Lutathera (Lutetium Lu 177 Dotatate)*

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DESCRIPTION

Note: For off-label use see Medical Policy 05.01.09 Off-Label Drug Use

In January 2018, the U.S. Food and Drug Administration (FDA) approved Lutathera® (Lutetium Lu 177 dotatate), a radiolabeled somatostatin analog (SSA) indicated for the treatment of adults with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut (gastroduodenal), midgut (distal small intestine and proximal colon), and hindgut (distal colorectal and pancreas) neuroendocrine tumors.

Neuroendocrine cells are widely distributed throughout the body, and tumors arising from these cells can occur in most organs. GEP-NETs in the digestive system, including the tubular gastrointestinal tract and the pancreas (gastroenteropancreatic), are generally divided into two major categories, well-differentiated neuroendocrine tumors (NETs) and poorly differentiated (high-grade) neuroendocrine carcinomas. These two major categories of neuroendocrine tumors behave differently in terms of biologic aggressiveness and in approach to treatment.

Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which have been referred to as carcinoid tumors or pancreatic islet cell tumors, are generally indolent, but all are potentially malignant, and the clinical course may be highly variable. Symptomatic disease may be due to either tumor bulk, including pain and/or bowel obstruction, or due to secretion of serotonin and other vasoactive substances, sometimes referred to as carcinoid syndrome.

The general treatment approach to well-differentiated GEP-NETs involves resecting potentially resectable disease, including a metastasectomy (surgical removal of metastases). Unresectable, asymptomatic disease may involve observation, especially if tumor burden is limited, or initial therapy with a somatostatin analog if tumor burden is high. Unresectable, symptomatic disease usually involves initial therapy with a somatostatin analog (e.g., octreotide or lanreotide), and dose escalation as needed, for control of symptoms of carcinoid syndrome and control of tumor growth. Individuals with radiologic or symptom progression despite somatostatin analog therapy may benefit from non-curative debulking therapy or nonsurgical liver-directed therapy. Individuals with more widespread disease that is not eligible for liver-directed therapy may benefit from systemic treatment with molecularly targeted agents, such as everolimus.

Lutathera® is a targeted form of systemic radiotherapy (radioactive drug), peptide receptor radionuclide therapy (PRRT) that binds to cell surface somatostatin receptors which may be present in certain tumors, and after binding to the receptor, the drug enters the cell allowing radiation to cause damage to the tumor cells. Most GEP-NETs express high-affinity receptors for somatostatin, and somatostatin-based imaging can provide information on tumor burden and location. Lutathera® has been proposed as a treatment option in adult individuals with GEP-NETs who progress despite first-line therapy.

Lutathera® is given by an intravenous (IV) infusion every eight weeks, for a total of four doses. It is a radiopharmaceutical and must be handled with appropriate safety measures to minimize radiation exposure.

Based on the product information label (2018) for Lutathera® (Lutetium Lu 177 dotatate), the common side effects include low levels of white blood cells (lymphopenia), high levels of enzymes in certain organs (increased GGT, AST and/or ALT), vomiting, nausea, high levels of blood sugar (hyperglycemia) and low levels of potassium in the blood (hypokalemia). Serious side effects include low levels of blood cells (myelosuppression), development of certain blood or bone marrow cancers (secondary myelodysplastic syndrome and leukemia), kidney damage (renal toxicity), liver damage (hepatotoxicity), abnormal levels of hormones in the body (neuroendocrine hormonal crises) and infertility. Lutathera® (Lutetium Lu 177 dotatate) can cause harm to a developing fetus; women should be advised of the potential risk to the fetus and to use effective contraception. Patients taking Lutathera® (Lutetium Lu 177 dotatate) are exposed to radiation. Exposure of other patients, medical personnel, and household members should be limited in accordance with radiation safety practices.

Clinical Context and Therapy Purpose
The purpose of lutetium 177 (Lu 177) dotatate in individuals with locally advanced or metastatic somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut who have progressed on first-line somatostatin analogues is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The purpose of Lu 177 dotatate in individuals with a bronchopulmonary or thymus somatostatin receptor-positive neuroendocrine tumor who have progressed on first-line somatostatin analogues is to provide a treatment option that is an alternative to or an improvement on existing therapies.

