# 06.01.38 Lutathera (Lutetium Lu 177 Dotatate)*

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## Summary

## Description

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

Radiopharmaceuticals are composed of a radioisotope bond to an organic molecule and are used for diagnostic and therapeutic purposes. The organic molecule conveys the radioisotope to specific organs, tissues, or cells. Lutetium 177 (Lu 177) dotatate, classified as peptide receptor radionuclide therapy is a radiolabeled-somatostatin analogue that binds to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors such as neuroendocrine tumors. It is then internalized and beta particle emission from Lu 177 induces cellular damage by formation of free radicals in somatostatin receptor-positive and neighboring cells.

## Summary of Evidence

For individuals with a treatment-refractory gastroenteropancreatic neuroendocrine tumor including foregut, midgut, and hindgut tumors who receive Lu 177 dotatate, the evidence includes 2 open-labeled RCTs, a multicenter registry, and a retrospective cohort study. Relevant outcomes are overall survival (OS), disease-specific survival, quality of life, and treatment-related mortality and morbidity. The randomized controlled trial results showed a consistent statistically significant and clinically meaningful effect on overall response rate, progression-free survival (PFS), and OS among individuals treated with Lu 177 dotatate compared to those treated with long-acting octreotide. The results of the retrospective cohort study were consistent with the treatment effect observed in the randomized controlled trial and provide additional support for a clinical benefit of Lu 177 dotatate in individuals with a gastroenteropancreatic neuroendocrine tumor. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with treatment-refractory bronchopulmonary or thymus neuroendocrine tumors who receive Lu 177 dotatate, the evidence includes a retrospective cohort study, a multicenter registry, and a bicenter, retrospective case series. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The retrospective cohort study included a small number of patients with bronchopulmonary (n=23) or thymus (n=2) neuroendocrine tumors. Among the 23 patients with bronchopulmonary neuroendocrine tumor, the median PFS was 20 months, the median time to progression was 25 months, and median OS was 52 months. Stratified results of individuals with thymus neuroendocrine tumors were not reported. The U.S. Food and Drug Administration in its review of the ERASMUS study for individuals with gastroenteropancreatic neuroendocrine tumor concluded that time to event analyses such as time to progression, PFS, and OS were not interpretable in the context of the single-arm ERASMUS study because of missing data at baseline, high dropout rates and open-label design of the study. The multicenter registry included 58 patients with bronchopulmonary tumors and reported 0 complete responses, 14 partial responses, a median PFS of 17.6 months, and a median OS of 44.8 months. The case series evaluated 48 patients with predominantly atypical carcinoid bronchopulmonary tumors, finding a median PFS survival and OS of 23 months and 59 months, respectively. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Although the evidence is insufficient, the National Comprehensive Cancer Network (NCCN) consensus (see Practice Guidelines and Position Statements below) gives a category 2A recommendation “based on a lower level of evidence” and medical policy, 05.01.09 Off-Label Drug Use, Lu 177 dotatate will be considered medically necessary in select individuals when the criteria have been met, see Policy below.

For individuals with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy and who receive Lu 177 dotatate the evidence includes systematic reviews and meta-analyses of single-arm studies a multicenter registry and 2 case series. Relevant outcomes include OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. One meta-analysis reported a pooled overall tumor response rate of 26% (95% confidence interval [CI], 18% to 35%). Another meta-analysis found improved PFS with Lu 177 dotatate compared to iobenguane I 131 among studies enriched with pheochromocytomas. One retrospective case series reported that 8/13 patients were able to reduce dosages of antihypertensive treatment at 3 months. Disease regression was reported in 5/14 patients with available computed tomography imaging. Out of 16 patients with available iobenguane scans, 10 patients had mild or negative uptake. However, patient outcomes were not stratified by iobenguane uptake status. No prospective studies directly comparing Lu 177 dotatate to iobenguane I 131 or assessing Lu 177 dotatate response in a fully non-iobenguane avid population were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Although the evidence is insufficient, the National Comprehensive Cancer Network (NCCN) consensus (see Practice Guidelines and Position Statements

below) gives a category 2A recommendation “based on a lower level of evidence” and medical policy, 05.01.09 Off-Label Drug Use, Lu 177 dotatate will be considered medically necessary in select individuals when the criteria have been met, see Policy below.

### Additional Information

Not applicable.

## OBJECTIVE

The objective of this evidence review is to determine whether the use of the radiopharmaceutical, Lutathera (Lutetium Lu 177 Dotatate), in adults with neuroendocrine tumors improves the net health outcome.

## PRIOR APPROVAL

Prior approval is required.

## POLICY

### Medically Necessary

Lutetium 177 (Lu 177) dotatate treatment is considered **medically necessary** in adult and pediatric individuals 12 years and older in **one of the following** (Choose one, 1-5):

1. **Distant metastases of bronchopulmonary or thymus neuroendocrine tumors**, with clinically significant tumor burden ***and***
    a. Low grade (typical) < 2 mitoses/10 HPF ***and***
    b. No necrosis; *OR* evidence of progression; *OR* Intermediate grade (atypical) 2-10 mitosis/10 HPF and/or foci of necrosis; ***and***
    c. Lutathera® (Lutetium Lu 177 Dotatate) will be given as primary therapy; **or**

2. **Gastroenteropancreatic neuroendocrine tumors (GEP-NETs),** including foregut (gastroduodenal), midgut (distal small intestine and proximal colon), and hindgut (distal colorectal and pancreas) neuroendocrine tumors that are unresectable, locally advanced, or metastatic disease, and either one of the following:
    a. Well differentiated disease (Ki-67 index of 20% or less) progression despite somatostatin analog therapy (e.g., octreotide or lanreotide) or molecularly targeted therapy (e.g., everolimus); **or**
    b. First-line therapy for well differentiated (Ki-67 index ≥10% and <20%) grade 2 disease, somatostatin receptor positive (SSRP) and clinically significant tumor burden ***or***

3. **Locally unresectable bronchopulmonary or thymus neuroendocrine tumors; *and***
    a. Low grade (typical) < 2 mitoses/10 HPF; ***and***
    b. No necrosis; ***and***
    c. Lutathera® (Lutetium Lu 177 Dotatate) will be used as subsequent therapy with progression on first line therapy (i.e., octreotide or lanreotide); ***or***

4. **Locally unresectable or metastatic pheochromocytoma or paraganglioma**; ***and***
    a. no prior treatment with radiolabeled somatostatin analog (i.e., octreotide or lanreotide); **or**

5. Poorly controlled **carcinoid syndrome** related to a neuroendocrine tumor; ***and***
    a. has symptom progression on octreotide LAR *OR* lanreotide, *OR* telotristat.

