Washington State Health Care Authority

Oncology: Radiopharmaceuticals - lutetium Lu 177 dotatate (Lutathera)

Medical policy no. 21.60.00.45-1 Effective: December 1, 2020

Note: *New-to-market drugs included in this class based on the Apple Health Preferred Drug List are non-preferred and subject to this prior authorization (PA) criteria. Non-preferred agents in this class require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed. If a drug within this policy receives a new indication approved by the Food and Drug Administration (FDA), medical necessity for the new indication will be determined on a case-by-case basis following FDA labeling.*

Background:

Lutetium Lu 177 dotatate (Lutathera) is approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Lutetium Lu 177 dotatate is a radiolabeled somatostatin analog that selectively binds to somatostatin receptors on neuroendocrine tumors (NETs) and is internalized. Beta emission from lutetium Lu 177 dotatate damages somatostatin receptor-positive cells via free radical formation to treat the malignancy.

Medical necessity

Drug	Medical Necessity
Lutetium Lu 177 dotatate **(Lutathera®)**	Lutetium Lu 177 dotatate may be considered medically necessary when used for the treatment of: • **Somatostatin receptor–positive** gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

Clinical policy:

Drug	Clinical Criteria (Initial Approval)
Lutetium Lu 177 dotatate **(Lutathera®)**	Lutetium Lu 177 dotatate may be considered medically necessary when **ALL** of the following are met: 1. Client has a diagnosis of somatostatin receptor-positive GEP-NETs, confirmed by somatostatin-based imaging demonstrating somatostatin receptor expression, in the foregut, midgut, or hindgut; **AND** 2. Documentation that the tumor is well-differentiated as determined by pathology reports with a Ki-67 proliferation index of ≤20%; **AND** 3. The GEP-NET is inoperable, locally advanced, or metastatic; **AND** 4. Evidence of disease progression is verified by CT or MRI during treatment with a long-acting somatostatin analogue (octreotide or lanreotide); **AND** 5. Client is 18 years of age or older; **AND** 6. The client meets all of the following laboratory criteria; **AND** a. Creatinine clearance ≥40 ml/min; b. Total bilirubin <3x upper limit normal;

	c. Hemoglobin ≥ 8g/dL; d. White blood cell count ≥2000/mm^3; e. Platelet count ≥ 75,000/mm^3; 7. The client is not pregnant **OR** breastfeeding; **AND** 8. Long-acting and short-acting somatostatin analogues have been discontinued for at least 4 weeks and 24 hours, respectively, prior to initiating lutetium Lu 177 dotatate; **AND** 9. There is no prior treatment with peptide receptor radioligand therapy for GEP-NETs; **AND** 10. Prescribed by an oncologist or specialist in the treatment of GEP-NETs If all of the above criteria are met, the request will be **approved for 9 months** (maximum of 4 total doses)
	Criteria (Reauthorization) Lutetium Lu 177 dotatate may be reauthorized when **ALL** of the following are met: 1. **ALL** (1 through 10) of the initial authorization criteria is met; **AND** 2. Less than 4 total doses have been administered in the client's lifetime. If all of the above criteria are met, the request may be **reauthorized for an additional 9 months** (to allow for a total maximum of 4 doses)

Dosage and quantity limits

Drug Name	Dose and Quantity Limits
Lutetium Lu 177 dotatate **(Lutathera®)**	1. Maximum of 7.4GBq (200mCi) per 8 weeks a. Infused over 30 minutes b. Recommended intravenous amino acid solution should be administered 30 minutes prior to Lutathera, and continue for 3 hours after. i. Premedicate with antiemetic medication(s) 30 minutes prior to amino acid solution administration. c. Continuation of long-acting octreotide 30 mg intramuscularly 4 to 24 hours after each dose of Lutathera is recommended. d. Refer to Lutathera package insert for required dose reductions based on adverse reactions. i. Amino acid solution dose should remain the same regardless of Lutathera dose. 2. Maximum of 4 total doses will be approved

Coding:

HCPCS Code	Description
A9513	Lutetium Lu 177, dotatate, therapeutic, 1 millicurie

Definitions

Term	Description
Somatostatin receptor-positive	• Requires sufficient tumor uptake on diagnostic somatostatin receptor scintigraphy or 68Ga-dotatate imaging
Well-differentiated	• Well-differentiated as determined by pathology reports.

