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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): lutetium (177Lu) chloride

Procedure No. EMEA/H/C/PSUSA/00010391/201612

Period covered by the PSUR: 6 July 2016 – 19 December 2016

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Scientific conclusions

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

Haematological disorders

Haematological disorders including anaemia, thrombocytopenia and leukopenia have been reported with considerable consistency from a number of studies describing the use of Lutetium 177 - Peptide receptor radionuclide therapy (Lu177-PRRT) for neuroendocrine tumours (NETs) in the pre-authorisation phase. Similarly, in the recent randomised clinical trial NETTER -1 the incidences of any grade of thrombocytopenia, lymphopenia and leucopenia were significantly higher in the Lu177-DOTATE treatment arm than in the control arm. There was also weak evidence of a higher incidence of anaemia in the treatment arm and a non-significant numerical imbalance in the percentage of patients with neutropenia. Haematological disorders are listed as an adverse effect of Lu177 PRRT in several European guidelines on its use. Three cases describing haematotoxicity with Lu177-PRRT for NETs have been received in Eudravigilance. All describe a temporal relationship and a positive rechallenge is suggested in one.

Haematological disorders have also been observed following Lu177 PSMA-targeted therapy for metastatic castrate-resistant prostate cancer (mCPRC). Additionally, the association is biologically plausible based on the known mechanism of action.

Based on the available evidence, the PRAC recommends that the product information for Lu177 should be updated in order to advise prescribers and patients of this issue.

Therapy-related myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)

Therapy-related myeloid neoplasms (t-MNs) were reported in 1-2% of patients treated with Lu177 PRRT for neuroendocrine tumours in a number of studies conducted prior to authorisation of Lu177. Moreover, recently published analysis of Lu177-DOTATATE in patients with neuroendocrine tumours (Brabander et al 2017) reported cases of myelodysplastic syndrome and acute leukaemia. According to the interim analysis of the NETTER-1 study published earlier this year, there was one case of MDS in the Lu-177 DOTATATE arm.

The MAH has received 3 post-marketing reports of MDS and 1 post-marketing report of AML. An additional bone-marrow examination confirmed case was identified in Eudravigilance in a patient without a history of previous chemo- or radiotherapy, after 4 cycles of Lu177 PRRT for metastatic carcinoid tumour of the ileum.

The potential association with therapy-related myeloid neoplasms is considered to be biologically plausible. Moreover, the effect appears to be rather specific, in that no other type of malignancy has been described. There is also some coherence with what is known about the long-term safety profile of other radiopharmaceuticals such as radioactive iodine. MDS / AML do not yet appear to have been observed during Prostate-specific membrane antigen targeted (PSMA-targeted) radioligand therapy for mCRPC (including that using Lu177). However, the toxicity may not have been observed due to different prognosis of the disease.

Consequently, the PRAC is of the view that healthcare professionals and patients should be advised that cases of MDS / AML have been reported following treatment with Lu177-PRRT for NETs and that a product information update is warranted.

Renal dysfunction

Radiolabelled somatostatin analogues are eliminated by the kidney. Biopsy-confirmed radiation nephropathy with thrombotic microangiopathy has been observed in association with another radioligand, 90Y-DOTATATE, and can lead to chronic kidney disease. Lu177 has a shorter penetration than 90 Y,

however. Data from the NETTER-1 study did not show evidence of renal toxicity in association with Lu177 thus far. Moreover, while a small number of relevant post-marketing reports have been received, they are confounded by previous medical history. However, patients in the studies to date including NETTER-1 and in the post-marketing cases have received amino acid infusions. This is in accordance with European clinical guidelines which list radiation nephropathy as a possible adverse effect of radioligand therapy of neuroendocrine tumours and recommend the use of amino acid infusions as renal protection.

Radiation nephropathy does not yet appear to have been observed in the context of PSMA-targeted radioligand therapy for mCRPC.

Taking all the information into consideration, the PRAC considers that the product information should be updated in order to reflect the available evidence and current guidance.

Xerostomia

An association between xerostomia and Lu177 is biologically plausible in the context of Lu177-PSMA radioligand therapy for mCRPC because the salivary glands express PSMA and are radiosensitive organs. A number of dosimetry analyses have observed the salivary glands to be among the organs to receive the highest dose during radioligand therapy for mCRPC. Moreover, an effect on the salivary glands has been observed during radioligand therapy for mCRPC with radioisotopes other than Lu177. According to the summary tabulation, the MAH has not yet received any reports of xerostomia. However, it is considered that as it tends to be mild and transient, under-reporting is likely.

Based on the biologic plausibility and available evidence the PRAC recommends that the Product Information be updated with a reflection of the current evidence.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisations

On the basis of the scientific conclusions for lutetium isotope of mass 177 the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing lutetium isotope of mass 177 is unchanged subject to the proposed changes to the product information.

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