**And all of the following**:

- Documented target lesions over-expressing somatostatin receptors are confirmed by an appropriate somatostatin receptor-based imaging study (See policy guidelines); ***and***
- Adequate bone marrow, renal and hepatic function as determined by the treating physician.

### Investigational

Lutathera® (Lutetium Lu 177 Dotatate) is considered **investigational** including but not limited to any of the following because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes:

- Greater than a total of 4 doses as per the U.S. Food and Drug Administration (FDA)-approved regimen
- Individuals 11 years of age or less
- When the above criteria have not been met
- For all other indications not listed above

## POLICY GUIDELINES

### Regimen

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

- The recommended dose of lutetium 177 (Lu 177) is 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.

The table below describes the grading of severity used in the Common Toxicity Criteria for Adverse Events (version 4.03).

### Common Toxicity Criteria for Adverse Events

| Grade | Description |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living and refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. |
| 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living and refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. |
| 4 | Life-threatening consequences; urgent intervention indicated. |
| 5 | Death related to adverse event. |

## 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)

## Somatostatin Receptor-Based Imaging

Preferred somatostatin receptor (SSTR)-based imaging options to assess receptor status include SSTR-positron emission tomography (PET)/computed tomography (CT) or SSTR-PET/magnetic resonance imaging (MRI). Octreotide single-photon emission computed tomography (SPECT)/CT may be used only if SSTR-PET is not available, as it is much less sensitive for defining SSTR-positive disease. Appropriate SSTR-PET radiotracers include Gallium 68 (Ga 68) dotatate, Ga 68 dotatoc, or Copper 64 (Cu 64) dotatate. SSTR-positive status is confirmed when uptake in measurable lesions is greater than the liver.

## Special Considerations

- There are theoretical concerns regarding the competition between somatostatin analogues and Lu 177 dotatate for somatostatin receptor binding. Therefore, the following is recommended:
  - Do not administer long-acting somatostatin analogues for 4 to 6 weeks prior to each Lu 177 dotatate treatment.
  - Stop short-acting somatostatin analogues 24 hours before each Lu 177 dotatate treatment.
  - Both long-acting and short-acting somatostatin analogues can be resumed 4 to 24 hours after each Lu 177 dotatate treatment.
- Lu 177 dotatate is a radiopharmaceutical and should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.
- Lu 177 dotatate should be discontinued permanently if the individual 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%.
- Lu 177 dotatate should be discontinued permanently if individual 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.

## Coding

See the Codes table for details.

# BACKGROUND

## Neuroendocrine Tumors

Neuroendocrine tumors are a heterogeneous group of tumors that originate from the neuroendocrine cells in the diffuse neuroendocrine system anywhere in the body but more commonly in the gastrointestinal tract and the respiratory system. Approximately 61% of all neuroendocrine tumors originate from the gastrointestinal system or pancreas and are referred to as gastroenteropancreatic neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors may further be characterized as functional or nonfunctional based on whether they secrete hormones that result in clinical symptoms particularly serotonin, which results in "carcinoid syndrome" that is characterized by flushing and diarrhea. Lung neuroendocrine tumors may also be referred to as pulmonary neuroendocrine tumors, pulmonary carcinoids, or bronchopulmonary neuroendocrine tumors. Bronchopulmonary neuroendocrine tumors comprise approximately 20% of all lung cancers and are classified into 4 subgroups: typical carcinoid tumor, atypical carcinoid tumor, large-cell neuroendocrine carcinoma, and small-cell lung carcinoma. Less than 5% of bronchopulmonary neuroendocrine tumors exhibit hormonally related symptoms such as carcinoid syndrome. Neuroendocrine tumors of the thymus account for only 5% of all tumors in the thymus and mediastinum.

Neuroendocrine tumors are classified as orphan diseases by the U.S. Food and Drug Administration (FDA). Based on an analysis of Surveillance, Epidemiology, and End Results Program registry data from 1973 to 2012, the overall incidence of neuroendocrine tumors has been reported to be in the range of 6.98 per 100,000 people per year.

## Diagnosis

Neuroendocrine tumors are not easy to diagnose because of the rarity of the condition. Symptoms are often nonspecific or mimic other disorders such as irritable bowel syndrome (in the case of gastroenteropancreatic neuroendocrine tumors) or asthma (in the case of a lung neuroendocrine tumors) resulting in an average diagnosis delay of 5 to 7 years after symptom onset. In many cases, diagnosis is incidental to imaging for other unrelated causes. Most gastroenteropancreatic neuroendocrine tumors express somatostatin receptors that can be imaged using a radiolabeled form of the somatostatin analogue octreotide (e.g., $^{111}$In pentetreotide).

## Treatment Approach

There is a general lack of prospective data to guide the treatment of neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors are chemotherapy-responsive neoplasms, and platinum-based chemotherapy represents the backbone of treatment for both early and advanced-stage tumors. Surgery alone or followed by chemotherapy along with treatment of hormone-related symptoms may be the initial approach for localized disease. For asymptomatic individuals with slow progression, observation with routine surveillance imaging is an option. The prognosis for individuals with metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors is highly variable. The median overall survival (from diagnosis) for individuals with metastatic pancreatic neuroendocrine tumors has been reported to range from 2 to 5.8 years while the median overall survival for small bowel neuroendocrine tumors has been reported as 7.9 years.

## Pharmacologic Treatment

### First-Line Treatment Options

#### Somatostatin Analogues (Octreotide and Lanreotide)

Somatostatin is a peptide that binds to somatostatin receptors that are expressed in a majority of carcinoid tumors and inhibits the secretion of a broad range of hormones. Somatostatin analogues (e.g., octreotide, lanreotide) were initially developed to manage the hormonal symptoms related to neuroendocrine tumors; they were found to exert antiproliferative activity, and clinical studies have demonstrated prolonged progression-free survival (PFS) in individuals with neuroendocrine tumors treated with somatostatin analogues. However, the role of somatostatin analogues in individuals with nonfunctioning neuroendocrine tumors is unclear.

Commercially available long-acting release forms of octreotide and lanreotide (e.g., Sandostatin LAR, Somatuline Depot), which are administered intramuscularly on a monthly basis, have largely eliminated the need for daily self-injection of short-acting subcutaneous formulations.

## Second-Line Treatment Options

Currently, there are no data to support a specific sequence of therapies and only streptozocin, everolimus, and sunitinib are FDA approved for the treatment of pancreatic neuroendocrine tumors.

