Therapeutic Radiopharmaceuticals in Oncology

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Next Review: 9/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Therapeutic Radiopharmaceuticals in Oncology when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

INITIAL TREATMENT
Lutetium 177 (Lu 177) dotatate treatment is considered medically necessary when conditions 1 through 8 are met:

1. Patient is an adult (≥18 years of age).
2. Patient has documented low or intermediate grade (Ki-67 index ≤20%), locally advanced or metastatic, gastroenteropancreatic (including foregut, midgut, and hindgut) or bronchopulmonary or thymus neuroendocrine tumor.
3. Patient has documented somatostatin receptor expression of a neuroendocrine tumor as detected by somatostatin receptor-based imaging (68Ga-dotate positron emission tomography or computed tomography, which is preferred) or somatostatin receptor scintigraphy.
4. Patient has documented disease progression while on octreotide long-acting release therapy.
5. Patient is not receiving long-acting somatostatin analogues for at least 4 weeks prior to initiating Lu 177 dotatate.
6. Patients does not have severe renal impairment (creatinine clearance, <30 mL/min).
7. Patient has adequate bone marrow and hepatic function as determined by the treating physician.
8. Patient has documented Karnofsky Performance Status score of 60 or greater.

CONTINUATION OF TREATMENT
Continuation of Lu 177 dotatate is considered medically necessary when conditions 1 through 5 are met:

1. No recurrent grade 2, 3, or 4 thrombocytopenia (see Table PG1).
2. No recurrent grade 3 or 4 anemia and neutropenia (see Table PG1).
3. No recurrent hepatotoxicity (see definition of hepatotoxicity in the Policy Guidelines section).
4. No recurrent grade 3 or 4 nonhematologic toxicity (see Table PG1).
5. Renal toxicity requiring a treatment delay of 16 weeks or longer (see definition of renal toxicity in the Policy Guidelines section).

**Iobenguane I 131**
Iobenguane I 131 is considered medically necessary when conditions 1 through 5 are met:
1. Patient has documented iobenguane scan positive, locally advanced or metastatic pheochromocytoma and paraganglioma.
2. Patient is 12 years or older.
3. Patient has progressed on prior therapy for pheochromocytoma or paraganglioma OR is not a candidate for chemotherapy.
4. Patient does not have severe renal impairment (creatinine clearance <30 mL/min).
5. Patient has platelet count greater than 80,000/mcL OR absolute neutrophil count greater than 1,200/mcL.

**When Policy Topic is not covered**
Lu 177 dotatate treatment is considered investigational in all other situations in which the above criteria are not met.

Lu 177 dotatate treatment greater than a total of 4 doses as per the Food and Drug Administration-approved regimen is considered investigational.

Iobenguane I 131 treatment is considered investigational for all other indications including neuroblastoma and gastroenteropancreatic neuroendocrine tumors.

Use of iobenguane I 131 not in accordance with FDA approved dosing (first dosimetric dose followed by two therapeutic doses administered 90 days apart) is considered investigational. See policy guidelines below.

**Considerations**
The recommended dose of lutetium 177 (Lu 177) dotatate is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses.

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 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%.

Lu 177 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.

Table PG1 describes the grading of severity used in the Common Toxicity Criteria for Adverse Events (version 4.03).

**Table PG1. Common Toxicity Criteria for Adverse Events, Version 4.03**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>2</td>
<td>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.</td>
</tr>
<tr>
<td>3</td>
<td>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 refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>5</td>
<td>Death related to adverse event.</td>
</tr>
</tbody>
</table>

**Iobenguane I 131**

- Iobenguane I 131 is administered intravenously as a dosimetric dose followed by two therapeutic doses administered 90 days apart.
  - The recommended dosimetric dose is 185 to 222 MBq (5 to 6 mCi) in patients greater than 50 kg and 3.7 MBq/kg (0.1 mCi/kg) in patients 50 kg or less.
The recommended therapeutic dose is 18,500 MBq (500 mCi) in patients greater than 62.5 kg and 296 MBq/kg (8 mCi/kg) in patients 62.5 kg or less.

