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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): galsulfase

Procedure No. EMEA/H/C/PSUSA/00001515/201905

Period covered by the PSUR: 1 June 2018 to 31 May 2019

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Scientific conclusions

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

The review of cases of severe respiratory and cardiac events with a close temporal association with Naglazyme infusion was not suggestive of a direct cardiac toxicity of Naglazyme. There is however some evidence from these cases that in patients with pre-existing congestive heart failure or severe cardiac valve disease Naglazyme treatment may result in acute volume overload.

Even though a definitive association between these type of events and Naglazyme cannot be established based on the currently available data, given the potentially severe clinical consequences of these events, it is proposed as a precaution to update the SmPC with a warning in Section 4.4 to reflect the potential risk of acute cardio-respiratory failure related to fluid volume overload.

Review of renal events in association with Naglazyme use revealed that the majority of cases were related to hypo-perfusion injury either from sepsis or cardiac failure. However, renal impairment can also occur through a type III hypersensitivity mechanism, whereby drug and anti-drug antibody complexes circulate and deposit into native tissue.

Potential formation of these drug and drug-antibody complexes is likely to occur in patients treated with enzyme replacement therapies, as these patients are known to develop high drug antibody titers while receiving a high antigenic load from their weekly infusions. The deposition of these drug and anti-drug antibody complexes induces a complement-mediated local inflammatory response, which can cause tissue damage.

This pathophysiologic mechanism of type III hypersensitivity has been confirmed in at least two patients treated with enzyme replacement therapies, including one treated with Naglazyme. Both patients had a confirmed diagnosis of alloimmune membranous glomerulonephritis.

Based on the available evidence and the strong biological plausibility the SmPC should be updated to include a warning related to immune-mediated reactions including membranous glomerulonephritis and the need to consider discontinuation of the administration of NAGLAZYME in patients experiencing such events.

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 Galsulfase the CHMP is of the opinion that the benefitrisk balance of the medicinal product(s) containing Galsulfase 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.