### Mechanistic Target of Rapamycin Inhibitors

The mechanistic target of rapamycin is an enzyme that regulates cell metabolism and proliferation in response to environmental stimuli. It is upregulated in a variety of malignancies in response to stimulation by growth factors and cytokines. Whole-exome genomic analysis has shown that approximately 15% of pancreatic neuroendocrine tumors are associated with somatic variants in genes associated with the mechanistic target of rapamycin pathway. Everolimus, an oral mechanistic target of rapamycin inhibitor, has been shown to significantly prolong PFS versus placebo in individuals with pancreatic neuroendocrine tumors (RADIANT-3 trial). and lung and gastrointestinal neuroendocrine tumors nonfunctional (RADIANT-4 trial). Everolimus is approved by the FDA for adults with progressive neuroendocrine tumors of pancreatic origin and adults with progressive, well-differentiated, nonfunctional neuroendocrine tumors of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic. The RADIANT-2 trial, conducted in individuals with progressive advanced neuroendocrine tumors associated with carcinoid syndrome, failed to show a statistically significant improvement in the primary endpoint of PFS.

### Tyrosine Kinase Receptor Inhibitors

Neuroendocrine tumors frequently overexpress the vascular endothelial growth factor and receptor. Sunitinib is a multi-targeted tyrosine kinase inhibitor that targets multiple signaling pathways and growth factors and receptors including vascular endothelial growth factor and receptor 1, 2, and 3. It has been shown that daily sunitinib at a dose of 37.5 mg improves PFS, overall survival, and the overall response rate as compared with placebo among individuals with advanced pancreatic neuroendocrine tumors. Sunitinib is FDA approved for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in individuals with unresectable locally advanced or metastatic disease.

## Chemotherapy

Response to chemotherapy for advanced neuroendocrine tumors of the gastrointestinal tract and lung is highly variable and, at best, modest. Tumor response rates are generally low and no PFS benefit has been clearly demonstrated. Therefore, the careful selection of patients is critical to maximize the chance of response and avoid unnecessary toxicity. In advanced neuroendocrine tumors, platinum-based regimens are generally used. They include cisplatin and etoposide (most widely used), carboplatin and etoposide, 5-fluorouracil, capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide.

## Peptide Receptor Radionuclide Therapy: Lutetium 177 Dotatate

Lutetium 177 dotatate is a radiolabeled-somatostatin analogue that binds to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors. It is then internalized and beta particle emission from lutetium 177 induces cellular damage by formation of free radicals in somatostatin receptor-positive and neighboring cells.

## Pheochromocytoma and Paraganglioma

Pheochromocytoma and paraganglioma are rare neuroendocrine tumors that originate from the chromaffin cells of the adrenal glands. Chromaffin cells produce catecholamine neurotransmitters, such as epinephrine, norepinephrine, and dopamine. Compared to the normal chromaffin cells, pheochromocytomas and paraganglioma express high levels of the norepinephrine transporter on their cell surfaces. The excess amount of norepinephrine causes the clinical signs and symptoms like hypertension, headache, sweating, tremor, and palpitation. While most pheochromocytoma and paraganglioma are non-malignant (non-metastatic), about 10% of pheochromocytoma are malignant and about 25% of paraganglioma are malignant (metastatic) which can spread to other parts of the body, such as the liver, lungs, bone, or distant lymph nodes.

The average age of diagnosis is 43 years old. The estimated annual incidence of pheochromocytoma and paraganglioma is approximately 1 in 300,000 population. The 5-year mortality rates for individuals with metastatic pheochromocytoma and paraganglioma has been reported as 37% depending on the primary tumor site and sites of metastases. In addition, the medical overall and disease-specific survival were 24.6 and 33.7 years for pheochromocytoma and paraganglioma.

## Diagnosis

The initial diagnosis of pheochromocytomas and paragangliomas includes biochemical testing, such as blood tests and urinalysis which measure the levels of metanephrine, a catecholamine metabolite in blood and urine. Imaging may be used to detect the location and size of tumors within the organs or tissues. Other advanced diagnostic procedures, such as $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy, octreotide scan, and fluorodeoxyglucose-positron emission tomography scan are used to further determine whether the tumors are malignant and metastatic.

Certain genetic disorders such as multiple endocrine neoplasia 2 syndrome, von Hippel-Lindau syndrome, Neurofibromatosis type 1, and hereditary paraganglioma syndrome are considered risk factors for pheochromocytomas and paragangliomas and therefore genetic testing is recommended for all individuals with pheochromocytoma or paraganglioma.

## Treatment Approach

Surgical resection is mostly reserved for benign tumors as curative surgical resection is nearly impossible in metastatic disease. For individuals with local, unresectable disease, palliative external beam radiotherapy may be used with or without cytoreductive resection for individuals with bone metastases.

## Peptide Receptor Radionuclide Therapy

Prior to the approval of Iobenguane I 131, there were no FDA-approved therapies for this indication. Lutetium 177 dotatate has been used off-label in this population. There is limited evidence for chemotherapy. In the case of unresectable progressive pheochromocytoma or paraganglioma, combination use of cyclophosphamide, dacarbazine, vincristine, doxorubicin, temozolomide, and thalidomide have been used. Tyrosine kinase receptor inhibitors such as sunitinib have also been used.

## Regulatory Status

On January 26, 2018 Lutathera® (Lutetium Lu 177 Dotatate) was approved by the FDA for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

On May 5, 2022, Novartis announced that it had temporarily suspended production of Lutathera at production sites in Ivrea, Italy and Millburn, New Jersey out of an abundance of caution as a result of potential quality issues identified in its manufacturing processes. This production suspension will impact both commercial and clinical trial supply in the US and Canada. At the time of announcement, the company expected resolution of these issues and resumption of some product supply within 6 weeks, subject to confirmation via an ongoing review. Novartis noted that there is currently no indication of risk to individuals from doses previously produced at these sites but has notified treatment sites to closely monitor individuals. Production of Lutathera was resumed ahead of schedule in early June 2022.

In April of 2024 the “Food and Drug Administration approved lutetium Lu 177 dotatate (Lutathera, Advanced Accelerator Applications USA, Inc., a Novartis company) for pediatric patients 12 years and older with somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors.”

# RATIONALE

This evidence review was created in May 2018 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 2026.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

## Gastroenteropancreatic Neuroendocrine Tumors including Foregut, Midgut, and Hindgut Tumors

### *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 following PICO was used to select literature to inform this review.