- Thyroid-blocking medications should be given prior to administration and after each dose.
- Iobenguane I 131 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.
- Iobenguane I 131 should be discontinued if
  - Platelet count is less than 80,000 mcL or absolute neutrophil count (ANC) is less than 1,200/mcL.
  - Patient has liver dysfunction defined as aspartate aminotransferase or alanine aminotransferase ≥ 2.5 times the upper limit of normal or total bilirubin > 1.5 times the upper limit of normal or develops liver disease (including hepatitis and chronic alcohol abuse).
  - Patient develops renal toxicity defined as a creatinine clearance of < 30 mL/min.

There are no specific CPT codes for Lu 177.

There is a specific HCPCS code:

C9031 Lutetium Lu 177, dotatate, therapeutic, 1 mCi.

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Individuals:**
  - With a treatment-refractory gastroenteropancreatic neuroendocrine tumor including foregut, midgut, and hindgut tumors
  - With a treatment-refractory bronchopulmonary or thymus neuroendocrine tumor
  - With unresectable, locally advanced or | **Interventions of interest are:**
  - Lutetium 177 dotatate
  - Lutetium 177 dotatate
  - Iobenguane I 131 | **Comparators of interest are:**
  - Standard of care
  - Standard of care
  - Standard of care | **Relevant outcomes include:**
  - Overall survival
  - Disease-specific survival
  - Quality of life
  - Treatment-related mortality
  - Treatment-related morbidity |

| Relevant outcomes include: | Overall survival
| Disease-specific survival
| Quality of life
| Treatment-related mortality
| Treatment-related morbidity | Overall survival
|
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. Similar to Lu 177, iobenguane I 131 is a radioactive therapeutic agent, which is similar in structure to norepinephrine. Due to its structural similarity with norepinephrine, iobenguane is taken up by the norepinephrine transporter where it accumulates in adrenergically innervated tissues including pheochromocytoma and paraganglioma cells. The beta and gamma radiation resulting from the radioactive decay causes an anti-tumor affect.

For individuals with a treatment-refractory gastroenteropancreatic neuroendocrine tumor including foregut, midgut, and hindgut tumors who receive Lu 177 dotatate, the evidence includes a randomized, open-labeled trial and a retrospective cohort study. The 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, and overall survival among patients 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 patients with a gastroenteropancreatic neuroendocrine tumor. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a treatment-refractory bronchopulmonary or thymus neuroendocrine tumors who receive Lu 177 dotatate, the evidence includes a retrospective cohort study. The 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 progression-free survival was 20 months, the median time to progression was 25 months, and median overall survival was 52 months. Stratified results of two patients with thymus neuroendocrine tumors were not reported. The Food and Drug Administration in its review of the ERASMUS study for patients with
gastroenteropancreatic neuroendocrine tumor concluded that time to event analyses such as time to progression, progression-free survival, 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. Of note, despite the current evidence base, National Comprehensive Cancer Network guidelines give a category 2A recommendation for use of Lu 177 dotatate for the treatment of bronchopulmonary and thymic locoregional advanced or distant metastases neuroendocrine tumors if there are clinically significant tumor burden and low grade (typical) or evidence of progression or intermediate grade (atypical). The evidence is insufficient to determine the effects of technology on health outcomes.

For individuals with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy and who receive iobenguane I 131, the evidence includes a single-arm prospective cohort study. The relevant outcomes include OS, disease-specific survival, quality of life, treatment-related mortality and morbidity. The pivotal study reported that 25% of patients (95% confidence interval 16.2% to 36.5%) met the primary endpoint of reduction in antihypertensive medication of at least 50% for at least 6 months along with 22.1% of patients having a confirmed, centrally reviewed partial response (95% confidence interval: 13.6% to 32.7%). Of these, 53% of patients who responded to therapy maintained a duration of response for at least 6 months. The single-arm nature of the trial prevents adequate interpretation of the results of time to event endpoint of OS which was a secondary endpoint of the trial. Given the severity and rarity of the disease condition with an associated high degree of morbidity and mortality, especially in metastatic disease, these outcomes represents a clinically meaningful benefit for patients. As with all other radiopharmaceuticals, iobenguane I 131 is associated with an increased risk for secondary hematologic malignancy including myelodysplastic syndrome or acute leukemias. Due to the risk of serious adverse reactions, iobenguane I 131 is only indicated for patients with unresectable, locally advanced or metastatic paraganglioma who require systemic anticancer therapy and have no other known curative options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

