

## MEDICAL / PHARMACY POLICY – 6.01.525

# Therapeutic Radiopharmaceuticals in Oncology

BCBSA Ref. Policy: 6.01.60 & 5.01.43

Effective Date: Apr. 1, 2026

Last Revised: Mar. 10, 2026

Replaces: 6.01.60


RELATED MEDICAL POLICIES:

5.01.544 Prostate Cancer Targeted Therapies

8.01.53 Cellular Immunotherapy for Prostate Cancer

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)  
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

## Introduction

Radiopharmaceuticals are a way of delivering radiation to the body. They combine both specific drugs and precise amounts of radiation. Depending on the drug and the type of radiation, the drug can either be swallowed or delivered directly into a vein. The drug and radiation then travel throughout the body. The specified organ then takes up the drug, which delivers the radiation to its intended target. In small amounts, this technique is used to help diagnose medical problems. In larger doses, radiopharmaceuticals are used to treat some types of cancer. This policy describes when various therapeutic radiopharmaceuticals may be considered medically necessary when used to treat certain types of cancers.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

Click on the hyperlinks below to navigate to the section pertaining to that drug:

Lutathera (lutetium 177 Lu 177 dotatate)

Pluvicto (lutetium Lu 177 vipivotide tetraxetan)

Xofigo (radium Ra 223 dichloride)

Drug	Medical Necessity
<b>Lutathera (lutetium 177 [Lu 177] dotatate)</b>	<p><b>Lutathera (lutetium 177 [Lu 177] dotatate) treatment may be considered medically necessary when ALL the following criteria are met:</b></p> <ul style="list-style-type: none"><li>• The individual is aged 12 years or older</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Has documented low or intermediate grade (Ki-67 index less than or equal to 20%), locally advanced or metastatic, gastroenteropancreatic (including foregut, midgut, and hindgut) neuroendocrine tumor</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Has documented somatostatin receptor expression of a neuroendocrine tumor as detected by somatostatin receptor-based imaging (<sup>68</sup>Ga-dotate, <sup>64</sup>Cu-Dotatate, or <sup>68</sup>Ga-Dotatoc positron emission tomography [PET]), or somatostatin receptor scintigraphy) (see <a href="#">Related Information</a>)</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Is not receiving long-acting somatostatin analogues (e.g., octreotide long-acting release or lanreotide) for at least 4 weeks prior to initiating Lu 177 dotatate and has discontinued use of short-acting octreotide for at least 24 hours prior to initiating Lu 177 dotatate</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Does not have severe renal impairment (creatinine clearance, less than 40 mL/min)</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Has adequate bone marrow and hepatic function as determined by the treating physician</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Has documented <a href="#">Karnofsky Performance Status</a> score of 60 or greater or the equivalent <a href="#">Eastern Cooperative Oncology Group</a> (ECOG) Performance Status score of 2 or less</li></ul>



Drug	Medical Necessity
	<p><b>AND</b></p> <ul style="list-style-type: none"> <li>Long-acting octreotide 30 mg IM is administered between 4 and 24 hours after each Lutathera dose</li> </ul>
<p><b>Pluvicto (lutetium Lu 177 vipivotide tetraxetan [Lu-177-PSMA-617])</b></p>	<p><b>Pluvicto (lutetium Lu 177 vipivotide tetraxetan [Lu-177-PSMA-617]) may be considered medically necessary for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) when ALL the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has been diagnosed with mCRPC</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has prostate-specific membrane antigen (PSMA)-positive as demonstrated by Gallium Ga 68 PSMA-11 imaging agent (e.g., Locametz, Illuccix) or piflufolastat F 18 imaging agent (e.g., Pylarify), which are corresponding radioactive diagnostic agents for positron emission tomography (PET)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has been previously treated with an androgen receptor (AR) pathway inhibitor (e.g., flutamide, nilutamide, bicalutamide, enzalutamide, apalutamide, darolutamide)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has received prior taxane-based chemotherapy (e.g., docetaxel, cabazitaxel) OR it is considered appropriate to delay taxane-based chemotherapy</li> </ul>
<p><b>Xofigo (radium Ra 223 dichloride)</b></p>	<p><b>Xofigo (radium Ra 223 dichloride) may be considered medically necessary when used for the treatment of adults with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease (e.g., lungs, liver, lymph node greater than 3cm).</b></p>

Drug	Investigational
<p><b>As listed</b></p>	<p><b>Lutathera treatment is considered investigational in all other situations in which the above criteria are not met, including for pheochromocytoma or paraganglioma.</b></p>



Drug	Investigational
	<p>Lutathera treatment greater than a total of 4 doses is considered investigational.</p> <p>Pluvicto is considered investigational for the treatment of mCRPC when the above criteria are not met.</p> <p>Pluvicto treatment greater than a total of 6 doses (administered once every 6 weeks) is considered investigational.</p> <p>Xofigo treatment greater than a total of 6 doses, typically delivered at 4-week intervals, is considered investigational.</p> <p>The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.</p>

Length of Approval	
Approval	Criteria
<b>Initial authorization</b>	<p>Lutathera may be approved up to 12 months and up to a total of 4 doses.</p> <p>Pluvicto may be approved up to 12 months and up to a total of 6 doses (administered once every 6 weeks; see <a href="#">Related Information</a> for dosage modifications).</p> <p>Xofigo may be approved up to 12 months and up to a total of 6 doses (typically administered every 4 weeks).</p>
<b>Re-authorization criteria</b>	<p>Lutathera treatment greater than a total of 4 doses is considered investigational.</p> <p>Pluvicto treatment greater than a total of 6 doses (administered once every 6 weeks) is considered investigational.</p>



## Length of Approval

Approval	Criteria
	<b>Xofigo treatment greater than a total of 6 doses, typically delivered at 4-week intervals, is considered investigational.</b>

## Documentation Requirements

**The Individual's medical records submitted for review for all conditions should document that medical necessity criteria are met.**

