA/00010319/201704) and the assessment of the present PSUR, the MAH conducted an analysis of of 'rash' and 'pruritus' cases. A total of 502 cases of rash and 252 cases of prurituis were retrieved. For pruritus, a positive dechallenge was reported in 21 cases and for rash in 56 cases. 3 cases of rash had a positive positive rechallenge versus 2 for pruritus. Inhibition of receptors for vascular endothelial growth factor (VEGRF) is related to dermatologic toxicities including rash and pruritus and could be a possible mechanism of action. Based on the total number of cases reporting rash (502 cases) and pruritus (252 cases), the described cases of positive rechallenge and the plausible mechanism of action, the PRAC concluded that ‘rash’ and ‘pruritus’ should be added as new adverse drug reactions with a frequency ‘common’ and ‘uncommon’ respectively in section 4.8 of the SmPC.

Following a request from the previous PSUR (PSUSA/00010319/201704) and the assessment of the present PSUR, the MAH conducted an in depth analysis of risk factors ofr renal impairment/failure. A total of 148 cases were indentified under the Standardised MedDRA Query (SMQ) 'acute renal failure' from all sources (30 cases reported in clinical trials and 118 cases reported during post-marketing). 47 cases had a fatal outcome and in 11 cases renal failure was the major cause of death. A positive dechallenge was reported in 16 cases and a positive re-challenge in 2 cases. Two possible mechanisms by which nintedanib causes renal impairment/failure have been identified: the first one is by direct effect of nintedanib on kidney through inhibition of Platelet-derived growth factor receptors (PDGFR) and VEGFR, the second one is through known side effects of nintedanib: diarrhoea and dehydration, which can possible lead to renal impairment/ failure. A total of 76 cases containing events of preferred terms (PTs) ‘diarrhoea’, ‘vomiting’, or ‘dehydration’, and 70 cases without these PTs have been reported in total. Two cases derived from blinded clinical trial. As requested the MAH performed an analysis of all risk factors for renal impairment/failure; grouping patients according to the presence or absence of co-reported diarrhoea, vomiting or dehydration. The same level of evidence (number of cases, relatedness to nintedanib in reported cases, plausible mechanism) is available for cases with/ without diarrhoea, vomiting or dehydration. In conclusion, based on the high number of reported cases in which the contributing role of nintedanib could not be excluded, the plausible mechanisms, the high number of cases with fatal outcome and the seriousness of such adverse drug reaction, the PRAC concluded that renal failure should be added as a new warning in section 4.4 and as a new adverse drug reaction with a frequency ‘unknown’ 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 (respiratory 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 (respiratory indication) the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing nintedanib (respiratory indication) is unchanged subject to th3e proposed changes to the product information

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