In individuals with unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant populations of interest are individuals with inoperable locally advanced or metastatic somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs) including foregut, midgut and hindgut who have progressed on first-line somatostatin analogues.

The relevant populations of interest are individuals with locally advanced or metastatic somatostatin receptor-positive bronchopulmonary or thymus neuroendocrine tumor who have progressed on first-line somatostatin analogues.

The relevant populations of interest are individuals with unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma.

Interventions
The therapy being considered is lutetium 177 (Lu 177) dotatate.

Comparators
For locally advanced or metastatic receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut the practices (listed alphabetically with no preference) are currently being used to make decisions about second-line treatment options for patients who have progressed on first-line somatostatin analogues: cytotoxic chemotherapy (e.g., 5-fluorouracil, capecitabine, dacarbazine, oxaliplatin, streptozocin, temozolomide), everolimus, hepatic-directed therapy (e.g., arterial embolization, hepatic chemoembolization, hepatic radioembolization, cytoreductive surgery/ablative therapies) for hepatic predominant disease, interferon alfa-2b and radiotherapy.

For locally advanced or metastatic somatostatin receptor-positive bronchopulmonary or thymus neuroendocrine tumor the following practices (listed alphabetically with no preference) are currently being used to make decisions about second-line treatment options for individuals who have progressed on first-line somatostatin analogues: everolimus, cisplatin plus etoposide, carboplatin plus etoposide, temozolomide, and radiotherapy.

For unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma, the relevant comparator is the current standard of care that differs based on tumor and patient characteristics. These options include external beam radiation therapy, ablation therapy, transarterial chemoembolization, radionuclide therapy with I 131-metaiodobenzylguanidine, chemotherapeutic agents including cyclophosphamide, dacarbazine, vincristine, doxorubicin, temozolomide, and thalidomide, and sunitinib.

Outcomes

The general outcomes of interest are overall survival (OS), median progression-free survival (PFS), and adverse events. In general, acute short-term safety outcomes occurring as a consequence of radiation include monitoring for lymphopenia, vomiting, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, hyperglycemia, and hypokalemia; long-term chronic toxicities that require monitoring are amyelodysplastic syndrome, renal failure, and leukemia.

Review of Evidence

Early case series and retrospective studies report that treatment of advanced GEP-NETs with Lutathera® (Lutetium Lu 177 Dotatate) was associated with tumor response, improved survival outcomes (such as stable disease, tumor regression, or longer median time to progression), and quality of life (Delpassand and et. al. 2014; Ezziddin et. al. 2014; Sabet et. al. 2015).

The FDA approval for the efficacy of Lutathera® (Lutetium Lu 177 Dotatate) is based on the results of two published studies:

In January 2018, the U.S. Food and Drug Administration approved Lutathera® (Lutetium Lu 177 Dotatate) for the treatment of somatostatin receptor-positive GEP-NETs in adults, largely based on support from the NETTER-1 trial. This phase 3, open label, randomized, multicenter clinical trial included 229 patients with advanced, progressive, well-differentiated midgut neuroendocrine tumors. The 229 patients were randomly assigned to receive either 177-Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (Lu-Dotatate group) or octreotide LAR alone (113 patients) administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary end point was progression free survival. Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile. The final analysis of overall survival will be conducted in the future as specified in the protocol; a pre-specified interim analysis of overall survival was

conducted and is reported here. At the data-cutoff date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the 177-Lu-Dotatate group versus 3% in the control group (P<0.001). In the planned interim analysis of overall survival, 14 deaths occurred in the 177-Lu-Dotatate group and 26 in the control group (P = 0.004). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the 177-Lu-Dotatate group as compared with no patients in the control group, with no evidence of renal toxic effects during the observed time frame. The authors concluded treatment with Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Preliminary evidence of an overall survival benefit was seen in an interim analysis; confirmation will be required in the planned final analysis. Clinically significant myelosuppression occurred in less than 10% of patients in the 177Lu-Dotatate group. (Funded by Advanced Accelerator Applications; NETTER-1 ClinicalTrials.gov number, NCT01578239)