### Lutathera

**For initial treatment the record should include the following:**

- History and physical supporting the diagnosis of low or intermediate grade (Ki-67 index less than or equal to 20%), locally advanced or metastatic, gastroenteropancreatic (including foregut, midgut, and hindgut) neuroendocrine tumor
- Result of somatostatin receptor-based imaging (<sup>68</sup>Ga-dotate, <sup>64</sup>Cu-Dotatate, or <sup>68</sup>Ga-Dotatoc positron emission tomography or computed tomography, which is preferred) or somatostatin receptor scintigraphy confirming somatostatin receptor expression of a neuroendocrine tumor
- Documentation that individual is not receiving long-acting somatostatin analogues (e.g., octreotide long-acting release or lanreotide) for at least 4 weeks prior to initiating Lu 177 dotatate and has discontinued use of short-acting octreotide for at least 24 hours prior to initiating Lu 177 dotatate
- Result of creatinine clearance (less than 40 mL/min), confirming that individual does not have severe renal impairment
- Documentation of adequate bone marrow and hepatic function
- Documented **Karnofsky Performance Status** score of 60 or greater

**For continuation of treatment, documentation of the following:**

- No recurrent grade 2, 3, or 4 thrombocytopenia
- No recurrent grade 3 or 4 anemia and neutropenia
- No recurrent hepatotoxicity
- No recurrent grade 3 or 4 nonhematologic toxicity
- No renal toxicity requiring a treatment delay of 16 weeks or longer

### Pluvicto

- The individual is an adult (19 years of age or older) with metastatic castration-resistant prostate cancer (mCRPC)



## Documentation Requirements

- Is prostate-specific membrane antigen (PSMA)-positive as demonstrated by Gallium Ga 68 PSMA-11 imaging agent (e.g., Locametz, Illuccix) or piflufolastat F 18 imaging agent (e.g., Pylarify)
- Has previously been treated with an androgen receptor (AR) pathway inhibitor (e.g., flutamide, nilutamide, bicalutamide, enzalutamide, apalutamide, darolutamide)
- Has received prior taxane-based chemotherapy (e.g., docetaxel, cabazitaxel) OR it is considered appropriate to delay taxane-based chemotherapy

### Xofigo

- The individual is an adult (19 years of age or older) with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease (e.g., lungs, liver, lymph node greater than 3 cm)

## Coding

Code	Description
<b>HCPCS</b>	
A9513	Lutetium lu 177, dotatate, therapeutic, 1 mCi (Lutathera)
A9606	Radium RA-223 dichloride, therapeutic, per UCI (Xofigo)
A9607	Lutetium lu 177 vipivotide tetraxetan, therapeutic, 1 mCi (Pluvicto)

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

### 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.

## **Lutathera (lutetium 177 [Lu 177] dotatate)**

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 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.

**Table 1** describes the grading of severity used in the Common Toxicity Criteria for Adverse Events (version 4.03).



**Table 1. Common Toxicity Criteria for Adverse Events, Version 4.03**

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.

**Table 2. Karnofsky Performance Status**

Karnofsky Performance Status Scale Definitions Rating (%) Criteria		
Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but can care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Source: [http://nccrc.org/files/news/karnofskyperformance\\_scale.pdf](http://nccrc.org/files/news/karnofskyperformance_scale.pdf) (Accessed April 7, 2025.)



**Table 3. Eastern Cooperative Oncology Group Performance Status**

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair

Source: [https://www.mactheknife.org/Scoring\\_systems/ECOG.html](https://www.mactheknife.org/Scoring_systems/ECOG.html) Accessed April 7, 2025.

## Pluvicto (Lutetium Lu 177 vipivotide tetraxetan)

Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) 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.

The recommended dose of Lu-177-PSMA-617 (Pluvicto) is 7.4 GBq (200 mCi) every 6 weeks for up to 6 doses.

Individuals should be well-hydrated during treatment.

Refer to the prescribing information for Lu-177-PSMA-617 for recommended dosage modifications for adverse reactions. The management of adverse reactions may require temporary dose interruption (extending the dosing interval from every 6 weeks up to every 10 weeks), dose reduction, or permanent discontinuation of treatment with Lu-177-PSMA-617. The dose of Lu-177-PSMA-617 may be reduced by 20% to 5.9 GBq (160 mCi) once; the dose should not be re-escalated.

Lu-177-PSMA-617 should be discontinued permanently if the individual develops any of the following:

- Recurrent Grade 3 or higher myelosuppression after one dose reduction



- Grade 3 or higher renal toxicity
- Recurrent renal toxicity after one dose reduction
- Recurrent Grade 3 dry mouth after one dose reduction
- Recurrent Grade 3 or higher gastrointestinal toxicity after one dose reduction
- Aspartate aminotransferase or alanine aminotransferase greater than 5 times the upper limit of normal in the absence of liver metastases
- Any unacceptable toxicity
- Any serious adverse reaction that requires treatment delay of greater than 4 weeks
- Any recurrent Grade 3 or 4 or persistent and intolerable Grade 2 adverse reaction after one dose reduction

See [Table 1](#) for common toxicity criteria for adverse events.

## Evidence Review

### Description

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.

Lutetium Lu 177 vipivotide tetraxetan (Pluvicto), commonly abbreviated as Lu-177-PSMA-617, is a radioligand therapy that targets prostate-specific membrane antigen (PSMA), which is highly expressed on prostate cancer cells. Lu-177-PSMA-617 is indicated for use in adults with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have already been treated with other anticancer treatments, including androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. Gallium Ga 68 gozetotide (Locametz) is a corresponding



radioactive diagnostic agent for positron emission tomography (PET) of PSMA-positive lesions, including for the selection of individuals with mCRPC for whom Lu-177-PSMA-617 therapy is indicated.