**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. Lung neuroendocrine tumors may also be referred to as pulmonary neuroendocrine tumors, pulmonary carcinoids, or bronchopulmonary 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. Neuroendocrine tumors are classified as orphan diseases by the 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 100000 people per year.1

**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 five to seven years after symptom onset.2 In many cases, diagnosis is incidental to imaging for other unrelated cause. Most gastroenteropancreatic neuroendocrine tumors express somatostatin receptors that can be imaged using a radiolabeled form of the somatostatin analogue octreotide (eg, 111In 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.3 Surgery alone or followed by chemotherapy along with treatment of hormone-related symptoms may be the initial approach for localized disease. For asymptomatic patients with slow progression, observation with routine surveillance imaging is an option. The prognosis for patients with metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors is highly variable. Based on retrospective analyses of large databases, the prognosis for patients with metastatic gastroenteropancreatic neuroendocrine tumors is variable. The median overall survival (from diagnosis) for patients with metastatic pancreatic neuroendocrine tumors has been reported to range from 2 to 5.8 years[4] while the median overall survival for small bowel neuroendocrine tumors has been reported as 7.9 years.5

**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 (eg, 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 patients with neuroendocrine tumors treated with somatostatin analogues.6,7 However, the
role of somatostatin analogues in patients with nonfunctioning neuroendocrine tumors is unclear.\textsuperscript{8}

Commercially available long-acting release forms of octreotide and lanreotide (eg, 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.\textsuperscript{9,10}

**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.\textsuperscript{11} Everolimus, an oral mechanistic target of rapamycin inhibitor, has been shown to significantly prolonged PFS vs placebo in patients with pancreatic neuroendocrine tumors (RADIANT-3 trial),\textsuperscript{12} and lung and gastrointestinal neuroendocrine tumors nonfunctional (RADIANT-4 trial).\textsuperscript{13} Note that 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 patients with progressive advanced neuroendocrine tumors associated with carcinoid syndrome failed to show a statistically significant improvement in the primary endpoint of PFS.\textsuperscript{14}

**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.\textsuperscript{11} 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 patients with advanced pancreatic neuroendocrine tumors.\textsuperscript{15} Note that sunitinib is FDA approved for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients 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.\textsuperscript{16}

Lutetium 177 Dotate

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.\textsuperscript{17} 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.\textsuperscript{18}

The average age of diagnosis is 43 years old. The estimated annual incidence of pheochromocytoma and paraganglioma is approximately 1 in 300000 population.\textsuperscript{19} The 5-year mortality rates for patients with metastatic pheochromocytoma and paraganglioma has been reported as 37% depending on the primary tumor site and sites of metastases.\textsuperscript{20} In addition, the medical overall and disease-specific survival were 24.6 and 33.7 years for pheochromocytoma and paraganglioma.\textsuperscript{21}

**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 \textsuperscript{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.\textsuperscript{17}

Certain genetic disorders such as multiple endocrine neoplasia 2 syndrome, von Hippel-Lindau syndrome, Neurofibromatosis type 1, hereditary paraganglioma syndrome\textsuperscript{22} are considered risk factors for pheochromocytomas and
paragangliomas and therefore genetic testing is recommended for all patients with pheochromocytoma or paraganglioma.\textsuperscript{17}