Long-term safety and survival were evaluated in an investigator-sponsored, open-label, single-arm, single-institution (Erasmus) retrospective study of over 1200 patients with somatostatin receptor positive neuroendocrine tumors who received 177-Lu-Dotatate treatment. Primary tumor sites included bronchus, foregut, midgut, hindgut, pancreas and unknown. Patient populations were heterogeneous for baseline tumor status (progressive versus non-progressive) and treatments received prior to 177-Lu-Dotatate. Of these patients, the safety analysis included 610 patients, 360 (60%) of which had metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs), treated with a cumulative dose of at least 100 mCi (3.7 GBq) 177-Lu-Dotatate. Median follow-up was 78 months. Long-term toxicity included acute leukemia in four patients (0.7%) and myelodysplastic syndrome in nine patients (1.5%). There was no therapy-related long-term renal or hepatic failure. Overall response rate, defined as complete or partial response, in patients with midgut and pancreatic NETs with progressive disease at baseline was 84% and 81%, respectively. Median overall survival for GEP-NETs was only reported for pancreas (71 months [95% CI 56-86]) and midgut (60 months), due to small numbers of other gastrointestinal primaries. A subset analysis of PFS in patients with midgut tumors and progressive disease at baseline was 24 months [95% CI 18-30].

Summary of Evidence

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are a rare group of cancers that affects the pancreas or different parts of the gastrointestinal tract, such as the stomach, intestines, colon and rectum. Approximately one of 27,000 people are diagnosed with GEP-NET each year. GEP-NETs have limited treatment options after initial therapy fails to keep the cancer from growing. Lutathera® (Lutetium Lu 177 Dotatate) is the first radioactive drug, or radiopharmaceutical, that has been approved for the treatment of GEP-NETs. More specifically Lutathera® is indicated for adult patients with somatostatin receptor-positive GEP-NETs, including foregut, midgut and hindgut

neuroendocrine tumors. Lutathera received an orphan drug designation and is also the first available FDA approved Peptide Receptor Radionuclide Therapy (PRRT), a form of treatment comprising of a targeting molecule that carries a radioactive component. The safety and effectiveness of Lutathera® (Lutetium Lu 177 Dotatate) for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults has been evaluated in a multi-center open label phase 3 trial the NETTER-1 trial and the Erasmus retrospective study. Based on the clinical data from these two trials the evidence is sufficient to determine that this technology results in meaningful improvement in net health outcomes for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut (gastroduodenal), midgut (distal small intestine and proximal colon), and hindgut (distal colorectal and pancreas) neuroendocrine tumors in adults.

Bronchopulmonary and Thymus Neuroendocrine Tumors
Neuroendocrine tumors are thought to arise from cells throughout the diffuse endocrine system. They comprise a broad family of tumors, the most common of which are the gastrointestinal (GI) tract, lung, and bronchi (so-called bronchopulmonary), thymus, and pancreas. Sites of origin within the GI tract include the stomach, small intestine, appendix, and rectum. Other less common neuroendocrine tumors include those arising in the parathyroid, thyroid, adrenal, and pituitary glands.

Approximately one-third of neuroendocrine (carcinoid) tumors arise in the lungs or thymus, and two-thirds arise in the GI tract. Bronchial and thymic neuroendocrine tumors have been associated with adrenocorticotropic hormone (ACTH) production and are a cause of Cushing's syndrome.

Neuroendocrine tumors are generally subclassified by site of origin, stage, and histologic characteristics.

The classification of lung and thymus neuroendocrine tumors varies from that of gastropancreatic neuroendocrine tumors in some classification systems, and does not include Ki-67 and includes the assessment of necrosis. Well differentiated neuroendocrine tumors of the lung and thymus are either considered typical or atypical using histologic criteria.

- Typical (low grade, < 2 mitoses/10 HPF, and no necrosis)
- Atypical (intermediate grade, 2-10 months/10 HPF and/or foci of necrosis)

Neuroendocrine tumors are classified histologically based on tumor differentiation and tumor grade (1-3):

- Well differentiated, low grade (Grade 1; G1)
- Well differentiated, intermediate grade (Grade 2; G2)
- Poorly differentiated, high grade (Grade 3; G3)

