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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): naldemedine

Procedure No. EMEA/H/C/PSUSA/00010753/201903

Period covered by the PSUR: 21/09/2018 To: 21/03/2019

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Scientific conclusions

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

The MAH identified nine cases of gastrointestinal perforation in their global database. Two of the nine cases have been classified as cases of interest by the MAH, one of which they consider 'possibly related' and other 'probably related'. Both of these cases were fatal. Two of the nine cases were excluded by the MAH because they were not considered valid, and in the remaining five cases the MAH excluded a causal relationship in addition to the reporter. Whilst the more limited information provided in these five cases is acknowledged the assessor considers that the potential role of Naldemedine cannot be excluded in all of these.

None of the identified cases are without significant confounding factors and the difficulties in definitively determining causality are acknowledged. Nevertheless, given the times to onset and the mechanism of action of Naldemedine which leads to an increase in the propulsive contractions of the intestinal muscle it is considered that Naldemedine could plausibly have contributed to perforation events in these patients who were already at increased risk due to the presence of additional risk factors including underlying disease and concomitant treatments.

Overall, whilst the limitations in the evidence base solely for Naldemedine are acknowledged it is considered that supporting information is also provided by other agents in the class which are mechanistically indistinguishable from Naldemedine and which have similar effects on the GI tract. It is therefore considered that the presented cases are sufficient to support an update to the product information to both section 4.4 and 4.8. The agreed update is aligned with the wording reflected in the product informations for methylnaltrexone and naloxegol. Cases of gastrointestinal perforation have been reported in post-marketing setting, including fatal cases, when naldemedine was used in patients who were at an increased risk of gastrointestinal perforation. Naldemedine must not be used in patients with known or suspected gastrointestinal obstruction or in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation. Gastrointestinal perforation is added a new adverse reaction with a frequency "Not known". The package leaflet 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 naldemedine the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing naldemedine 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.