**Treatment Approach**

Surgical resection is mostly reserved for benign tumors as curative surgical resection is nearly impossible in metastatic disease. For patients with local, unresectable disease, palliative external beam radiotherapy may be used with or without cytoreductive resection for patients with bone metastases.\textsuperscript{23}

Prior to the approval of Iobenguane I 131, there was no FDA approved therapies for this indication. Radiotherapy options include off-label use of I 131-metaiodobenzylguanidine (\textsuperscript{131}I-MIBG) for patients with MIBG-positive tumors.\textsuperscript{17,23}\textsuperscript{131}I-MIBG contains radioactive iodine and the compound is structurally similar to norepinephrine.[9492103] When \textsuperscript{131}I-MIBG is delivered to the target tissue, it gives off beta-radiation killing neuroendocrine tumors. Due to the nature of the radiopharmaceutical mechanism of action, \textsuperscript{131}I-MIBG can cause toxicities including nausea, vomiting, anemia, leukocytopenia, and thrombocytopenia.[23921531] 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.\textsuperscript{24,30} Tyrosine kinase receptor inhibitors such as sunitinib have also been used.\textsuperscript{26}

**Regulatory Status**

On January 26, 2018, Lutathera\textsuperscript{®} (lutetium 177 dotatate) was approved by the FDA for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors, including foregut, midgut, and hindgut neuroendocrine tumors in adults.

On July 30, 2018, AZEDRA (iobenguane I 131) injection was approved by the FDA for the treatment of adult and pediatric patient’s age 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

**Rationale**

This evidence review was created in July 2018 with a search of the MEDLINE database through June 1, 2019.

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 (QOL), 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, two domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent one 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 patients with locally advanced or metastatic somatostatin receptor-positive gastroenteropancreatic 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 question addressed in this evidence review is: Does Lu 177 dotatate improve the net health outcome in patients with treatment-refractory gastroenteropancreatic neuroendocrine tumors?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are patients with inoperable locally advanced or metastatic somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor who have progressed on first-line somatostatin analogues.

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

**Comparators**
The following 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 (eg, 5-fluorouracil, capecitabine, dacarbazine, oxaliplatin, streptozocin, temozolomide), everolimus, hepatic-directed therapy (eg, 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 amyelodysplastic syndrome, renal failure, and leukemia.

Timing
Neuroendocrine tumors are a group of heterogeneous malignancies and survival depends on multiple factors such as tumor type (location), tumor characteristics (high or low grade), and stage at diagnosis (locoregional or advanced metastasis). A one-year follow-up would generally be sufficient to assess median PFS in patients who have progressed after first-line therapy.

Setting
Treatment is administered in an inpatient care setting by an oncologist 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.

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 retrospective cohort ERASMUS study. Results of the NETTER-1 study were originally published by Strosberg et al (2017). However, the 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. Study characteristics and results are summarized in Tables 1 and 2.

In the NETTER-1 trial, patients 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 > 6months). 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.

Table 1. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NETTER-1</td>
<td>Belgium, France, Germany, Italy, Portugal, Spain, U.S.</td>
<td>41</td>
<td>2012-2016</td>
<td>Adults with metastasized or locally advanced, inoperable, histologically confirmed, progressive midgut NETs</td>
<td>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 177 dotatate dose and every 4 wk after completion of Lu 177 dotatate treatment until disease progression or week 76 of the trial</td>
</tr>
</tbody>
</table>

NET: neuroendocrine tumor.

Table 2. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median PFS (95% CI), mo</th>
<th>Median OS (95% CI), mo</th>
<th>ORR (95% CI), %</th>
<th>CR (95% CI), %</th>
<th>PR (95% CI), %</th>
<th>Median DOR (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NETTER-1</td>
<td></td>
<td></td>
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</table>
The purpose of 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.

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 Tables 3 and 4.

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 (ie, 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."