### *Populations*
The relevant population of interest is 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.

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

### *Comparators*
The following practices (listed alphabetically with no preference) that are currently being used as second-line treatment options for individuals who have progressed on first-line somatostatin analogues include: 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.

### *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 myelodysplastic syndrome, renal failure, and leukemia.

## Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

## Review of Evidence

## Randomized Controlled Trials
The evidence for use of Lu 177 dotatate for patients in midgut carcinoid tumors consists of the open-label NETTER-1 RCT (NCT01578239) and in patients with gastroenteropancreatic neuroendocrine tumors consists of the open-label NETTER-2 RCT (NCT03972488) and the retrospective cohort ERASMUS study. Results of the NETTER-1 study were originally published by Strosberg et al (2017). However, the U.S. Food and Drug Administration (FDA) reviewed updated results and therefore data for the NETTER-1 study reported herein are based on the FDA documents and not the published study. Similarly, results of the ERASMUS study were published by Kwekkeboom et al (2008) and by Brabander et al (2017). However, the 2017 published results included efficacy data for 443 patients with gastroenteropancreatic and bronchopulmonary and thymus neuroendocrine tumors. In its review, the FDA only assessed data for 360 patients with gastroenteropancreatic neuroendocrine tumors and therefore data for ERASMUS study reported herein are based on the FDA documents and not the published studies. The NETTER-2 study is ongoing but preliminary results have been published. Study characteristics and results are summarized in in the tables below.

In the NETTER-1 trial, individuals with Ki-67 index of 20% or less (a grading parameter for neuroendocrine tumors index), Karnofsky Performance Status score of 60 or greater, confirmed presence of somatostatin receptors on all lesions (octreoscan uptake ≥ normal liver) and creatinine clearance of 50 mL/min or greater were included. Randomization was stratified by octreoscan tumor uptake score (grade 2, 3, or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤ 6 or > 6 months). The major efficacy outcome measure was PFS as determined by a blinded independent radiology committee per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. Additional efficacy outcome measures were overall response rate assessed by an independent review committee, duration of response, and OS. The result showed a consistent statistically significant and clinically meaningful effect on overall response rate, PFS, and OS among patients given Lu 177 dotatate compared with those given high-dose long-acting octreotide.

Inclusion criteria for the NETTER-2 trial were similar to NETTER-1 except that both grade 2 (Ki-67 ≥10% and ≤ 20%) and grade 3 (Ki-67 >20% and ≤55%) were included, and patients with a creatinine clearance <40 mL/min were excluded. Randomization was stratified by tumor grade and origin. The primary outcome was PFS per the RECIST version 1.1 criteria. Other efficacy outcomes were objective response rate, time to deterioration in quality of life, disease control rate, duration of response, and OS.

**Table 1: Summary of Key Randomized Controlled Trial Characteristics**

| Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | Active | Comparator |
| NETTER-2 | 9 countries in North America, Europe, and Asia | 45 | 2020-2022 | Patients with newly-diagnosed, locally advanced or metastatic, inoperable, higher grade 2 to 3, well-differentiated GEP-NETs | 151 patients given Lu 177 dotatate 7.4 GBq (200 mCi) every 8 wk for 4 cycles plus long-acting octreotide 30 mg every 8 wk until completion of Lu 177 dotatate treatment, then every 4 wk until disease progression or treatment discontinuation for another reason | 75 patients given long-acting octreotide (60 mg every 4 wk) |
| NETTER-1 | Belgium, France, Germany, Italy, Portugal, Spain, U.S. | 41 | 2012-2016 | Adults with metastasized or locally advanced, inoperable, histologically confirmed, | 116 patients given Lu 177 dotatate 7.4 GBq (200 mCi) every 8 wk for up to 4 administrations plus long-acting octreotide 30 mg 4-24 h after each Lu | 113 patients given long-acting octreotide (60 mg every 4 wk) |

| Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | Active | Comparator |
| | | | | progressive midgut NETs | 177 dotatate dose and every 4 wk after completion of Lu 177 dotatate treatment until disease progression or week 76 of the trial | |

GEP-NET: gastroenteropancreatic neuroendocrine tumor; Lu 177: lutetium 177; NET: neuroendocrine tumor;

**Table 2: Summary of Key RCT Results**

| Trial | Median PFS (95% CI), months | Median OS (95% CI), months | ORR (95% CI), % | CR (95% CI), % | PR (95% CI), % | Median DOR (95% CI), months |
|---|---|---|---|---|---|---|
| NETTER-2 | | | | | | |
| N | 226 | | 226 | 226 | 226 | |
| Lu 177 dotatate | 22.8 (9.4 to NE) | NR | 43 (35 to 51.3) | 5 | 38 | Not reported |
| Control | 8.5 (7.7 to 13.8) | NR | 9.3 (3.8 to 18.3) | 0 | 9 | Not reported |
| OR or HR (95% CI) or p | 0.276 (0.182 to 0.418) | NR | 7.81 (3.32 to 18.40) | Not reported | Not reported | Not reported |
| NETTER-1 | | | | | | |
| N | 229 | 229 | 229 | 229 | 229 | |
| Lu 177 dotatate | NR (NE)[a] | NR (31.0 to NE) | 13 (7 to 19) | 1 (1%) | 14 (12%) | NR (2.8 to NE) |
| Control | 8.5 (5.8 to 9.1) | 27.4 (22.2 to NE) | 4 (0.1 to 7) | 0 | 4 (4%) | 1.9 (1.9 to NE) |
| HR (95% CI) or p | 0.21 (0.13 to 0.32) | 0.52 (0.32 to 0.84)[b] | .015 | Not reported | Not reported | Not reported |

CI: confidence interval; CR: complete response; DOR: duration of response; HR: hazard ratio; Lu 177: lutetium 177; NE: not evaluable; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RCT: randomized controlled trial.

[a] Median follow-up 10.5 mo at time of primary analysis of PFS (range, 0-29 mo).

[b] Interim analysis of OS not statistically significant based on prespecified significance criteria.

The purpose of a limitations assessment is to identify notable limitations detected in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement. While this limitations analysis is not comprehensive, no notable limitations were identified for studies evaluated in this section.

