LUTATHERA (\(^{177}\)Lutetium oxodotreotide), radiopharmaceutical

**Important clinical benefit in well-differentiated (G1 and G2), progressive, unresectable or metastatic intestinal neuroendocrine tumours, expressing somatostatin receptors in adults, and moderate clinical improvement compared to octreotide CR 60 mg administered alone.**

**Insufficient level of evidence to justify its reimbursement in well-differentiated (G1 and G2), progressive, unresectable or metastatic non-intestinal neuroendocrine tumours, expressing somatostatin receptors.**

**Main points**

- **LUTATHERA 370 MBq/mL** has a Marketing Authorization (MA) in the treatment of well-differentiated (G1 and G2), progressive, unresectable or metastatic gastroenteropancreatic neuroendocrine tumours (GEP-NET), expressing somatostatin receptors in adults.

- In intestinal NETs, the superiority of the progression-free survival of LUTATHERA, in combination with octreotide CR 30 mg has been demonstrated compared to octreotide CR 60 mg alone. The progression-free survival median was not reached in the LUTATHERA and octreotide CR 30 mg combination group and was 8.5 months in the comparator group. A conservative intermediate analysis from an ongoing study did not demonstrate a difference in overall survival between the 2 treatment groups.

- In non-intestinal NETs, more data is needed to support the reimbursement of LUTATHERA.

**Therapeutic strategy**

Treatments for NETs are discussed in regional staff meetings, as part of the nationwide NET network, RENATEN, certified by the INCa. Disease management depends on the origin and characteristics of the tumour.

- **Role of the medicinal product in the therapeutic strategy**
  - **Well-differentiated (G1 and G2), progressive, unresectable or metastatic intestinal NETs, expressing somatostatin receptors in adults:**
    In light of data from the NETTER-1 study, Peptide Receptor Radionuclide Therapy (PRRT) with LUTATHERA is a 2nd line treatment, after progression of the disease with octreotide in well-differentiated (G1, G2), progressive, metastatic intestinal NETs, expressing somatostatin receptors. LUTATHERA can be used in monotherapy or in combination. Despite the uncertainties on the long-term safety of LUTATHERA treatment, especially its myelotoxicity, the everolimus profile seems more unfavourable. Where tumours are defined as exhibiting homogeneous somatostatin receptor expression, LUTATHERA could be preferred to everolimus. Given the lack of comparative data, the role of LUTATHERA compared to everolimus is not known.
  - **Well-differentiated (G1 and G2), progressive, unresectable or metastatic non-intestinal NETs, expressing somatostatin receptors in adults:**
    Given the absence of data versus the clinically-relevant comparators whereas the comparison was possible, LUTATHERA has no role in the therapeutic strategy.
Clinical data

- The evaluation of $^{177}$Lutetium oxodotreotide is mainly based on a phase III, randomised, open-label study versus octreotide CR 60 mg (NETTER-1 study) in 229 patients with well-differentiated (G1 and G2), progressive, unresectable or metastatic, midgut NET expressing somatostatin receptors. The superiority of $^{177}$Lutetium oxodotreotide combined with octreotide CR 30 mg compared to octreotide CR 60 mg was demonstrated in terms of progression-free survival: median not reached in the $^{177}$Lutetium oxodotreotide group, for median follow-up of 10.5 versus 8.5 months in the comparator group, for median follow-up of 6.7 months (HR= 0.177 (CI 95% = [0.108; 0.289], p<0.0001). No difference on overall survival has been demonstrated to date.

- The data available in this study only relates to patients with midgut NET whereas the MA covers all gastroenteropancreatic NETs. This study cannot guarantee the transferability of the results observed in midgut NET to other GEP-NETs. The results of another, non-comparative study, provide descriptive and exploratory data on the efficacy of $^{177}$Lutetium oxodotreotide in NETs other than midgut NET, especially of the pancreas.

Among the adverse effects occurring in more than 5% of the patients from the $^{177}$Lutetium oxodotreotide group, gastrointestinal disorders (nausea, vomiting, diarrhoea, abdominal disorders), fatigue, blood disorders (thrombocytopenia, lymphocytopenia, anaemia, neutropenia), loss of appetite, alopecia, disturbed taste and vertigo were reported. In the comparator group, 5% of the patients did not experience any of these effects. It should be noted that several adverse events were attributed to administration of the amino acid solution combined with LUTATHERA, especially nausea and vomiting.

Special prescription requirements

- Medicinal product for hospital use only, requiring special monitoring during treatment.
- Radiopharmaceutical medicinal product.
- Need for a companion test: imaging positive for somatostatin receptors.
- LUTATHERA must be administered concomitantly with a hyperosmolar solution of amino acids which has the status of a hospital preparation.

Benefit of the medicinal product

- The actual clinical benefit* of LUTATHERA is:
  - Important in well-differentiated (G1 and G2), progressive, unresectable or metastatic intestinal NETs, expressing somatostatin receptors in adults
  - Insufficient in well-differentiated (G1 and G2), progressive, unresectable or metastatic non-intestinal NETs, expressing somatostatin receptors in adults
- LUTATHERA provides clinical added value** (CAV III, moderate) compared to octreotide CR 60 mg administered alone in the treatment of well-differentiated (G1 and G2), progressive, unresectable or metastatic intestinal NETs, expressing somatostatin receptors in adults
- Approval for hospital treatment.

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"