Table 3. Summary of Key Nonrandomized Trials Characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERASMUS Study</td>
<td>Retrospective cohort</td>
<td>Netherlands</td>
<td>2000-2012</td>
<td>Patients with somatostatin-positive GEP-NETs with a life expectancy of &gt;12 wk and Karnofsky Performance Scale score ≥50</td>
<td>360 patients given Lu 177 dotatate 7.4 GBq (200 mCi) every 6-13 wk for up to 4 doses</td>
<td>34.8 mo</td>
</tr>
</tbody>
</table>

GEP-NET: gastroenteropancreatic neuroendocrine tumor.

Table 4. Summary of Key Nonrandomized Trial Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Duration of Response (95% CI), mo</th>
<th>Overall Response Rate (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERASMUS Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>360</td>
<td>360</td>
</tr>
<tr>
<td>Lu 177 dotatate</td>
<td>35 (17 to 38)</td>
<td>16 (13 to 21)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

The purpose of the limitations tables (see Tables 5 and 6) 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 5. Relevance Limitations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intervention&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Comparator&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Outcomes&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Follow-Up&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERASMUS Study</td>
<td>28,29,</td>
<td>2. This was a single cohort study. There was no comparator.</td>
<td>2. Investigator-assessed ORR not a validated surrogate outcome measure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

ORR: overall response rate.

<sup>a</sup> 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.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> 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.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Allocation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Blinding&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-Up&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Power&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Statistical&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>NETTER-1</td>
<td>28,29,</td>
<td>1. Not blinded to treatment assignment</td>
<td>1. Baseline tumor assessments obtained for only 578/1214 (48%) of patients</td>
<td>2. FDA noted that protocol along with a statistical analysis plan was retrospectively generated</td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

FDA: Food and Drug Administration.


<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Follow-Up 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).
Section Summary: Gastroenteropancreatic Neuroendocrine Tumors Including Foregut, Midgut, and Hindgut Tumors
The evidence for use of Lu 177 dotatate consists of an open-labeled RCT and a retrospective cohort study. The RCT results showed a consistent statistically significant and clinically meaningful effect on overall response rate, PFS, and OS among patients 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 RCT and provide additional support for a clinical benefit of Lu 177 dotatate in patients with gastroenteropancreatic neuroendocrine tumors.

Bronchopulmonary or Thymus neuroendocrine tumors

Clinical Context and Therapy Purpose
The purpose of Lu 177 dotatate in patients 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 question addressed in this evidence review is: Does Lu 177 dotatate improve the net health outcome in patients with treatment-refractory bronchopulmonary or thymus somatostatin receptor-positive neuroendocrine tumor?

The following PICOTS were used to select literature to inform this review.

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

Interventions
The therapy being considered is Lu 177 dotatate.

Comparators
The following 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: everolimus, cisplatin plus etoposide, carboplatin plus etoposide, temozolomide, and radiotherapy.

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.

**Timing**

Neuroendocrine tumors are a group of heterogeneous malignancies and survival depends on multiple factors such as tumor type (location), tumor characteristics (high or low grade), and stage at diagnosis (locoregional or advanced metastasis). A one-year follow-up would generally be sufficient to assess median PFS in patients who have progressed after first-line therapy.

**Setting**

Treatment is administered in an inpatient care setting by an oncologist who is 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.

**Retrospective Studies**

The evidence for use of Lu 177 dotatate in patients with bronchopulmonary or thymus neuroendocrine tumors consists of the retrospective ERASMUS cohort study. 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 patients with bronchopulmonary or thymus neuroendocrine tumors. The FDA concluded that time to event analyses such as time to progression, PFS, and OS was 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 information on patients with bronchopulmonary or thymus neuroendocrine tumor was therefore obtained from the published ERASMUS study that included 23 patients with bronchopulmonary and 2 patients with thymus neuroendocrine tumor. 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 two patients with thymus neuroendocrine tumors were not reported.

The purpose of the limitations tables (see Tables 7 and 8) 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. Relevance Limitations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intervention&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Comparator&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Outcomes&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Follow-Up&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERASMUS Study&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>2. This was a single cohort study without a comparator</td>
<td>2. Investigator-assessed ORR not a validated surrogate outcome measure</td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

ORR: overall response rate.