### Table 3. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Duration of Follow-up[e] |
|---|---|---|---|---|---|
| NETTER-2 | | | | | 1. OS data was immature at the time of publication |
| NETTER-1 | | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
OS: overall survival.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

### Table 4. Study Design and Conduct Limitations

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| NETTER-2 | | 1. Not blinded to treatment assessment | | | | |
| NETTER-1 | 1. Participants not randomly allocated because design was a retrospective single cohort study | 1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician | | 1. Baseline tumor assessments obtained for only 578/1214 (48%) of patients | 2. FDA noted that protocol along with a statistical analysis plan was retrospectively generated | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FDA: U.S. Food and Drug Administration.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

### Retrospective Studies

In the ERASMUS study, 1214 patients with heterogeneous etiologies in terms of primary tumor site received Lu 177 dotatate as part of expanded access protocol at a single center in the Netherlands. Most patients had gastroenteropancreatic neuroendocrine tumors of the foregut, midgut, and hindgut, as well as the digestive tract, bronchus, and pancreatic neuroendocrine tumors. Other neuroendocrine tumors were also included in the trial, specifically medullary thyroid cancer, pheochromocytoma, paraganglioma, neuroblastoma, and Merkel cell carcinoma. Non-neuroendocrine somatostatin receptor-positive tumors including melanoma, nondifferentiated thyroid cancers, non-small-cell lung cancer, breast cancer, lymphoma, and malignant meningioma were also treated. From this heterogeneous cohort, 601 patients were assessed per RECIST criteria of whom 360 with foregut, midgut, or hindgut gastroenteropancreatic neuroendocrine tumors were retrospectively identified and analyzed. The major efficacy outcome was investigator-assessed overall response rate. Fifty-five percent of patients received a concomitant somatostatin analogue. Study characteristics and results are summarized in the tables below.

In this cohort of 360 patients, the investigator-assessed overall response rate was 16% and the median duration of response was 35 months among 58 responders. The FDA did not view time to event analyses such as time to progression, PFS, and OS to be interpretable in the context of the single-arm ERASMUS study because of missing data at baseline, high dropout rates, and the open-label design of the study. However, the FDA considered that "these data provide statistically conservative estimates that were verifiable and are clinically meaningful for patients with gastroenteropancreatic neuroendocrine tumors. The results provide additional support for the indicated population that are consistent with the observed benefit in other populations of patients with the disease (i.e., in NETTER-1), the biology of the disease itself, the mechanism of action of Lu 177 dotatate, and the limited treatment options available for these patients."

The SEPTRALU registry sought to elucidate the safety and efficacy of Lu 177 dotatate in the treatment of neuroendocrine tumors of various etiologies. Results from the registry were published by Mitjavila et al (2023) for 522 patients across 24 centers in Spain which included stratified outcomes for pancreatic (n=182), midgut (n=148), and other gastroenteropancreatic neuroendocrine tumors (n=60). Study characteristics and results are summarized in the tables below The disease control rate, defined as the sum of complete response, partial response, and stable disease, was 84.8%, 93.5%, and 85.4%, respectively. After a median follow-up of 21.2 months, median PFS was 19.8 months, 31.3 months, and 24.3 months, respectively. Median OS was 34.2 months and 50.8 months for pancreatic and midgut tumors and was not reached for other gastroenteropancreatic tumors.

### Table 5: Summary of Key Nonrandomized Trials Characteristics

| Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| ERASMUS Study | Retrospective cohort | Netherlands | 2000-2012 | Patients with somatostatin-positive GEP-NETs with a life expectancy of >12 wk and Karnofsky Performance Scale score ≥50 | 360 patients given Lu 177 dotatate 7.4 GBq (200 mCi) every 6-13 wk for up to 4 doses | 34.8 months |
| SEPTRALU Registry | Registry | Spain | 2014-2022 | Patients with somatostatin-positive GEP-NETs and unresectable, metastatic, or progressive disease | 522 patients give Lu 177 dotatate 7.4 GBq (200 mCi) every 8-10 wk for up to 4 doses | 21.2 months |

GEP-NET: gastroenteropancreatic neuroendocrine tumor; Lu 177: lutetium 177.

**Table 6: Summary of Key Nonrandomized Trial Results**

| **Study** | **Median Duration of Response (95% CI), months** | **Overall Response Rate (95% CI), %** | |
|---|---|---|---|
| ERASMUS Study | | | |
| N | 360 | 360 | N/A |
| Lu 177 dotatate | 35 (17 to 38) | 16 (13 to 21) | N/A |
| **SEPTRALU Registry** | | | |
| Pancreatic NETs (N) | NA | 182 | 182 |
| Lu 177 dotatate | NA | 84.8 (NR) | 19.8 (16.8 to 28.1) |
| Midgut NETs (N) | NA | 148 | 148 |
| Lu 177 dotatate | NA | 93.5 (NR) | 31.3 (25.7 to not reached) |
| Other GEP-NETs (N) | NA | 60 | 60 |

| | | | |
|---|---|---|---|
| Lu 177 dotatate | NA | 85.4 (NR) | 24.3 (18.0 to not reached) |

CI: confidence interval; Lu 177: lutetium 177. NA: not applicable; NR: not reported.

The purpose of the limitations tables (see the tables below) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

**Table 7: Study Relevance Limitations**

| Trial | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| ERASMUS Study | | | 2. This was a single cohort study. There was no comparator. | 2.Investigator-assessed ORR not a validated surrogate outcome measure | |
| SEPTRALU Registry | | | 2. This was a single-arm registry with no comparator. | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ORR: overall response rate.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8: Study Design and Conduct Limitations**

| Trial | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness [d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| NETTER-1 | 1. Participants not randomly allocated because design was a retrospective single cohort study | 1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed | | 1. Baseline tumor assessments obtained for only 578/1214 (48%) of patients | 2. FDA noted that protocol along with a statistical analysis plan was retrospectively generated | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | by treating physician | | | | |
| SEPTRALU Registry | 1. Participants not randomly allocated because design was retrospective registry. | 1-3. Blinding unclear. | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: Gastroenteropancreatic Neuroendocrine Tumors Including Foregut, Midgut, and Hindgut Tumors

The evidence for use of Lu 177 dotatate consists of 2 open-labeled RCTs, a multicenter registry, and a retrospective cohort study. The RCT results showed a consistent statistically significant and clinically meaningful effect on overall response rate, PFS, and OS (only available for 1 trial) among individuals treated with Lu 177 dotatate compared to those treated with long-acting octreotide. The results of the retrospective studies were consistent with the treatment effect observed in the RCT and provide additional support for a clinical benefit of Lu 177 dotatate in individuals with gastroenteropancreatic neuroendocrine tumors.

## Bronchopulmonary or Thymus Neuroendocrine Tumors

### *Clinical Context and Therapy Purpose*

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.