Pheochromocytomas/Paragangliomas
Pheochromocytomas are rare neuroendocrine tumors that originate from the chromaffin cells of the adrenal medulla in 80% to 90% of cases. Chromaffin cells produce catecholamine neurotransmitters, such as epinephrine, norepinephrine, and dopamine. Ectopic/extra-adrenal pheochromocytomas arise from sympathetic and para-aortic sympathetic ganglia are called paragangliomas. Pheochromocytomas and paragangliomas occur in 0.05% to 0.1% of hypertensive individuals, and their combined annual incidence in the United States is estimated to be between 500 and 600 cases. Approximately 10% to 15% of pheochromocytomas and paragangliomas are malignant, but it could be up to 40%. Pheochromocytomas release catecholamines (epinephrine and norepinephrine and their metabolites metanephrine and normetanephrine, resulting in hypertension, arrhythmia, and or hyperglycemia). About 40% of paragangliomas secrete catecholamines. Head and neck paragangliomas only secrete catecholamines about 5% of the time and often it is dopamine.

The peak incidence of occurrence for pheochromocytomas is between the third and fifth decades of life, but they generally occur at a younger age and are more likely to be bilateral in patients with familial disease. Paragangliomas are more likely to be malignant than pheochromocytomas in the adrenal medulla (about 40% versus 10%). Pheochromocytomas and paragangliomas associated with a familial syndrome tend to be more aggressive and are more likely to metastasize than sporadic tumors.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Neuroendocrine and Adrenal Tumors version 4.2021 and the NCCN Drugs and Biologics Compendium® (Accessed 2022) include category 2A recommendations for use of Lutathera® (Lutetium Lu 177 Dotatate), unless otherwise described, noted in the following NCCN recommended usage:

- **Neuroendocrine and Adrenal Tumors - Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2), Lung, and Thymus**: Consider as subsequent therapy for management of locoregional unresectable bronchopulmonary/thymic disease if somatostatin receptor positive imaging and progression on octreotide or lanreotide.
- **Neuroendocrine and Adrenal Tumors - Well-Differentiated Grade 3 Neuroendocrine Tumors**: Treatment for unresectable locally advanced/metastatic disease with favorable biology (e.g., relatively low Ki-67 [<55%], positive SSR-based PET imaging) that has clinically significant tumor burden or evidence of progression.
- **Neuroendocrine and Adrenal Tumors - Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2), Lung, and Thymus**: Consider for poorly controlled carcinoid syndrome if somatostatin receptor positive imaging and progression on octreotide/lanreotide in combination with
    - either octreotide LAR or lanreotide for persistent symptoms (ie. flushing, diarrhea)
    - telotristat for persistent diarrhea

- **Neuroendocrine and Adrenal Tumors - Pheochromocytoma/Paraganglioma**: Treatment if somatostatin receptor positive imaging for
    - locally unresectable disease
    - distant metastases in addition to octreotide or lanreotide
- **Neuroendocrine and Adrenal Tumors - Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2), Lung, and Thymus**: Preferred management of locoregional advanced disease of the gastrointestinal tract and/or distant metastases for
    - clinically significant tumor burden
    - somatostatin receptor positive imaging and progression on octreotide/lanreotide

  Recommendation rating: 1 for progressive mid-gut tumors. 2A for all others
- **Neuroendocrine and Adrenal Tumors - Neuroendocrine Tumors of the Pancreas (Well Differentiated Grade 1/2)**: Preferred for the management of symptomatic, clinically significant tumor burden, or progressive locoregional advanced disease and/or distant metastatic disease if somatostatin receptor positive imaging and progression on octreotide/lanreotide
    - As the primary treatment for pheochromocytoma/paraganglioma that is locally unresectable disease or distant metastases if somatostatin receptor positive imaging.
- **Neuroendocrine and Adrenal Tumors - Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2), Lung, and Thymus:** Management of distant metastatic bronchopulmonary/thymic disease if somatostatin receptor positive and progression on octreotide/lanreotide in patients with clinically significant tumor burden and low grade (typical carcinoid) histology, evidence of progression, intermediate grade (atypical carcinoid) histology, or symptomatic (useful in certain circumstances)
    - as primary therapy
    - consider as subsequent therapy if progression on first-line therapy

Summary of Evidence Bronchopulmonary and Thymus Neuroendocrine Tumors and Pheochromocytomas/Paragangliomas

Both category 2A recommendations are "based upon lower-level evidence, there is National Comprehensive Cancer Network (NCCN) consensus that the intervention is appropriate" and outcomes reported from a subset of participants with primary bronchial NETs in the ERASMUS study and a retrospective case series of individuals with functional metastatic paraganglioma and pheochromocytoma treated with lutetium Lu 177 dotatate (Brabander et. al. 2017; Kong et. al. 2017). Also, based on medical policy 05.01.09 Off-Label Drug Use the above indications meet the criteria of this medical policy for off- label use. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Practice Guideline and Position Statements