## 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 four subgroups: typical carcinoid tumor, atypical carcinoid tumor, large-cell neuroendocrine carcinoma, and small-cell lung carcinoma.<sup>2</sup> 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.<sup>3</sup>

Neuroendocrine tumors are classified as orphan diseases by the US 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.<sup>4</sup>

### **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 tumor) resulting in an average diagnosis delay of five to seven years after symptom onset.<sup>5</sup> 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.,<sup>111</sup> 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.<sup>6</sup> 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<sup>7</sup> while the median overall survival for small bowel neuroendocrine tumors has been reported as 7.9 years.<sup>8</sup>

## **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.<sup>9</sup> However, the role of somatostatin analogues in individuals with nonfunctioning neuroendocrine tumors is unclear.<sup>10</sup>

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.<sup>11,12</sup>



## ***Second-Line Treatment Options***

Currently, there is no data to support a specific sequence of therapies and only streptozocin (Zanosar), everolimus (Afinitor/Zortress), and sunitinib (Sutent) 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.<sup>13</sup> Everolimus (Afinitor/Zortress), an oral mechanistic target of rapamycin inhibitor, has been shown to significantly prolong PFS vs placebo in individuals with pancreatic neuroendocrine tumors (RADIANT-3 trial).<sup>14</sup> and lung and gastrointestinal neuroendocrine tumors nonfunctional (RADIANT-4 trial).<sup>15</sup> 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 end point of PFS.<sup>16</sup>

## ***Tyrosine Kinase Receptor Inhibitors***

Neuroendocrine tumors frequently overexpress the vascular endothelial growth factor and receptor. Sunitinib (Sutent) 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.<sup>13</sup> 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.<sup>17</sup> 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 individuals 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.<sup>18</sup>

## ***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.<sup>19</sup> 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 Adjallé R, Plouin PF, Pacak K, et al. Treatment of malignant pheochromocytoma. 2009;41(9): 687-96. PMID 19672813].

The average age of diagnosis is 43 years old. The estimated annual incidence of pheochromocytoma and paraganglioma is approximately 1 in 300,000 population.<sup>20</sup> 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.<sup>21</sup> In addition, the medical overall and disease-specific survival were 24.6 and 33.7 years for pheochromocytoma and paraganglioma, respectively.<sup>22</sup>



## 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 <sup>123</sup>I-metaiodobenzylguanidine (MIBG) scintigraphy, octreotide scan, and fluorodeoxyglucose- PET scan is used to further determine whether the tumors are malignant and metastatic.<sup>19</sup>

Certain genetic disorders such as multiple endocrine neoplasia 2 syndrome, von Hippel-Lindau syndrome, Neurofibromatosis type 1, hereditary paraganglioma syndrome<sup>23</sup> are considered risk factors for pheochromocytomas and paragangliomas and therefore genetic testing is recommended for all individuals with pheochromocytoma or paraganglioma.<sup>19</sup>

## 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.<sup>24</sup>

## Peptide Receptor Radionuclide Therapy: Iobenguane I 131

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.<sup>25,26</sup> Tyrosine kinase receptor inhibitors such as sunitinib (Sutent) have also been used.<sup>27</sup>

## Metastatic Castration-Resistant Prostate Cancer

Prostate cancer is the second leading cause of cancer-related deaths among American men with 313,780 new cases and 35,770 disease-related deaths estimated for 2025.<sup>46</sup> About 6 in 10 cases of prostate cancer are diagnosed in men who are 65 years of age or older, and the disease is



rare in men under 40 years of age. Prostate cancer disproportionately affects African American men and Caribbean men of African ancestry compared to men of other races. The disease is less common in Asian American, Hispanic, and Latino men than in non-Hispanic White men. The reasons for these racial and ethnic differences are not well understood. Typically, prostate cancer is suspected based on increased levels of prostate-specific antigen (PSA) upon screening.

## Grading

Clinical staging is based on the digital rectal exam and biopsy results. T1 lesions are not palpable while T2 lesions are palpable but appear to be confined to the prostate. T3 lesions extend through the prostatic capsule, and T4 lesions are fixed to or invade adjacent structures. The most widely used grading scheme for a prostate biopsy is the Gleason system.<sup>47</sup> It is an architectural grading system ranging from 1 (well-differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is a high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization.<sup>48</sup> A cross-walk of these grading systems are shown in [Table 4](#).

**Table 4. Prostate Cancer Grading Systems**

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well-differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9-10	Undifferentiated (high grade)

## Treatment

Early localized disease can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose prostate cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous.<sup>46</sup> In individuals with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly



chemotherapy. Androgen deprivation therapy (ADT) is generally the initial treatment for individuals with advanced prostate cancer. Unfortunately, while ADT is effective at producing tumor response and improving quality of life, most individuals' disease will eventually progress on ADT.

### **Castration-Resistant Prostate Cancer**

Prostate cancer that progresses while the individual is on ADT is referred to as castration-resistant prostate cancer (CRPC).<sup>46</sup> Androgen pathways are important in the progression of CRPC, therefore, even after progression, continued ADT is generally used in conjunction with other treatments. Several drugs have been developed that either inhibit enzymes involved in androgen production or inhibit the androgen receptor, such as abiraterone and enzalutamide. Taxane chemotherapy with docetaxel or cabazitaxel may also be used after progression. Immunotherapy (sipuleucel-T) or radium 223 are additional options for select men.

### **Prostate-Specific Membrane Antigen–Positive Metastatic Castration-Resistant Prostate Cancer**

Prostate-specific membrane antigen (PSMA) is a transmembrane glutamate carboxypeptidase that is highly expressed on prostate cancer cells and high PSMA expression is an independent biomarker of poor prognosis.<sup>49</sup> Metastatic lesions are PSMA-positive in most individuals with metastatic CRPC (mCRPC) and high expression has been independently associated with reduced survival. More recently, radioligand therapies such as lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) have demonstrated the ability to selectively target prostate cancer cells in individuals who have PSMA-positive mCRPC

### **Radionuclide Therapy: Lutetium Lu 177 vipivotide tetraxetan (Pluvicto)**

Lu-177-PSMA-617 is a radioligand therapeutic agent with 2 components: a drug that delivers the therapy to cancer cells and a radioactive particle.<sup>50</sup> In the case of Lu-177-PSMA-617, the delivery vehicle is PSMA-617 and the radioactive component is lutetium-177. Upon binding of Lu-177-PSMA-617 to PSMA-expressing cells, the beta-minus emission from lutetium-177 delivers radiation to PSMA-expressing cells, as well as to surrounding cells, and induces DNA damage which can lead to cell death. Individuals should be selected for treatment with Lu-177-PSMA-617 using gallium Ga 68 gozetotide or an approved PSMA-11 imaging agent based on PSMA expression in tumors.