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest is individuals with locally advanced or metastatic somatostatin receptor-positive bronchopulmonary or thymus neuroendocrine tumor who have progressed on first-line somatostatin analogues. Bronchopulmonary neuroendocrine tumors comprise approximately 20% of all lung cancers. Neuroendocrine tumors of the thymus account for only 5% of all tumors in the thymus and mediastinum.

### *Interventions*
The therapy being considered is Lu 177 dotatate.

### *Comparators*
The following practices (listed alphabetically with no preference) that are currently being used as second-line treatment options for individuals who have progressed on first-line somatostatin analogues include: carboplatin plus etoposide, everolimus, cisplatin plus etoposide, radiotherapy, and temozolomide.

### *Outcomes*
The general outcomes of interest are OS, median 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 include myelodysplastic syndrome, renal failure, and leukemia.

## Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

## Review of Evidence

## Retrospective Studies
The evidence for use of Lu 177 dotatate in individuals with bronchopulmonary or thymus neuroendocrine tumors consists of the retrospective ERASMUS cohort study and a bicenter, retrospective case series. The ERASMUS study design and characteristics are described in the previous section. Unlike the previous indication, where the FDA considered a subset of 360 patients with gastroenteropancreatic neuroendocrine tumors as supportive evidence, the FDA identified multiple problems with ERASMUS data that precluded drawing conclusions about treatment efficacy in individuals with bronchopulmonary or thymus neuroendocrine tumors. The FDA concluded that time to event analyses such as time to progression, PFS, and OS were not interpretable in the context of the single-arm ERASMUS study because of missing data at baseline, high dropout rates, and the open-label design of the study.

The ERASMUS study included 23 patients with bronchopulmonary and 2 patients with thymus neuroendocrine tumors. Among the 23 patients with bronchopulmonary neuroendocrine tumor, the median PFS was 20 months, the median time to progression was 25 months, and median OS was 52 months. Stratified results of 2 patients with thymus neuroendocrine tumors were not reported.

Zidan et al (2022) published data from a retrospective case series assessing the efficacy of Lu 177 dotatate in 48 patients with somatostatin receptor-positive lung neuroendocrine tumors treated between 2006 and 2019 at 2 centers in Australia and Israel. Median patient age was 64 years. The series included 13 (27%) women and 43 (90%) atypical carcinoid tumors. The majority of patients (98%) were treated for radiographic disease progression, with 1 individual receiving treatment for uncontrolled symptoms. Of 40 patients with RECIST-measurable disease at 3 months, 8 (20%) had a partial response, 27 (68%) had stable disease, and 5 (12%) had disease progression. In 26 patients with RECIST-measurable stable

disease, 10 patients were classified as partial response and 1 patient as progressive disease by Gallium 68 (Ga 68) dotatate positron emission tomography (PET)/computed tomography (CT). At a median follow-up of 42 months, the median PFS and OS were 23 months (95% confidence interval [CI], 18 to 28) and 59 months (95% CI, 50 to not reached), respectively.

The SEPTRALU registry (see Table 5) sought to elucidate the safety and efficacy of Lu 177 dotatate in the treatment of neuroendocrine tumors of various etiologies. Results from the registry were published by Mitjavila et al (2023) for 522 patients across 24 centers in Spain which included stratified outcomes for bronchopulmonary tumors (n=56). The disease control rate was 77.6% with 0 complete responses, 14 (28.6%) partial responses, and 24 (49.0%) patients with stable disease. After a median follow up of 21.2 months, median PFS was 17.6 months (95% CI, 14.4 to 33.1) and median OS was 44.8 months (95% CI, 19.9 to not reached).

The purpose of the limitations tables (see Tables 9 and 10) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

**Table 9: Study Relevance Limitations**

| Trial | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| ERASMUS Study | | | 2. This was a single cohort study without a comparator | 2. Investigator-assessed ORR not a validated surrogate outcome measure | |
| Zidan et al (2022) | | 1. Patients received variable cycles of therapy, with or without radiosensitizing chemotherapy | 2. This was a retrospective case series without a comparator | 2. Investigator-assessed DCR not a validated surrogate outcome measure | |
| SEPTRALU Registry | | | 2. This was a single-arm registry with no comparator. | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
DCR: disease control rate; ORR: overall response rate.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 10: Study Design and Conduct Limitations**

| Trial | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness [d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| ERASMUS Study | 1. Participants not randomly allocated because design was a retrospective single cohort study | 1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician | | 1. Baseline tumor assessments obtained for only 578 (48%) of patients | 2. FDA noted that protocol along with statistical analysis plan were retrospectively generated | |
| Zidan et al (2022) | 1. Participants not randomly allocated because design was retrospective case series | 1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician | | | | |
| SEPTRALU Registry | 1. Participants not randomly allocated because design was retrospective registry | 1-3. Blinding unclear | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FDA: U.S. Food and Drug Administration.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: Bronchopulmonary or Thymus Neuroendocrine Tumor

The evidence for use of Lu 177 dotatate consists of the retrospective ERASMUS cohort study, a multicenter registry, and a bicenter, retrospective case series. The ERASMUS study included a small number of patients with bronchopulmonary (n=23) and thymus (n=2) neuroendocrine tumors. Results for the 2 individuals with thymus neuroendocrine tumors were not reported separately. The multicenter registry included 58 patients with bronchopulmonary tumors and reported 0 complete responses, 14 partial responses, a median PFS of 17.6 months, and a median OS of 44.8 months. The case series evaluated 48 patients with predominantly atypical carcinoid bronchopulmonary tumors. Across studies, median PFS and OS ranged from 20 to 23 months and 52 to 59 months, respectively. No RCTs were identified.

## Safety

In the safety analysis, exposure data from 922 patients who received at least 1 dose of Lu 177 dotatate treated in the NETTER-1 and ERASMUS studies were analyzed. Drug exposure in NETTER-1 was a total of 600 mCi or more of Lu 177 dotatate in 79.3% of patients treated, and 26% of patients received cumulative doses of 800 mCi or more. Seventy-six percent of patients received all 4 planned doses. Dose reductions were reported in 6% of patients and drug discontinuation in 13% of patients. The most common adverse events observed in patients treated with Lu 177 dotatate were nausea (65%), vomiting (53%), fatigue (38%), diarrhea (26%), abdominal pain (26%), and decreased appetite (21%). The most common grade 3 and 4 adverse events with Lu 177 dotatate were lymphopenia (44%), increased gamma-glutamyl transferase (20%) vomiting (7%), nausea and elevated aspartate aminotransferase (5% each), as well as increased alanine aminotransferase, hyperglycemia, and hypokalemia (4% each). In the ERASMUS study, with a median follow-up of more than 4 years, the most serious chronic toxicities reported were myelodysplastic syndrome (2%), renal failure (2%), cardiac failure (2%), acute leukemia (1%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

## Pheochromocytoma and Paraganglioma

### *Clinical Context and Therapy Purpose*

The purpose of Lu 177 dotatate 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.