National Comprehensive Cancer Network (NCCN)

- **National Comprehensive Cancer Network (NCCN): Drugs and Biologics Compendium Neuroendocrine and Adrenal Tumors**
    - **Neuroendocrine Tumors of the Gastrointestinal Tract, Lung and Thymus (Carcinoid Tumors)**
        - Recommended: Bronchopulmonary/thymus locoregional unresectable low grade (typical) consider peptide receptor radionuclide therapy (PRRT) with Lutathera (177Lu-dotatate) (if somatostatin receptor positive and progression on octreotide/lanreotide)
        - Recommended: Management of distant metastatic bronchopulmonary/thymic disease if somatostatin receptor positive imaging and progression on octreotide/lanreotide in patients with clinically significant tumor burden and low grade (typical) histology, evidence of progression, or intermediate grade (atypical) histology
            - As primary therapy
            - Consider as subsequent therapy if progression on first-line therapy
              Category of evidence: 2A
    - **Pheochromocytoma/Paraganglioma**
        - Recommended: Treatment for locally unresectable disease or distant metastases if somatostatin receptor positive imaging.
          Category of evidence: 2A

  (*Accessed 04/2022*)

- **National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors Version 4.2021**
    - **Principles of Peptide Receptor Radionuclide Therapy (PRRT) with 177Lu-Dotatate**
        - Lutetium Lu 177 Dotatate (177Lu-Dotatate) is a radiolabeled somatosatatin analog (SSA) used as PRRT (peptide receptor radionuclide therapy).
        - It is approved by the FDA for the treatment of somatostatin receptor positive gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) including foregut, midgut, and hindgut NET in adults.
        - Currently the are no randomized data, but there are reports of treatment efficacy and favorable outcomes when PRRT is used for PanNETS, pheochromocytomas, paragangliomas, and bronchopulmonary/thymic NETs. If feasible, participation in clinical trials of PRRT is strongly recommended for patients with such a rare groups of NET.
    - **Key eligibility**
        - Well-differentiated NET
        - Somatostatin receptor expression (SSR) of NET as detected by somatostatin receptor (SSR) PET/CT or SSR PET/MR
        - Adequate bone marrow, renal and hepatic function
    - **Footnotes**

- PET/CT or PET/MRI of skull base to mid-thigh with IV contrast when possible. Data are limited to the optimal timing of scans following administration of SSAs
- SSR PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC

- **Preparing Eligible Patients for 177 Lu-Dotatate**

- Do not administer long-acting somatostatin analogs (SSAs) (such as lanreotide, octreotide) for 4-6 weeks prior to each 177Lu-dotatate treatment. Administer short-acting octreotide as needed for symptom control of carcinoid syndrome; discontinue at least 24 hours prior to initiating 177Lu-dotatate.
- Counsel patients about the risks of:
  - Radiation exposure to themselves and others
  - Myelosuppression
  - Secondary myelodysplastic syndrome (NDS) and leukemia
  - Renal toxicity
  - Hepatic toxicity
  - Embryo-fetal toxicity
  - Infertility
  - Neuroendocrine hormonal crisis or carcinoid crisis: flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms
  - Nausea/vomiting (related to amino acid infusion required as part of therapy)
  - Discuss radiation safety precautions during and after 177Lu-dotatate.
  - Verify pregnancy status in females of reproductive potential.
  - Advise on use of effective contraception for up to 7 months (females) and 4 months (males) after last dose of 177Lu-dotatate.
- **Dose and Administration**
  - 177Lu-dotatate is administered intravenously (IV) via peripheral IV at dose of 200 mCi over 30-40 minutes every 8 weeks for a total of 4 treatments
  - Amino acid solution
- IV infusion of amino acids is a critical part of 177Lu-dotatate therapy for nephroprotection.
- Amino acids are administered 30 minutes before, concurrently with, and 3 hours after 177Lu-dotatate.
- Commercial amino acid formulation infused at high rates are more emetogenic than compound amino acids.
- Solutions containing only arginine/lysine are only available through compounding pharmacies but are much less emetogenic than commercial amino acid solutions. Options for amino acids are as follows:
  - Arginine 2.5% lysine2.5% in 1000 mL NaCl infused at 250 mL/hour for 4 hours.
  - Commercial amino acid formulation (typically containing approximately 20 amino acids) mixed in sterile water for total volume of approximately 2000 mL. Infusion rate can be increased to roughly 300-500 mL/hr, as tolerated. Recommend starting at low rate of 50 mL/hr and increasing by 10 mL/hr every 10 minutes as tolerated based on symptoms such as nausea. 177Lu-