## **Xofigo (radium Ra 223)**

Xofigo (radium Ra 223) is a therapeutic radiopharmaceutical that was approved by the US Food and Drug Administration (FDA) in 2013 and is used for the treatment of individuals with castration-resistant prostate cancer with symptomatic bone metastases. It should not be given to those with metastases to the liver, lung or enlarged lymph nodes greater than 3 cm. It delivers alpha-emitting radiation particles directly to tumors found in the bone, limiting damage to surrounding healthy tissue, including the bone marrow. It is given by an IV injection at a dose of 50kBq (1.35 microcurie) per kg body weight, once every 4 weeks for a total of 6 injections. It is given either by a radiation oncologist or a nuclear medicine physician.

## **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, a multicenter registry, 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 (RCT) results showed a consistent statistically significant and clinically meaningful effect on overall response rate, progression-free survival (PFS), and overall survival 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 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 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, a multicenter registry, and a bicenter, retrospective case series. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The retrospective cohort study included a small number of individuals with bronchopulmonary (n=23) or thymus (n=2) neuroendocrine tumors. Among the 23 individuals 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 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 individuals 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 individuals with predominantly atypical carcinoid bronchopulmonary tumors, finding a median PFS and OS of 23 months and 59 months, respectively. 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) tumor or evidence of progression or intermediate grade (atypical) tumor. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 two case series. Relevant outcomes include overall survival, 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 progression-free survival (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 three months. Disease regression was reported in 5/14 individuals with available CT imaging. Out of 16 individuals with available iobenguane scans, 10 individuals had mild or negative uptake. However, individual 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.

For individuals with PSMA-positive mCRPC who have failed other anticancer therapies, including androgen receptor pathway inhibition and/or taxane-based chemotherapy, who receive Lutetium (Lu) 177 vipivotide tetraxetan (Lu177-PSMA-617), the evidence includes a systematic review and two RCTs. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The systematic review, which included a heterogeneous population of individuals with mCRPC, demonstrated a higher proportion of individuals responding to PSMA-targeted radionucleotide therapy based on a PSA decrease of 50% or more compared to controls; the review was also limited by the inclusion of mostly retrospective studies with small numbers of individuals. The VISION RCT compared Lu-177-



PSMA-617 plus investigator-determined standard of care (SOC) to SOC alone in individuals with PSMA-positive mCRPC who had been treated with AR pathway inhibitors and taxane-based chemotherapy. Results demonstrated that Lu-177-PSMA-617 plus SOC significantly prolonged the median overall survival (15.3 vs. 11.3 months) and radiographic PFS (8.7 vs. 3.4 months) compared to SOC alone. The incidence of Grade 3 or higher adverse events was greater with Lu-177-PSMA-617 than without (52.7% vs. 38.0%). The phase 2 TheraP trial compared Lu-177-PSMA-617 to cabazitaxel. Unlike the VISION trial, in TheraP, previous treatment with AR pathway inhibitors was not necessary for participants. Also, the TheraP trial used two PET/computed tomography (CT) scans to identify PSMA-positive status and excluded individuals with discordant findings using gallium-68-labeled PSMA-11 and 2-fluorine-18[18F]fluoro-2-deoxy-D-glucose (FDG). The primary endpoint of PSA response, defined by a reduction of at least 50% from baseline, was achieved more often by individuals who received Lu-177-PSMA-617 (66%) compared to cabazitaxel (37%). In this RCT, the incidence of Grade 3 or higher adverse events was greater with cabazitaxel (53%) compared to Lu-177-PSMA-617 (33%). In a subsequent publication of this study with a median follow-up of 35.7 months, the OS did not differ between treatment groups (19.1 vs. 19.6 months). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in [Table 5](#).

**Table 5. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
<a href="#">NCT03206060</a>	Lu-177-DOTATATE (Lutathera) in Therapy of Inoperable Pheochromocytoma/ Paraganglioma	13090	Jan 2027
<a href="#">NCT04665739</a>	Testing Lutetium Lu 177 Dotatate in Patients with Somatostatin Receptor Positive Advanced Bronchial Neuroendocrine Tumors	78	Jan 2033
<a href="#">NCT04086485</a>	Lu-177-DOTATATE (Lutathera) in Combination with Olaparib in Inoperable Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)	56	Jan 2028



NCT No.	Trial Name	Planned Enrollment	Completion Date
<a href="#">NCT03691064</a>	Post-Authorization Long-Term Safety Study of Lutathera (SALUS)	1014	Jun 2028
<a href="#">NCT03972488<sup>a</sup></a>	A Phase III Multi-center, Randomized, Open-label Study to Evaluate the Efficacy and Safety of Lutathera in Patients With Grade 2 and Grade 3 Advanced GEP-NET (NETTER-2)	226	Oct 2027
<a href="#">NCT04954820</a>	A Prospective Randomized Phase II Study Assess the Schema of Retreatment With Lutathera® ([177Lu]Lu-DOTA-TATE) in Patients With New Progression of Intestinal Well-differentiated Neuroendocrine Tumor (ReLUTH)	146	Oct 2031
<a href="#">NCT01876771</a>	An Open-label Phase II Study of Lutetium-177 [DOTA0, Tyr3] Octreotate (Lu-DOTA-TATE) Treatment in Patients With Somatostatin Receptor Positive Tumours	500	Dec 2042
<a href="#">NCT06121271</a>	Trial of Lu-177 DOTATATE (Lutathera) in Unlicensed Indications Including Bronchial and Thymic Neuroendocrine Tumour, Paraganglioma/Phaeochromocytoma, Medullary Thyroid Carcinoma, and Repeat Peptide Receptor Radionuclide Therapy	110	Nov 2027
<a href="#">NCT06320067</a>	Studying Treatments in Patients Receiving Androgen Deprivation Therapy (ADT) and Androgen Receptor Signalling Inhibitors (ARSI) for Metastatic Prostate Cancer: Evaluation of Drug and Radiation Efficacy: A 2nd Multi-arm Multi-stage Randomised Controlled Trial (STAMPEDE2).	8000	Mar 2034
<a href="#">NCT06496581</a>	A Randomized Phase III Trial Evaluating the Efficacy and Safety of Standard of Care +/- 177Lu-PSMA617 in de Novo Metastatic Hormone-sensitive Prostate Cancer Patients Having a PSA ≥ 0.2 ng/mL at 6-8 Months After Systemic Treatment Initiation	500	Aug 2039
<a href="#">NCT04720157<sup>a</sup></a>	An Open-label, Randomized, Phase III Study Comparing 177Lu-PSMA-617 in Combination With Standard of Care, Versus Standard of Care Alone, in Adult Male Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC)	1144	Feb 2026
<a href="#">NCT04689828<sup>a</sup></a>	PSMAfore: A Phase III, Open-label, Multi-Center, Randomized Study Comparing 177Lu-PSMA-617 vs. a Change of Androgen Receptor-directed Therapy in the Treatment of Taxane Naïve Men With Progressive Metastatic Castrate Resistant Prostate Cancer	470	Sep 2025
<a href="#">NCT04663997</a>	A Randomized Phase II Study of 177 LuPSMA-617 vs Docetaxel in Patients With Metastatic Castration-Resistant Prostate Cancer and PSMA-Positive Disease	200	Dec 2025



NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05150236	Phase II Study of Radionuclide 177Lu-PSMA Therapy Versus 177Lu-PSMA in Combination With Ipilimumab and Nivolumab for Men With Metastatic Castration Resistant Prostate Cancer (mCRPC)	93	Dec 2024

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or the 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).<sup>42</sup> Regarding individual 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 individuals;
- 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 individual release criteria in accordance with federal and/or local regulations.

### ***American Society of Clinical Oncology***

The American Society of Clinical Oncology (ASCO) guideline on systemic therapy in individuals with metastatic castration-resistant prostate cancer (mCRPC) was updated in May 2025.<sup>62</sup> Relevant recommendations regarding lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) are below:

"For patients previously treated with ADT [androgen-deprivation therapy], ARPI [androgen receptor pathway inhibition], and docetaxel, and have progressive mCRPC, the Panel recommends Lu-177-PSMA-617 for PSMA [prostate-specific membrane antigen]-positive disease or chemotherapy using cabazitaxel (evidence quality: moderate; strength of recommendation: strong)."

The Panel also states that "currently, the role of PSMA PET [positron emission tomography]-CT [computed tomography] is limited to identify PSMA-expressing tumors for patients who will benefit with Lu-177-PSMA-617. In selected patients, PSMA PET can be used to stage patients with a rising PSA [prostate-specific antigen] and concern for progression not visualized on conventional imaging. Prospective data on using PSMA PET scans for response assessment are still emerging, and at this time, the Panel does not recommend their routine use."

In 2023, ASCO published a rapid recommendation update related to Lu-177-PSMA-617 based on the Food and Drug Administration (FDA) approval of F-18 flutemetamol.<sup>63</sup> Their updated recommendation stated:

"The panel recommends that either Ga-68 PSMA-11, F-18 piflutemetamol, or F-18 flutemetamol be used as radiotracers to determine eligibility currently (type: informal consensus, benefits outweigh harms; evidence quality: low; strength of recommendation: weak)."

### ***National Comprehensive Cancer Network Guidelines***

The National Comprehensive Cancer Network (NCCN) guideline for prostate cancer (v2.2025) provides the following relevant recommendations with regard to the use of Lu-177-PSMA-617.<sup>60</sup>



"The NCCN Panel recommends Lu-177-PSMA-617 as a category 1, useful in certain circumstances treatment option for patients with  $\geq 1$  PSMA -positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy. PSMA-negative lesions are defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components  $\geq 1.0$  cm, lymph nodes  $\geq 2.5$  cm in short axis, and solid organ metastases  $\geq 1.0$  cm in size. Although the FDA has approved Ga-68 PSMA-11 for use with Lu-177-PSMA-617, the panel believes that F-18 piflufolastat PSMA and F-18 flotufolastat PSMA can also be used in the same space due to multiple reports describing the equivalency of these imaging agents."

The National Comprehensive Cancer Network (NCCN) guidelines (v.3.2025) for neuroendocrine and adrenal tumors have published key eligibility criteria for individuals 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. Due to lack of randomized data, the NCCN encourages participation in clinical trials of lutetium 177 dotatate for rare groups of neuroendocrine tumors including pancreatic neuroendocrine tumors, pheochromocytomas, paragangliomas, and bronchopulmonary/thymic neuroendocrine tumors.

**Table 6** summarizes the NCCN guidelines for neuroendocrine and adrenal tumors.<sup>43</sup>

**Table 6. Recommendations for Use of Lutetium 177 Dotatate for Neuroendocrine Tumors**

Treatment Category	Recommendation Category
<b>Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)</b>	
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 $\geq 10\%$ , and clinically significant tumor burden	2A
<b>Pancreatic Neuroendocrine Tumors (Well-Differentiated Grade 1/2)</b>	
Preferred regimen option in locoregional advanced and/or distant metastases after disease progression on somatostatin analogues	2A



Treatment Category	Recommendation Category
First-line option for locoregional advanced and/or distant metastases if somatostatin receptor-positive, Ki-67 ≥10%, and clinically significant tumor burden	2A
<b>Well-Differentiated Grade 3 Neuroendocrine Tumors</b>	
Option for favorable biology tumors (relatively low Ki-67, slow growing) if somatostatin receptor-positive	
<b>Pheochromocytoma/Paraganglioma</b>	
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 individuals 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.<sup>44</sup> The guideline states that there is some evidence to support using lutetium 177 dotatate in some individuals, 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 individuals with lung neuroendocrine tumors.<sup>45</sup> The final consensus statement was that peptide receptor radionuclide therapy may be an option for individuals with somatostatin receptor positive tumors (grade B recommendation).

**Medicare National Coverage**

There is no national coverage determination.



## Regulatory Status

On May 15, 2013, Xofigo (radium Ra 223 dichloride) was approved by the FDA for the treatment of individuals with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease.

On January 26, 2018, Lutathera (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 April 23, 2024 the FDA expanded the approval of this product and for the same indication to pediatric individuals 12 years and older.

On July 30, 2018, AZEDRA (iobenguane I 131) injection was approved by the FDA for the treatment of adult and pediatric individual's aged 12 years and older with iobenguane scan positive, unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. The manufacturer discontinued production of AZEDRA in August 2023 with the intention to ensure sufficient supply for existing individuals through Q1 2024.<sup>1</sup> The decision was not related to safety or efficacy concerns. Azedra is not further addressed in this policy.

An iobenguane I 123 product (AdreView) has been available since 2008. Use of this product is limited to diagnosis of metastatic pheochromocytoma or neuroblastoma, with no therapeutic indications. It is not reviewed in this policy.