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest is individuals with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma.

### *Interventions*

The therapies being considered Lu 177 dotatate injection.

### *Comparators*

The following practices are currently being used to treat unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma: external beam radiation therapy, ablation therapy, transarterial chemoembolization, and chemotherapeutic agents, including cyclophosphamide, dacarbazine, vincristine, doxorubicin, temozolomide, and thalidomide, and sunitinib.

### *Outcomes*

The general outcomes of interest are OS, disease-specific survival, 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 a myelodysplastic syndrome, renal failure, and leukemia.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

## Review of Evidence

The evidence for the use of Lu 177 dotatate in individuals with pheochromocytoma or paraganglioma consists of a systematic review of single-arm studies and a case series.

## Systematic Reviews

Prado-Wohlwend et al (2022) published a systematic review and meta-analysis of therapy with iobenguane I 131 or Lu 177 dotatate in patients (N=1248) with metastatic pheochromocytoma and paranglioma. Twenty-seven studies were included in the analysis, 4 of which were prospective, 9 focused on Lu 177 dotatate, 17 focused on iobenguane I 131, and 1 compared the 2 agents. A regression model analysis found that treatment with iobenguane I 131 yielded a 10 months lower PFS compared to Lu 177 dotatate (95% CI, -11.7 to -8.5). A subsequent Bayesian linear regression model found that the mean difference in PFS was dependent on the proportion of pheochromocytomas in the study sample, with PFS decreasing by 1.9 months (95% CI, -2.01 to -1.78) for each 10% increase in the proportion of pheochromocytomas.

Satapathy et al (2019) published a systematic review and meta-analysis of peptide receptor radionuclide therapy with Lu 177 dotatate and/or Yttrium 90 (Y 90) dotatoc in patients with advanced pheochromocytoma and paraganglioma. Eleven nonrandomized studies were evaluable for objective response rate and disease control rate, representing 179 patients and 151 patients, respectively. For Lu 177 dotatate, the pooled objective response rate was 26% (95% CI, 18% to 35%) with a disease control rate of 83% (95% CI, 75% to 90%). In contrast, the pooled objective response rate and disease control rate for Y 90 dotatoc was 24% (95% CI, 15% to 35%) and 85% (95% CI, 71% to 93%), respectively. Included studies varied in response criteria used and concomitant use of other treatment modalities, such as iobenguane I 131 or radiosensitizing chemotherapy.

## Nonrandomized Studies

The SEPTRALU registry (see Table 5) sought to elucidate the safety and efficacy of Lu 177 dotatate in the treatment of neuroendocrine tumors of various etiologies. Results from the registry were published by Mitjavila et al (2023) for 522 patients across 24 centers in Spain which included stratified outcomes for pheochromocytoma or paraganglioma (n=31). The disease control rate was 84.6% with 0 complete responses, 5 (19.2%) partial responses, and 17 (65.4%) patients with stable disease. After a median follow-up of 21.2 months, median PFS was 30.6 months (95% CI, 14.4 to not reached) and median OS was not reached (95% CI, 15.1 to not reached).

Severi et al (2021) assessed the efficacy of Y 90 dotatoc (n=12) or Lu 177 dotatate (n=34) in consecutive patients with somatostatin receptor-positive progressive locally advanced or metastatic pheochromocytoma or paraganglioma enrolled across multiple study protocols at a single center in Italy from 2008 to 2018. Lu 177 dotatate was administered at dosages of 3.7 or 5.5 GBq/cycle, with lower dosages used in patients with risk factors for bone marrow or renal toxicity. Disease control rate, defined as the sum of partial responses and stable disease, was 82.4% with Lu 177 dotatate and 75% with Y 90 dotatoc after a median follow-up of 73 months. For Lu 177 dotatate, median PFS was not reached and and median OS was 143.5 months (95% CI, 103.1 to 146.2). For Y 90 dotatoc, median PFS was 74.5 months (95% CI, 8.4 to not reached) and median OS was 92.1 months (95% CI, 57.1 to 92.1). A disease control rate of 92% was achieved in patients receiving a full dosage of Lu 177 dotate, compared to 55% in those receiving a reduced dosage. Corresponding median PFS was not reached versus 27.5 months, respectively. Study relevance, design, and conduct limitations are summarized in Tables 11 and 12.

Kong et al (2017) assessed the efficacy of 177 Lu dotatate in a retrospective analysis of 20 consecutive patients with unresectable paraganglioma or pheochromocytoma and high somatostatin receptor expression. Fourteen patients were treated for uncontrolled hypertension and 6 were treated for progressive or symptomatic metastatic disease or local recurrence. Nine patients received radiosensitizing chemotherapy. Of 16 patients who received iobenguane scans, 6 had concordant positive uptake, 6 had mild uptake, and 4 had negative scans. Overall, 5 patients had disease regression, with 4 partial RECIST responses and 1 minor morphologic regression observed on CT out of 14 evaluable patients. At 3 months post-treatment, 8/13 patients (62%) required reduced doses of antihypertensive medications compared with baseline. The remaining 5 patients had no change in medication dose but attained symptom control. During a median follow-up of 28 months (range, 5 to 74 months) median OS was not reached (5 deaths) and median PFS was 39 months. During follow-up, 2 patients had tumor progression, 5 patients had recurrence of hypertension, and 2 others were treated with further maintenance therapies for persistent disease with favorable response. The most common toxicity observed was grade 2 lymphopenia. One patient experienced catecholamine crisis following treatment and catecholamine crisis could not be excluded in 1 patient who died from cardiac arrest after a third cycle of treatment. The authors noted that given the favorable efficacy and potential logistic and radiation safety advantages of Lu 177 dotatate compared to iobenguane I 131, further prospective trials are warranted. Patient outcomes were not stratified by iobenguane uptake status. Study relevance, design, and conduct limitations are summarized in Tables 11 and 12.