<sup>a</sup> 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.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> 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.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Allocation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Blinding&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow Up&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Power&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Statistical&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERASMUS US Study&lt;sup&gt;31&lt;/sup&gt;</td>
<td>1. Participants not randomly allocated because design was a retrospective single cohort study</td>
<td>1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician</td>
<td>1. Baseline tumor assessment s obtained for only 578 (48%) of patients</td>
<td>2. FDA noted that protocol along with statistical analysis plan were retrospectively generated</td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

FDA: Food and Drug Administration.


<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
Follow-Up 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).

Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

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 that included a small number of patients with bronchopulmonary (n=23) and thymus (n=2) neuroendocrine tumors. Results for the two patients with thymus neuroendocrine were not reported separately. 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 four planned doses. Dose reductions were reported for 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 four 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 iobenguane I 131 in patients 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 question addressed in this evidence review is: Does iobenguane I 131 improve the net health outcome in patients with unresectable locally advanced or metastatic pheochromocytoma and paraganglioma?

The following PICOs were used to select literature to inform this review.
Patients
The relevant population of interest are patients with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma.

Interventions
The therapy being considered is iobenguane I 131 injection. Iobenguane is a radiolabeled structural analog of norepinephrine that binds to norepinephrine reuptake transporter on chromaffin cells within adrenal glands. Due to its structural similarity to norepinephrine, iobenguane is actively transported by norepinephrine reuptake transporter and accumulates within tumor cells. The beta and gamma radiation resulting from the radioactive decay of I131 destroys tumor cells. Treatment is administered in an inpatient care setting by an oncologist 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.

Comparators
For patients with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma, the relevant comparator is the current standard of care that differs based on tumor and patients 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 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.

Under a special protocol assessment, a new primary endpoint in oncology using reduction in the antihypertensive medication of at least 50% for at least 6 months was used in the pivotal trial. This endpoint was considered specifically to measure the antitumor activity of iobenguane I 131 in patients with pheochromocytoma or paraganglioma because hypertension is a key contributor to the disease-associated morbidity and is correlated with decreased tumor activity. Further, evidence that iobenguane I 131 demonstrated anti-tumor activity, and not a merely antihypertensive activity, the primary endpoint was supported by an evaluation of ORR by established response criteria, i.e. radiologic response by RECIST.

Non-Randomized Studies
The evidence for use of iobenguane I 131 for patients with pheochromocytoma or paraganglioma consists of the multicenter, open-label, single-arm prospective
MIP-IB12B (NCT00874614) study that included 74 intention-to-treat participants. Study characteristics and results are summarized in Tables 9 and 10.

In the pivotal trial, patients age 12 years and old with a diagnosis of either pheochromocytoma or paraganglioma who were ineligible for curative therapy who failed a prior therapy were included. The primary efficacy outcome measure was the proportion of patients with 50% or greater reduction (including discontinuation) of all antihypertensive medication(s) lasting for at least 6 months after administering the last therapeutic dose of iobenguane I 131. Secondary efficacy outcome measures included best confirmed overall tumor response by RECIST 1.0 including complete response and partial response, changes from baseline in overall QOL, and OS. A total of 74 patients received the dosimetric dose. Following dosimetry, 68 patients received at least 1 therapeutic dose, and 50 patients received 2 therapeutic doses administered at least 90 days apart. The study period consists of a 12-month efficacy phase and a 4-year long-term follow-up phase. In these heavily pre-treated patients with pheochromocytoma or paraganglioma, 25% patients met the definition of the primary outcome measure and 22% achieved best overall response as per RECIST among patients given at least one therapeutic dose of iobenguane I 131.

**Table 9. Summary of Key Nonrandomized Trials Characteristics**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Type</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP-IB12B</td>
<td>Single-arm prospective cohort</td>
<td>US</td>
<td>10</td>
<td>June 2009 to February 2021&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Patients with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma</td>
<td>Iobenguane I 131 (n=74)</td>
<td>1 year</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.