On December 17, 2021, Illucix (gallium Ga 68 gozetotide) was approved by the FDA as a radioactive diagnostic agent indicated for PET of PSMA-positive lesions in men with prostate cancer with: 1) suspected metastasis who are candidates for initial definitive therapy or 2) suspected recurrence based on elevated serum PSA level.<sup>52 53</sup> The labeling was updated in March 2023 to include selection of individuals with metastatic prostate cancer for whom treatment with Lu-177-PSMA-617 is indicated.

On March 23, 2022, Pluvicto (lutetium Lu 177 vipivotide tetraxetan) was approved by the FDA for use in adult individuals with PSMA-positive mCRPC who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.<sup>50</sup> In March 2025, this indication was updated to also include individuals with PSMA-positive mCRPC who have been treated with AR pathway inhibition and are considered appropriate to delay taxane-based chemotherapy.<sup>50</sup>

On March 23, 2022, Locametz (gallium Ga 68 gozetotide) was approved by the FDA as a radioactive diagnostic agent indicated for PET of PSMA-positive lesions in men with prostate cancer: 1) with suspected metastasis who are candidates for initial definitive therapy; or 2) with



suspected recurrence based on elevated serum PSA level; or 3) for selection of individuals with metastatic prostate cancer, for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated.<sup>50,51</sup>

On May 5, 2022, Novartis announced that it had temporarily suspended production of Lutathera and Pluvicto 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.<sup>28</sup> 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.<sup>29</sup>

On May 26, 2022, Pylarify (piflufolastat F 18) was approved by the FDA as a radioactive diagnostic agent indicated for PET of PSMA-positive lesions in men with prostate cancer with: 1) suspected metastasis who are candidates for initial definitive therapy or 2) suspected recurrence based on elevated serum PSA level.<sup>51, 52</sup>

## References

1. Society of Nuclear Medicine and Molecular Imaging. Lantheus to Discontinue Production of Azedra. August 18, 2023; <https://snmmi.org/Web/News/Articles/Lantheus-to-Discontinue-Production-of-Azedra.aspx>. Accessed February 2, 2026.
2. Gustafsson BI, Kidd M, Chan A, et al. Bronchopulmonary neuroendocrine tumors. *Cancer*. Jul 01 2008; 113(1): 5-21. PMID 18473355
3. Bohnenberger H, Dinter H, König A, et al. Neuroendocrine tumors of the thymus and mediastinum. *J Thorac Dis*. Nov 2017; 9(Suppl 15): S1448-S1457. PMID 29201448
4. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol*. Oct 01 2017; 3(10): 1335-1342. PMID 28448665
5. Frilling A, Akerström G, Falconi M, et al. Neuroendocrine tumor disease: an evolving landscape. *Endocr Relat Cancer*. Oct 2012; 19(5): R163-85. PMID 22645227
6. Sorbye H, Strosberg J, Baudin E, et al. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer*. Sep 15 2014; 120(18): 2814-23. PMID 24771552
7. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis in patients with metastatic pancreatic endocrine carcinomas. *Pancreas*. Apr 2009; 38(3): 255-8. PMID 19066493
8. Ter-Minassian M, Chan JA, Hooshmand SM, et al. Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database. *Endocr Relat Cancer*. Apr 2013; 20(2): 187-96. PMID 23319495



9. Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol.* Aug 2015; 26(8): 1604-20. PMID 25646366
10. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut.* Jan 2012; 61(1): 6-32. PMID 22052063
11. Berg K, Leyden J, Goldstein G, et al. Neuroendocrine tumor European patient experience: results from the first global NET patient survey - a collaboration between the International Neuroendocrine Cancer Alliance and Novartis [abstract]. *Endocrine Abstracts.* 2015;37:EP1139.
12. O'Toole D, Ducreux M, Bommelaer G, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer.* Feb 15 2000; 88(4): 770-6. PMID 10679645
13. Strosberg J. Advances in the Treatment of Pancreatic Neuroendocrine Tumors (pNETs). *Gastrointest Cancer Res.* Jul 2013; 6(4 Suppl 1): S10-2. PMID 24312683
14. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* Feb 10 2011; 364(6): 514-23. PMID 21306238
15. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet.* Mar 05 2016; 387(10022): 968-977. PMID 26703889
16. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet.* Dec 10 2011; 378(9808): 2005-2012. PMID 22119496
17. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* Feb 10 2011; 364(6): 501-13. PMID 21306237
18. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Neuroendocrinology.* 2016; 103(2): 186-94. PMID 26731334
19. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* Jun 2014; 99(6): 1915-42. PMID 24893135
20. Lefebvre M, Foulkes WD. Pheochromocytoma and paraganglioma syndromes: genetics and management update. *Curr Oncol.* Feb 2014; 21(1): e8-e17. PMID 24523625
21. Hamidi O, Young WF, Gruber L, et al. Outcomes of patients with metastatic phaeochromocytoma and paraganglioma: A systematic review and meta-analysis. *Clin Endocrinol (Oxf).* Nov 2017; 87(5): 440-450. PMID 28746746
22. Hamidi O, Young WF, Iñiguez-Ariza NM, et al. Malignant Pheochromocytoma and Paraganglioma: 272 Patients Over 55 Years. *J Clin Endocrinol Metab.* Sep 01 2017; 102(9): 3296-3305. PMID 28605453
23. Pheochromocytoma and Paraganglioma Treatment. National Cancer Institute. August 25, 2022. <https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq>. Accessed February 2, 2026.
24. Gunawardane PTK, Grossman A. Phaeochromocytoma and Paraganglioma. *Adv Exp Med Biol.* 2017; 956: 239-259. PMID 27888488
25. Ayala-Ramirez M, Feng L, Habra MA, et al. Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas: insights from the largest single-institutional experience. *Cancer.* Jun 01 2012; 118(11): 2804-12. PMID 22006217
26. Fliedner SM, Lehnert H, Pacak K. Metastatic paraganglioma. *Semin Oncol.* Dec 2010; 37(6): 627-37. PMID 21167381
27. Ayala-Ramirez M, Choungnet CN, Habra MA, et al. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. *J Clin Endocrinol Metab.* Nov 2012; 97(11): 4040-50. PMID 22965939