dotatate infusion should begin after at least 250 mL of amino acids have been infused.
    - Aggressive anti-emetic prophylaxis is recommended with a 5HT3 receptor antagonist with or without NK1 receptor blocker.
- **Post Treatment Instructions**
    - Detailed instructions on post treatment radiation risk reduction strategies should be provided per institutional radiation safety guidelines.
    - Complete blood count (CBC), serum chemistry including renal and hepatic functions should be monitored.
    - Somatostatin analogs (SSAs) (octreotide or lanreotide) can be administered 4-24 hours after each 177Lu-dotatate treatment.
- **Timing of Somatostatin Analogs (SSAs) (Octreotide or Lanreotide) in relation to 177 Lu-Dotatate**
    - Most patients treated with PRRT will have progressed on a first line SSA.
    - Generally, patients with hormonally functional tumors should continue octreotide or lanreotide along with 177Lu-dotatate. It is unclear whether patients with nonfunctional tumors benefit from continuation of SSA treatment during and after 177Lu-dotatae treatment.
    - There are theoretical concerns regarding the competition between SSAs and 177Lu-dotatate for somatostatin receptor binding. Therefore, the following is recommended:
- Do not administer long-acting SSAs for 4-6 weeks prior to each 177Lu-dotatate treatment.
- Stop short-acting SSAs 24 hours before each 177Lu-dotatate treatment.
- SSAs (short and long-acting) can be resumed 4-24 hours after each 177Lu-dotatate treatment.

(*Accessed April 2022*)

Regulatory Status

Lutathera® (Lutetium Lu 177 Dotatate) was FDA approved January 2018 for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

- Dosage and Administration: Administer 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses.

The safety and effectiveness of Lutathera® (Lutetium Lu 177 Dotatate) has not been established in the pediatric population.

PRIOR APPROVAL

Prior approval is required.

POLICY

See Related Medical Policy

- 05.01.09 Off-Label Drug Use

Bronchopulmonary or Thymus Neuroendocrine Tumors (NETs)

Scenario 1: Lutathera® (Lutetium Lu 177 Dotatate) is considered **medically necessary** for the treatment of bronchopulmonary or thymus neuroendocrine tumors (NETs) when the individual meets **all of the following** criteria:

- 18 years of age or older; **and**
- Diagnosed with locally unresectable disease classified as **all of the following:**
  - Low grade (typical) < 2 mitoses/10 HPF; **and**
  - No necrosis; **and**
- Documented target lesions over-expressing somatostatin receptors confirmed by an appropriate somatostatin receptor-based imaging study including **one of the following**:
  - Positron Emission Tomography (PET)/Computed Tomography (CT); **or**
  - Positron Emission Tomography (PET)/Magnetic Resonance Imaging (MRI) of skull base to mid-thigh
    - with IV contrast, when possible; **or**

  Note: Somatostatin receptor PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC;

And all of the following:

- Disease progression on octreotide or lanreotide; **and**
- Lutathera® (Lutetium Lu 177 Dotatate) will be used as subsequent therapy with progression on first line therapy (octreotide or lanreotide); **and**

And the following:

- Documented adequate bone marrow, renal and hepatic function. Any one of following would be considered contraindications:
  - Hgb $\leq$ 8.0 g/dl
  - Platelets < 75,000 mm^3
  - Serum creatinine 40% increase in baseline serum creatinine or creatinine clearance less than 40 mL/minute or 40% decrease in baseline creatinine clearance
  - Total bilirubin > 3 x upper limit of normal
  - WBC < 2000/mm^3

Note: *See Policy Guidelines below for more information*

Scenario 2: Lutathera® (Lutetium Lu 177 Dotatate) is considered **medically necessary** for the treatment of bronchopulmonary or thymus neuroendocrine tumors (NETs) when the individual meets **all of the following** criteria:

- 18 years of age or older; **and**
- Diagnosed with distant metastases; **and**
  one of the following:

- Clinically significant tumor burden and low grade (typical) < 2 mitoses/10 HPF and no necrosis; **or**
- Evidence of progression; **or**
- Intermediate grade (atypical) 2-10 mitosis/10 HPF and/or foci of necrosis; **and**

All of the following:

- Lutathera® (Lutetium Lu 177 Dotatate) will be given as primary therapy; **and**
- Documented target lesions over-expressing somatostatin receptors confirmed by an appropriate somatostatin receptor-based imaging study including **one of the following**:
  - Positron Emission Tomography (PET)/Computed Tomography (CT); **or**
  - Positron Emission Tomography (PET)/Magnetic Resonance Imaging (MRI) of skull base to mid-thigh
    - with IV contrast, when possible; **or**

  Note: Somatostatin receptor PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC;

And all of the following:

- Documented adequate bone marrow, renal and hepatic function. Any one of following would be considered contraindications:
  - Hgb $\leq$ 8.0 g/dl
  - Platelets < 75,000 mm^3
  - Serum creatinine 40% increase in baseline serum creatinine or creatinine clearance less than 40 mL/minute or 40% decrease in baseline creatinine clearance
  - Total bilirubin > 3 x upper limit of normal
  - WBC < 2000/mm^3

  Note: *See Policy Guidelines below for more information*

Metastatic Pheochromocytoma or Paraganglioma

Lutathera® (Lutetium Lu 177 Dotatate) is considered **medically necessary** *as primary treatment* for *locally unresectable or metastatic pheochromocytoma or paraganglioma* when the individual meets **all of the following** criteria:

- 18 years of age or older; **and**
- Documented target lesions over-expressing somatostatin receptors confirmed by an appropriate somatostatin receptor-based imaging study including **one of the following**:
  - Positron Emission Tomography (PET)/Computed Tomography (CT); **or**
  - Positron Emission Tomography (PET)/Magnetic Resonance Imaging (MRI) of skull base to mid-thigh
    - with IV contrast, when possible; **or**

  Note: Somatostatin receptor PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC;

And all of the following:

- No prior treatment with radiolabeled somatostatin analog (i.e., octreotide or lanreotide); **and**

- Adequate bone marrow, renal and hepatic function

Note: *See Policy Guidelines below for more information*

Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumor(s) (GEP-NETs): Medically Necessary

Lutathera® (Lutetium Lu 177 Dotatate) is considered **medically necessary** for the treatment of *somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut (gastroduodenal), midgut (distal small intestine and proximal colon), and hindgut (distal colorectal and pancreas) neuroendocrine tumors* when **all of the following** criteria are met:

- 18 years of age or older; **and**
- Diagnosed with unresectable, locally advanced, or metastatic disease; **and**
- Disease progression despite somatostatin analog therapy (e.g., octreotide or lanreotide) or molecularly targeted therapy (e.g., everolimus); **and**
- Documented target lesions over-expressing somatostatin receptors confirmed by an appropriate somatostatin receptor-based imaging study including **one of the following**:
    - Positron Emission Tomography (PET)/Computed Tomography (CT); **or**
    - Positron Emission Tomography (PET)/Magnetic Resonance Imaging (MRI) of skull base to mid-thigh
        - with IV contrast, when possible; **or**

  Note: Somatostatin receptor PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC;

And all of the following:

- The pathology report documented the tumor is well differentiated with a Ki-67 index of 20% or less (*Note*: *see Policy Guidelines below*); **and**
- Adequate bone marrow, renal and hepatic function (**See contraindications in investigational statement below*)

  Note: *See Policy Guidelines below*

All Lutathera Requests: Investigational

Lutathera® (Lutetium Lu 177 Dotatate) is considered **investigational** including but not limited to any of the following:

- Beyond 4 doses
- Pediatric patients (17 years or less)
- When the above criteria have not been met
- For all other indications not indicated above

Based on the peer reviewed medical literature the safety and effectiveness for indications other than the medically necessary indication listed above has not been established. Also, the FDA approved label indication state the safety and efficacy beyond 4 doses of Lutathera® (Lutetium Lu 177 Dotatate) has not been studied and the safety and effectiveness of Lutathera has not been established in pediatric patients. Additional studies are needed to further investigate the safety and efficacy of Lutathera® (Lutetium

Lu 177 Dotatate) for patient populations for other than those indications listed above. The evidence is insufficient to demonstrate the effects on net health outcomes except for the indications listed above as medically necessary.