<sup>a</sup> Estimated study completion date

**Table 10. Summary of Key Nonrandomized Trial Results**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Proportion of responders (95% CI)</th>
<th>Proportion with ORR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% Responders with duration of response ≥ 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP-IB12B [FDA review, Label]&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>68</td>
<td>68</td>
<td>15</td>
</tr>
</tbody>
</table>
Iobenguanen I 131 | 25% (16.2 to 37.5%) | 22% (14 to 33%) | 53%b

CI: confidence interval; FDA: Food and Drug Administration; ORR: overall response rate.

*a Best confirmed overall tumor response: a response of CR, or PR that was confirmed by repeat assessment performed no less than 4 weeks after the criteria for response were first met

b Median duration of response was 6.5 months

The purpose of a study limitations assessment is to identify notable limitations detected in each study (See Table 11 and 12). 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 study limitation analysis is not comprehensive, no notable limitations were identified for studies evaluated in this section.

Table 11. Relevance Limitations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow-Up⁵</th>
</tr>
</thead>
</table>

FDA: Food and Drug Administration.

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.

⁵ Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Follow-Up⁶</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP-IB12B</td>
<td></td>
<td>1. Participants not randomly allocated 4.</td>
<td>1. Not blinded to treatment assignment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section Summary: Pheochromocytoma and Paraganglioma
The evidence for use of iobenguane I 131 consist of a single-arm prospective study that the reported primary endpoint was achieved by 25% of patients (95% CI 16.2% to 36.5%), and antitumor activity of Iobenguane I 131 was demonstrated with 22.1% of patients having a confirmed, centrally reviewed partial response (95% CI: 13.6% to 32.7%). Of these, 53% of patients who responded to therapy maintained a duration of response for at least 6 months. The single-arm nature of the trial prevents adequate interpretation of the results of time to the event endpoint of OS which was a secondary endpoint of the trial. Given the severity and rarity of the disease condition with an associated high degree of morbidity and mortality, especially in metastatic disease, these outcomes represents a clinically meaningful benefit for patients. Specifically, a decrease in the incidence and severity of hypertension represented by a 50% or greater decrease in antihypertensive medications for at least 6 months experienced by 25% of patients, in conjunction with an observed antitumor response of 22%, represents a clinically meaningful benefit for patients. The evidence is sufficient that the treatment results in an improvement in net health outcomes.

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 a randomized, open-labeled trial and a retrospective cohort study. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. The RCT results showed a consistent statistically significant and clinically meaningful effect on overall response rate, PFS, and OS among patients 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 RCT and provide
additional support for a clinical benefit of Lu 177 dotatate in patients with a gastroenteropancreatic neuroendocrine tumor. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a treatment-refractory bronchopulmonary or thymus neuroendocrine tumors who receive Lu 177 dotatate, the evidence includes a retrospective cohort study. The relevant outcomes are OS, disease-specific survival, QOL, 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 two patients with thymus neuroendocrine tumors were not reported. The FDA in its review of the ERASMUS study for patients 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. Of note, despite the current evidence base, National Comprehensive Cancer Network guidelines give a category 2A recommendation for use of Lu 177 dotatate for the treatment of bronchopulmonary and thymic locoregional advanced or distant metastases neuroendocrine tumors if there are clinically significant tumor burden and low grade (typical) or evidence of progression or intermediate grade (atypical). The evidence is insufficient to determine the effects of technology on health outcomes.