28. Novartis. Novartis provides update on production of radioligand therapy medicines. May 5, 2022; <https://www.novartis.com/news/media-releases/novartis-provides-update-production-radioligand-therapy-medicines>. Accessed February 2, 2026.
29. Novartis. Novartis resumes production and delivery of radioligand therapy medicines ahead of schedule. June 30, 2022; <https://www.novartis.com/news/media-releases/novartis-resumes-production-and-delivery-radioligand-therapy-medicines-ahead-schedule>. Accessed February 2, 2026.
30. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. Jan 12 2017; 376(2): 125-135. PMID 28076709
31. Food and Drug Administration, Center for Drug Evaluation and Research. Application Number: 208700Orig1s000 Multi-Disciplinary Review. Addendum to Review, NDA 208700. 2018; [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/208700Orig1s000MultidisciplineR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208700Orig1s000MultidisciplineR.pdf). Accessed February 2, 2026.
32. Novartis Inc. Lutathera (lutetium Lu 177 dotatate) injection, for intravenous use administration of Lutathera (Prescribing Label). 2024; [https://www.novartis.com/us-en/sites/novartis\\_us/files/lutathera.pdf](https://www.novartis.com/us-en/sites/novartis_us/files/lutathera.pdf). Accessed February 2, 2026.
33. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. May 01 2008; 26(13): 2124-30. PMID 18445841
34. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-Term Efficacy, Survival, and Safety of [ 177 Lu-DOTA 0 ,Tyr 3 ]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. *Clin Cancer Res*. Aug 15 2017; 23(16): 4617-4624. PMID 28428192
35. Singh S, Halperin D, Myrehaug S, et al. [ 177 Lu]Lu-DOTA-TATE plus long-acting octreotide versus high dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. Jun 29 2024; 403(10446): 2807-2817. PMID 38851203
36. Mitjavila M, Jimenez-Fonseca P, Belló P, et al. Efficacy of [ 177 Lu]Lu-DOTATATE in metastatic neuroendocrine neoplasms of different locations: data from the SEPTRALU study. *Eur J Nucl Med Mol Imaging*. Jul 2023; 50(8): 2486-2500. PMID 36877234
37. Zidan L, Irvani A, Oleinikov K, et al. Efficacy and Safety of 177 Lu-DOTATATE in Lung Neuroendocrine Tumors: A Bicerter study. *J Nucl Med*. Feb 2022; 63(2): 218-225. PMID 34049983
38. Prado-Wohlwend S, Del Olmo-García MI, Bello-Arques P, et al. Response to targeted radionuclide therapy with [ 131 I]MIBG AND [ 177 Lu]Lu-DOTA-TATE according to adrenal vs. extra-adrenal primary location in metastatic paragangliomas and pheochromocytomas: A systematic review. *Front Endocrinol (Lausanne)*. 2022; 13: 957172. PMID 36339441
39. Satapathy S, Mittal BR, Bhansali A. 'Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: A systematic review and meta-analysis'. *Clin Endocrinol (Oxf)*. Dec 2019; 91(6): 718-727. PMID 31569282
40. Severi S, Bongiovanni A, Ferrara M, et al. Peptide receptor radionuclide therapy in patients with metastatic progressive pheochromocytoma and paraganglioma: long-term toxicity, efficacy and prognostic biomarker data of phase II clinical trials. *ESMO Open*. Aug 2021; 6(4): 100171. PMID 34139487
41. Kong G, Grozinsky-Glasberg S, Hofman MS, et al. Efficacy of Peptide Receptor Radionuclide Therapy for Functional Metastatic Paraganglioma and Pheochromocytoma. *J Clin Endocrinol Metab*. Sep 01 2017; 102(9): 3278-3287. PMID 28605448
42. Love C, Desai NB, Abraham T, et al. ACR-ACNM-ASTRO-SNMMI Practice Parameter for Lutetium-177 (Lu-177) DOTATATE Therapy. *Clin Nucl Med*. Jun 01 2022; 47(6): 503-511. PMID 35507433
43. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 2.2024. [https://www.nccn.org/professionals/physician\\_gls/pdf/neuroendocrine.pdf](https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf). Accessed February 2, 2026.
44. North American Neuroendocrine Tumor Society. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Management of Metastatic and/or Unresectable Pheochromocytoma and Paraganglioma. 2021;



[https://nanets.net/images/2021/2021\\_NANETS\\_Consensus\\_Guidelines\\_for\\_Surveillance\\_and\\_Management\\_of\\_Metastatic\\_and\\_or\\_Unresectable\\_Pheochromocytoma\\_and\\_Paraganglioma.pdf](https://nanets.net/images/2021/2021_NANETS_Consensus_Guidelines_for_Surveillance_and_Management_of_Metastatic_and_or_Unresectable_Pheochromocytoma_and_Paraganglioma.pdf). Accessed February 2, 2026.