	• Includes low-grade (G1) and intermediate-grade (G2) tumors. • Low-grade well-differentiated tumors have a Ki-67 index of <3% • Intermediate-grade well differentiated tumors have a Ki-67 index between 3 and 20%

Evidence Review:

Disease background: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

Neuroendocrine tumors (NETs) may originate in any organ, though primarily develop in the pancreas or gastrointestinal tract (GEP-NETs).[1] While still relatively rare, GEP-NETs are the second most prevalent form of gastrointestinal-tract cancer, with an incidence between 3.5 and 7 cases per 100,000 people per year.[2] GEP-NETs may precipitate carcinoid syndrome, most commonly associated with flushing, diarrhea, and valvular heart disease.[1] The 5 year survival rate for low, intermediate, and high grade NETs is approximately 79%, 74%, and 40%, respectively.[1] Treatment with medication may be required in symptomatic or progressive tumors that are unresectable (inoperable). First line treatment includes long-acting somatostatin analog therapy.[3] Systemic treatment with everolimus or radiolabeled somatostatin analogs (i.e. lutetium Lu 177 dotatate) may be recommended when tumor progression occurs with use of long-acting somatostatin analogs.[3]

Lutetium Lu 177 dotatate

Lutetium Lu 177 dotatate was approved in 2018 by the FDA for the treatment of somatostatin receptor-positive GEP-NETs).[4] This medication is a radiolabeled somatostatin analog that selectively binds to somatostatin receptors on NETs and is internalized. Beta emission from lutetium Lu 177 dotatate damages somatostatin receptor-positive cells via free radical formation.[4]

FDA approval was largely based on the NETTER-1 trial, a phase 3 randomized study of 229 patients with somatostatin receptor-positive GEP-NETs conducted at 41 centers in 8 countries. The primary site of tumor was in the ileum (73%) with metastases most common in the liver (83%) and lymph nodes (62%).[5] Progression-free survival was defined as the time from randomization to documented disease progression by imaging, or death. CT or MRI was conducted at least every 12 weeks. The treatment group demonstrated at 79% risk reduction in disease progression or death compared to standard of care (HR 0.21, $p<0.0001$). At month 20, 65.2% and 10.8% of participants in the treatment and standard of care groups, respectively, were progression free, accounting for a number needed to treat of 2. Median time to progression-free survival in the standard of care group was 8.4 months and had not yet been determined in the treatment group.

Eighty-six (86%) of patients in the treatment group experienced a treatment-related adverse event compared to 34% in the standard of care group. The most common adverse reactions included nausea/vomiting in the treatment group, and fatigue, asthenia, abdominal pain, and diarrhea among both groups. While 95% of patients in the treatment group experienced an adverse effect, 97% of them were grade 1 or 2, defined by the National Cancer Institute Common Terminology Criteria for Adverse Events. Although rates of grade 3 and 4 adverse events were mostly comparable among both groups, the treatment group experienced significantly more neutropenia, thrombocytopenia, and lymphopenia. Eight patients required adverse event-related dose reduction for lutetium Lu 177 dotatate.

References

1. Cives M, Strosberg J. An update on gastroenteropancreatic neuroendocrine tumors. Oncology (Williston Park, NY). 2014;28(9):749-56, 758.
2. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017; 3(10):1335-1342.
3. Chan, JA. Kulke, M. Metastatic well-differentiated gastrointestinal neuroendocrine (carcinoid) tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion. In: UpToDate, Goldberg, RM (Ed). UpToDate, Waltham, MA, 2018.
4. Lutathera (lutetium Lu 177 dotatate) injection package insert. NJ: Advanced Accelerator Applications USA, Inc.; 2018 Jan.

5. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of (177) Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125-135.[PubMed 28076709]
6. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Neuroendocrine and Adrenal Tumors, version 1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
7. Hicks RJ, Kwekkeboom DJ, Krenning E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. Neuroendocrinology. 2017;105(3):295-30

History

Date	Action and Summary of Changes
06/17/2020	Approved by DUR Board
4/08/2020	New Policy final
3/19/2020	Criteria requiring Karnofsky Performance Status Scale to be greater than 60 was removed
3/9/2020	Alternative therapies section removed
2/14/2020	New policy draft created