For individuals with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy and who receive iobenguane I 131, the evidence includes a single-arm prospective cohort study. The relevant outcomes include OS, disease-specific survival, QOL, treatment-related mortality and morbidity. The pivotal study reported that 25% of patients (95% CI 16.2% to 36.5%) met the primary endpoint of reduction in antihypertensive medication of at least 50% for at least 6 months along with 22.1% of patients having a confirmed, centrally reviewed partial response (95% CI: 13.6% to 32.7%). Of these, 53% of patients who responded to therapy maintained a duration of response for at least 6 months. The single-arm nature of the trial prevents adequate interpretation of the results of time to the event endpoint of OS which was a secondary endpoint of the trial. Given the severity and rarity of the disease condition with an associated high degree of morbidity and mortality, especially in metastatic disease, these outcomes represents a clinically meaningful benefit for patients. As with all other radiopharmaceuticals, iobenguane I 131 is associated with an increased risk for secondary hematologic malignancy including myelodysplastic syndrome or acute leukemias. Due to the risk of serious adverse reactions, iobenguane I 131 is only indicated for patients with unresectable, locally advanced or metastatic paraganglioma who require systemic anticancer therapy and have no other known curative options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.
SUPPLEMENTAL INFORMATION
Practice Guidelines and Position Statements
The National Comprehensive Cancer Network guidelines (v.1.2019) for neuroendocrine and adrenal tumors added key eligibility criteria for patients treated with lutetium 177 dotatate for neuroendocrine tumors. Eligibility criteria include low or intermediate grade neuroendocrine tumor (proliferation index Ki-67 < 20%), detection of somatostatin receptor expression using somatostatin-based receptor imaging, and adequate bone marrow, renal and hepatic function. Table 13 summarizes the National Comprehensive Cancer Network guidelines for neuroendocrine and adrenal tumors.34

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

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Recommendation Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-gut locoregional advanced or distant metastases gastrointestinal neuroendocrine tumors after disease progression on somatostatin analogues</td>
<td>1</td>
</tr>
<tr>
<td>Bronchopulmonary/thymic locoregional advanced or distant metastases neuroendocrine tumors if there is clinically significant tumor burden and low grade (typical) or evidence of progression or intermediate grade (atypical)</td>
<td>2A</td>
</tr>
<tr>
<td>Locoregional advanced or distant metastases gastrointestinal neuroendocrine tumors after disease progression on somatostatin analogues</td>
<td>2A</td>
</tr>
<tr>
<td>Locoregional advanced or distant metastases pancreatic neuroendocrine tumors after disease progression on somatostatin analogues</td>
<td>2A</td>
</tr>
</tbody>
</table>

The National Comprehensive Cancer Network guidelines (v.1.2019) for neuroendocrine and adrenal tumors gives iobenguane I 131 category 2A recommendation for treatment of patients with locally unresectable or distant metastatic tumors with positive MIBG (iobenguane) scan.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 14.

#### Table 14. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03325816a</td>
<td>Phase I/II Trial of Anti-PD-1 Checkpoint Inhibitor Nivolumab and 177Lu-DOTA0-Tyr3-Octreotate for Patients With Extensive-Stage Small Cell Lung Cancer</td>
<td>56</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>NCT03206060</td>
<td>Lu-177-DOTATATE (Lutathera) in Therapy of Inoperable Pheochromocytoma/Paraganglioma</td>
<td>90</td>
<td>Jan 2024</td>
</tr>
<tr>
<td>NCT00874614</td>
<td>A Phase II Study Evaluating the Efficacy and Safety of Ultratrace Iobenguane I 131 in Patients With Malignant Relapsed/Refractory Pheochromocytoma/Paraganglioma</td>
<td>74</td>
<td>Feb 2021</td>
</tr>
<tr>
<td>NCT03561259</td>
<td>A Phase II Single-arm Study of Therapeutic Iobenguane (131-I) for Relapsed, High-risk Neuroblastoma Subjects</td>
<td>65</td>
<td>Mar 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

#### REFERENCES


Billing Coding/Physician Documentation Information

A9513  Lutetium Lu 177, dotatate, therapeutic, 1 mCi (New Code 1/1/2019)

C9031  Lutetium Lu 177, dotatate, therapeutic, 1 mCi (deleted eff 1/1/2019)

Additional Policy Key Words

N/A

Policy Implementation/Update Information

9/1/18  New Policy. Considered Medically Necessary when criteria is met.

9/1/19  Policy statement added that Iobenguane I 131 is considered medically necessary when the specified conditions are met.

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