EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2018
EMA/895480/2018
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): lutetium (177Lu) chloride

Procedure No. EMEA/H/C/PSUSA/00010391/201712

Period covered by the PSUR: 20 June 2017 – 19 December 2017

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for lutetium (177Lu) chloride, the scientific conclusions of CHMP are as follows:

Nine cases of hepatotoxicity (including one fatal case of liver failure in a patient with extensive liver metastases, cryptogenic cirrhosis and pre-existing superior mesenteric vein thrombosis, 2 cases of liver injury, and 5 cases of new or worsening ascites) have now been identified 1 day – 3 months following treatment with Lu-177 peptide receptor radionuclide therapy (PRRT) in Eudravigilance. In most cases the reporter considered that hepatotoxicity was at least possibly related to Lutetium 177, as well as the underlying disease. There have also been reports of hepatotoxicity particularly following treatment with Lu-177 PRRT in a number of prospective single-arm studies published in the literature. Clinical guidelines advise that patients with liver metastases may be most susceptible to hepatotoxicity with PRRT and recommend monitoring liver function before each treatment cycle. Moreover, adverse reactions within the hepatobiliary SOC are associated with the recently authorised Lu-177 labelled somatostatin analogue Lutathera. Therefore, the PRAC considers that advice to healthcare professionals (HCPs) on cases of suspected hepatotoxicity following Lu-177 PRRT is warranted.

Two cases have been identified in Eudravigilance describing carcinoid crisis following treatment with Lutetium 177 peptide receptor radionuclide therapy, including 1 literature case. Both demonstrated a positive rechallenge. Three literature publications also described this phenomenon, with a positive rechallenge in a number of the cases described. Most of the cases identified in Eudravigilance and reported in the literature were serious and time to onset, where reported, was within 48 hours. Clinical guidelines advise that peptide receptor radionuclide therapy (PRRT) may exacerbate the syndromes associated with functional tumours due to sudden massive release of hormones and receptor stimulation. It is noted that carcinoid crisis is considered an adverse reaction of the recently authorised product Lutathera, a Lu177-labelled somatostatin analogue indicated for PRRT of neuroendocrine tumours. Given the serious nature of the cases identified and the consistency of reporting, the PRAC considers that there should be a warning to HCPs in the product information that carcinoid crisis and hormone release syndromes may occur during use of Lu-177 for PRRT and it should also be listed as an adverse reaction.

In the initial analysis of the NETTER-1 trial, a randomised open-label trial comparing Lu177-PRRT plus Octreotide LAR versus octreotide alone in 229 patients with neuroendocrine tumours , 65 patients (59%) in the Lu177 arm compared with 13 patients (12%) in the control arm reported nausea of any grade ($p<0.001$). Additionally, 52 patients (47%) reported vomiting of any grade compared with 11 patients (10%) in the control arm ($p<0.001$). Although in Lu-177 PRRT, nausea and vomiting have been attributed to the amino acid infusion given as renal protection, this was not the case for all reports of nausea and vomiting in the NETTER-1 trial. Moreover, a number of publications have been identified which report nausea and vomiting both in patients undergoing treatment with Lu177 as peptide receptor radionuclide therapy for neuroendocrine tumours and as prostate specific membrane antigen-targeted Lu177 radioligand therapy for metastatic castration resistant prostate cancer. Irradiation of the stomach due to treatment of malignancy can be associated with acute toxicity manifesting as nausea and vomiting within 24 hours. The PRAC is therefore of the view that the product information should be updated to advise HCPs and patients of this adverse reaction.

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 lutetium (177Lu) chloride the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing lutetium (177Lu) chloride 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.