Policy Guidelines

Regimen The prescribing regimen must be in compliance with the FDA-approved dosing

- Dosing: 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses
- Every 8-week time frame may be subject to change depending on any adverse reactions (e.g., thrombocytopenia, anemia, renal toxicity, hepatotoxicity) causing delay in administration
- Total doses should **not** exceed 4 doses.

Ki-67 -Well-differentiated neuroendocrine tumors include low grade (G1) and intermediate-grade (G2) tumors, which correlate with a defined Ki-67 proliferation index, as determined by an immunohistochemical stain.

- Well-differentiated, low grade neuroendocrine tumors have a Ki-67 index of < 3%.
- Well-differentiated, intermediate grade neuroendocrine tumors have Ki-67 index of 3-20%.
- Well-differentiated neuroendocrine tumor varies from that of gastropancreatic neuroendocrine tumors in some classification systems, and in particular does not include Ki-67 and includes the assessment of necrosis.
- Well differentiated neuroendocrine tumors of the lungs and thymus are either considered typical (low grade, < 2 mitoses/10 HPF and no necrosis) or atypical (intermediate grade, 2-10 mitosis/10 HPF and/or foci of necrosis), using histologic criteria.

Neuroendocrine Tumor Grades: Neuroendocrine tumors are classified histologically based on tumor differentiation and tumor grades (1-3):

- Well differentiated, low grade (Grade 1; G1)
- Well differentiated, intermediate grade (Grade 2; G2)
- Poorly differentiated, high grade (Grade 3; G3)

Special Considerations

- Before initiating Lutathera® (Lutetium Lu 177 Dotatate), discontinue any long-acting somatostatin analogs for at least 4 weeks and short acting octreotide at least 24 hours prior to each Lutathera® dose.
- During Lutathera® treatment, administer long-acting octreotide 30 mg intramuscularly 4 to 24 hours after each Lutathera® dose and short-acting octreotide for symptomatic management.
- Following Lutathera® treatment, continue using long-acting octreotide 30 mg intramuscularly every 4-weeks after completing Lutathera® until disease progression or for up to 18-months following treatment initiation.
- Do not administer long-acting octreotide within 4 weeks of each subsequent Lutathera® dose and withhold short-acting octreotide for at least 24 hours before each Lutathera® dose.

- Pre-medicate with anti-emetics 30 minutes before recommended amino acid solution. Initiate recommended intravenous amino acid solution 30 minutes before Lutathera® infusion; continue during and for 3 hours after Lutathera® infusion.
- According to the manufacturer's safety information, Lutethera® must be handled with appropriate safety measures to minimize radiation exposure, and pregnancy status in females of reproductive potential should be verified prior to initiating Lutethera®.
- Other warnings and precautions for Lutathera® listed within the prescribing information include but may not be limited to:
    - Embryo-fetal toxicity
    - Hepatotoxicity
    - Infertility risk
    - Leukemia
    - Myelosuppression
    - Neuroendocrine hormonal crisis
    - Renal toxicity
    - Secondary myelodysplastic syndrome (MDS)
- Lutethera® should be discontinued permanently if the patient develops hepatotoxicity defined as bilirubinemia greater than 3 times the upper limit of normal (grade 3 or 4), or hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.
- Lutethera® dotatate should be discontinued permanently if patient develops renal toxicity defined as a creatinine clearance of less than 40 mL/min calculated using Cockcroft-Gault equation with actual body weight, or 40% increase in baseline serum creatinine, or 40% decrease in baseline creatinine clearance calculated using Cockcroft-Gault equation with actual body weight.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- A9513 Lutetium Lu 177, Dotatate, therapeutic 1 millicurie (Lutathera)

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POLICY HISTORY

Date	Reason	Action
May 2021	Annual Review	Policy Renewed
May 2021	Annual Review	Policy Revised
May 2020	Annual Review	Policy Renewed
May 2019	Annual Review	Policy Revised
May 2018		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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