45. North American Neuroendocrine Tumor Society. Commonwealth Neuroendocrine Tumour Research Collaboration and the North American Neuroendocrine Tumor Society Guidelines for the Diagnosis and Management of Patients With Lung Neuroendocrine Tumors: An International Collaborative Endorsement and Update of the 2015 European Neuroendocrine Tumor Society Expert Consensus Guidelines. 2021; [https://nanets.net/images/guidelines/20021\\_COMMNETS\\_NANETS\\_Lung\\_Guidelines.pdf](https://nanets.net/images/guidelines/20021_COMMNETS_NANETS_Lung_Guidelines.pdf). Accessed February 2, 2026.
46. Prostate Cancer. American Cancer Society. <https://www.cancer.org/cancer/prostate-cancer.html>. Accessed February 2, 2026.
47. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Rep*. Mar 1966; 50(3): 125-8. PMID 5948714
48. SEER Database. <https://seer.cancer.gov/seerinqury/index.php?page=view&id=20170036&type=q>. Accessed February 2, 2026.
49. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. Sep 16 2021; 385(12): 1091-1103. PMID 34161051
50. Pluvicto (lutetium Lu 177 vipivotide tetraxetan). Prescribing Information. Novartis Pharmaceuticals Corporation; East Hanover, NJ. Revised June 2025.
51. Lutathera (lutetium Lu 177 dotatate). Prescribing Information. Advanced Accelerator Applications USA, Inc.; Millburn, NJ. Revised October 2024.
52. Locametz (kit for the preparation of gallium Ga 68 gozetotide injection). Prescribing Information. Novartis Pharmaceuticals Corporation; East Hanover, NJ. Revised March 2025.
53. Pylarify (piflufolastat F 18). Prescribing Information. Progenics Pharmaceuticals, Inc.; Billerica, MA. Revised May 2021.
54. Illuccix (kit for the preparation of gallium Ga 68 gozetotide injection). Prescribing Information. Grand River Aseptic Manufacturing; Grand Rapids, MI. Revised December 2025.
55. Sadaghiani MS, Sheikhabahaei S, Werner RA, et al. 177 Lu-PSMA radioligand therapy effectiveness in metastatic castration-resistant prostate cancer: An updated systematic review and meta-analysis. *Prostate*. May 2022; 82(7): 826-835. PMID 35286735
56. Hofman MS, Emmett L, Sandhu S, et al. [ 177 Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*. Feb 27 2021; 397(10276): 797-804. PMID 33581798
57. Calais J, Gafita A, Eiber M, et al. Prospective phase 2 trial of PSMA-targeted molecular Radiotherapy with 177 Lu-PSMA-617 for metastatic castration-resistant Prostate Cancer (RESIST-PC): efficacy results of the UCLA cohort. *J Nucl Med*. Oct 2021; 62(10): 1440-1446. PMID 34016732
58. Chi KN, Armstrong AJ, Krause BJ, et al. Safety Analyses of the Phase 3 VISION Trial of [ 177 Lu]Lu-PSMA-617 in Patients with Metastatic Castration-resistant Prostate Cancer. *Eur Urol*. Apr 2024; 85(4): 382-391. PMID 38185538
59. Hofman MS, Emmett L, Sandhu S, et al. Overall survival with [ 177 Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial. *Lancet Oncol*. Jan 2024; 25(1): 99-107. PMID 38043558
60. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer (version 4.2024). [www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Accessed February 2, 2026.
61. Xofigo (Radium Ra 223 dichloride) Injection. Prescribing Information. Bayer HealthCare Pharmaceuticals Inc.; Whippany, NJ. Revised December 2019.
62. Garje R, Riaz IB, Naqvi SAA, et al. Systemic Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer: ASCO Guideline Update. *J Clin Oncol*. Jul 10 2025; 43(20): 2311-2334. PMID 40315400.
63. Garje R, Rumble RB, Parikh RA. Systemic Therapy Update on 177 Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol*. Nov 2024; 42(31): 3751-3752. PMID 37931186.



## History

Date	Comments
04/01/19	New policy, approved March 19, 2019. This policy replaces 6.01.60. Policy created with literature review through October 2018. The use of lutetium 177 dotatate may be considered medically necessary for individuals with gastroenteropancreatic tumors when criteria are met.
11/01/19	Interim Review, approved October 8, 2019. Policy updated with literature review through June 2019; references added. Policy statement added that lobenguane I 131 is considered medically necessary when the specified conditions are met. Removed HCPCS codes J3490 and J9999. Added HCPCS code A4641.
01/01/20	Coding update. Removed HCPCS code A4641. Added new HCPCS code A9590 (new code effective 1/1/20)
10/01/20	Annual Review, approved September 17, 2020. Policy updated with literature review through May 2020; no references added. Policy statements unchanged.
11/01/21	Annual Review, approved October 5, 2021. Policy updated with literature review through May 24, 2021; no references added. Policy statement unchanged.
08/01/22	Interim Review, approved July 12, 2022. Policy reformatted and updated with literature review. References added. Pluvicto™ added as medically necessary when criteria are met. Xofigo® was moved from policy 5.01.544 Prostate Cancer Targeted Therapies as medically necessary when criteria are met. Added HCPCS codes A9593, A9594, A9595, A9596 and A9606.
10/01/22	Annual Review, approved September 12, 2022. Policy updated with literature review through June 10, 2022; references added. Investigational policy statement added for the use of lutetium 177 dotatate for all other indications, including pheochromocytoma and paraganglioma. Clarifications added to the policy statement on Lutetium 177 Initial Treatment for consistency with NCCN guidelines. Additional minor editorial refinements made to policy statements; intent unchanged. Added HCPCS codes A9607 and A9800. Removed HCPCS code A9699.
12/01/22	Interim Review, approved November 7, 2022. Updated background content. References added. Policy statements unchanged. Removed HCPC codes A9593, A9594, A9595, A9596, A9800.
04/01/23	Interim Review, approved March 20, 2023. Added 64Cu-Dotatate, or 68Ga-Dotatoc PET tracers to examples of somatostatin receptor-based imaging that can be used in preparation for Lutathera administration as noted also in the Related Information section.
10/01/23	Annual Review, approved September 25, 2023. Policy updated with literature review through May 29, 2023; references added. Added policy statement that Pluvicto is considered investigational when the Pluvicto policy criteria are not met. Other minor



Date	Comments
	editorial refinements to policy statements made; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
01/01/25	Annual Review, approved December 10, 2024. Policy updated with literature review through August 27, 2024; references added. Policy statements were removed related to iobenguane I 123 as the product has been withdrawn from the market by the manufacturer. Added FDA expansion indication for Lutathera to pediatric individuals 12 years of age and older. Added statement for dosing of concomitant medications that long-acting octreotide 30 mg IM should be given 4 to 24 hours after each Lutathera dose, otherwise policy statements unchanged. Removed HCPCS code A9590.
02/01/25	Interim Review, approved January 27, 2025. Added ECOG Performance Status score of 2 or less as an equivalent to the policy criterion of documented Karnofsky Performance Status score of 60 or greater. Policy intent unchanged. Other policy statements unchanged.
05/01/25	Annual Review, approved April 21, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Updated Pluvicto (lutetium Lu 177 vipivotide tetraxetan [Lu-177-PSMA-617]) coverage criteria to include treatment of certain individuals with prostate cancer who have not received prior taxane-based chemotherapy.
04/01/26	Annual Review, approved March 10, 2026. Updated coverage criteria for Pluvicto removing first reference to previous treatment with a taxane-based chemotherapy as was duplicative. Updated Lutathera removing requirement individual has had disease progression while on octreotide long-acting release or lanreotide therapy.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