**Table 11: Study Relevance Limitations**

| Trial | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Severi et al (2021) | | 1. Patients received variable doses of therapy and concomitant use of other treatment modalities was not standardized | 2. This was a case series without planned direct comparison to other agents, including Y 90 dotatoc | 2. Investigator-assessed DCR not a validated surrogate outcome measure | |
| Kong et al (2017) | 1. Patients had variable degrees of iobenguane uptake | 1. Patients received variable doses of therapy and concomitant use of other | 2. This was a retrospective study without a comparator | 1. Patients outcomes were not stratified by iobenguane uptake status | |

| Trial | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| | | treatment modalities was not standardized | | | |
| SEPTRALU Registry | | | 2. This was a single-arm registry with no comparator. | | |

DCR: disease control rate; Y 90: Yttrium 90.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

### Table 12: Study Design and Conduct Limitations

| Trial | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Severi et al. (2021) | 1. Participants not randomly allocated and evaluated across multiple study protocols<br>4. Inadequate control for selection bias | 1. Not blinded to treatment assignment | | | | |
| Kong et al. (2017) | 1. Participants not randomly allocated | 1. Not blinded to treatment assignment | | 1. High loss to follow-up or missing data | | 3. Confidence intervals and/or p values not reported |
| SEPTRALU Registry | 1. Participants not randomly allocated because design was retrospective registry | 1-3. Blinding unclear | | | | |

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: Pheochromocytoma and Paraganglioma

The evidence for the use of Lu 177 dotatate consists of a systematic reviews and meta-analyses of single-arm studies, a multicenter registry, and 2 case series. One meta-analysis reported a pooled overall tumor response rate of 26% (95% CI, 18% to 35%). Another meta-analysis found improved PFS with Lu 177 dotatate compared to iobenguane I 131 among studies enriched with pheochromocytomas. One retrospective case series reported that 8/13 individuals were able to reduce dosages of antihypertensive treatment at 3 months. Disease regression was reported in 5/14 patients with available CT imaging. Out of 16 patients with available iobenguane scans, 10 patients had mild or negative uptake. However, patient outcomes were not stratified by iobenguane uptake status. No prospective studies directly comparing Lu 177 dotatate to iobenguane I 131 or assessing Lu 177 dotatate response in a fully non-iobenguane avid population were identified.

## SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### *American College of Radiology et al*

In 2022, the American College of Radiology (ACR) issued a practice parameter for lutetium 177 dotatate therapy of gastroenteropancreatic tumors in collaboration with the American College of Nuclear Medicine (ACNM), the American Society of Radiation Oncology (ASTRO), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). Regarding patient selection and clinical evaluation, the practice parameter recommends the following:

- Verification of pathology and indication for therapy, including confirmation of somatostatin receptor expression;
- Discontinuation of somatostatin analog therapy with baseline laboratory evaluation;
- Discussion and mitigation of risks in special populations, including pregnant, lactating, and pediatric patients;
- Administration in the context of a quality management program;
- Documentation of informed consent;
- Treatment according to an established system of procedural steps unique for lutetium 177 dotatate; and
- Application of radiation precautions and patient release criteria in accordance with federal and/or local regulations.

### *National Comprehensive Cancer Network (NCCN)*

The National Comprehensive Cancer Network (NCCN) guidelines ( v.3.2025) for neuroendocrine and adrenal tumors have published key eligibility criteria for patients treated with lutetium 177 dotatate for neuroendocrine tumors. Eligibility criteria include well-differentiated neuroendocrine tumor , detection of somatostatin receptor expression using somatostatin-based receptor imaging, and adequate bone marrow, renal and hepatic function.

Table 13 summarizes the NCCN guidelines for neuroendocrine and adrenal tumors.

**Table 13. Recommendations for Use of Lutetium 177 Dotatate for Neuroendocrine Tumors**

| Treatment Category | Recommendation Category |
|---|---|
| **Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)** | |
| Mid-gut recurrent, locoregional advanced or distant metastases gastrointestinal neuroendocrine tumors after disease progression on somatostatin analogues | 1 |
| Preferred regimen option in locoregional advanced and/or distant metastases after disease progression on somatostatin analogues | 2A |
| First-line option for locoregional advanced and/or distant metastases if somatostatin receptor-positive, Ki-67 ⩾10%, and clinically significant tumor burden | 2A |
| **Pancreatic Neuroendocrine Tumors (Well-Differentiated Grade 1/2)** | |
| Preferred regimen option in locoregional advanced and/or distant metastases after disease progression on somatostatin analogues | 2A |
| First-line option for locoregional advanced and/or distant metastases if somatostatin receptor-positive, Ki-67 ⩾10%, and clinically significant tumor burden | 2A |
| **Lung/Thymus Neuroendocrine Tumors** | |
| Useful in certain circumstances for distant metastases if somatostatin receptor-positive and progression on somatostatin analogues | 2A |
| **Well-Differentiated Grade 3 Neuroendocrine Tumors** | |
| Option for favorable biology tumors (relatively low Ki-67, slow growing) if somatostatin receptor-positive | |
| **Pheochromocytoma/Paraganglioma** | |
| Locally unresectable or distant metastases paraganglioma/pheochromocytoma (consider use if somatostatin receptor-positive) | 2A |

The NCCN guidelines ( v.3.2025) for neuroendocrine and adrenal tumors gives iobenguane I 131 category 2A recommendation for treatment of patients with locally unresectable or distant metastatic pheochromocytoma or paraganglioma with positive MIBG (iobenguane) scan.

### *North American Neuroendocrine Tumor Society*

In 2021, the North American Neuroendocrine Tumor Society released a consensus guideline on management of metastatic and/or unresectable pheochromocytoma and paraganglioma. The guideline states that there is some evidence to support using lutetium 177 dotatate in some patients, but the consensus recommendation was to limit use to a clinical trial.

Also in 2021, the North American Neuroendocrine Tumor Society (and several other organizations) released a consensus guideline on management of patients with lung neuroendocrine tumors. The final consensus statement was that peptide receptor radionuclide therapy may be an option for patients with somatostatin receptor positive tumors (grade B recommendation).

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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89.

## CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

| Codes | Number | Description |
|---|---|---|
| CPT | | |
| | No code(s) | |
| | | |
| HCPCS | | |

| Codes | Number | Description |
|---|---|---|
| | A9513 | Lutetium Lu 177, Dotatate, therapeutic 1 millicurie (Lutathera) |
| | | |
| Type of Service | Radiopharmaceuticals Oncology | |
| Place of Service | Outpatient | |

## POLICY HISTORY

| Date | Reason | Action |
|---|---|---|
| January 2026 | Interim Review | Policy Revised |
| November 2025 | Annual Review | Policy Renewed |
| November 2024 | Annual Review | Policy Revised |
| September 2023 | Annual Review | Policy Revised |
| May 2023 | Annual Review | Policy Revised |
| May 2022 | 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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