LifeWise Assurance Company

MEDICAL / PHARMACY POLICY – 6.01.525

Therapeutic Radiopharmaceuticals in Oncology

BCBSA Ref. Policy:	6.01.60 & 5.01.43	
Effective Date:	May 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Apr. 21, 2025	5.01.544 Prostate Cancer Targeted Therapies
Replaces:	6.01.60	8.01.53 Cellular Immunotherapy for Prostate Cancer

Select a hyperlink below to be directed to that section.

∞ 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
Lutathera (lutetium 177 [Lu 177] dotatate)	**Lutathera (lutetium 177 [Lu 177] dotatate) treatment may be considered medically necessary when ALL the following criteria are met:** • The individual is aged 12 years or older **AND** • 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 **AND** • Has documented somatostatin receptor expression of a neuroendocrine tumor as detected by somatostatin receptor-based imaging (^{68}Ga-dotate, 64Cu-Dotatate, or 68Ga-Dotatoc positron emission tomography [PET]), or somatostatin receptor scintigraphy) (see **Related Information**) **AND** • Has documented disease progression while on octreotide long-acting release or lanreotide therapy as demonstrated on computed tomography (CT) or ^{68}Ga-dotate, 64Cu-Dotatate, or 68Ga-Dotatoc positron emission tomography (PET) (see **Related Information**) **AND** • 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 **AND** • Does not have severe renal impairment (creatinine clearance, less than 40 mL/min) **AND**

Drug	Medical Necessity
	• Has adequate bone marrow and hepatic function as determined by the treating physician **AND** • Has documented **Karnofsky Performance Status** score of 60 or greater or the equivalent **Eastern Cooperative Oncology Group** (ECOG) Performance Status score of 2 or less **AND** • Long-acting octreotide 30 mg IM is administered between 4 and 24 hours after each Lutathera dose
Pluvicto (lutetium Lu 177 vipivotide tetraxetan [Lu-177-PSMA-617])	**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:** • The individual is aged 18 years or older **AND** • Has been diagnosed with mCRPC **AND** • 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) **AND** • Has been previously treated with an androgen receptor (AR) pathway inhibitor (e.g., flutamide, nilutamide, bicalutamide, enzalutamide, apalutamide, darolutamide) and a taxane-based chemotherapy (e.g., docetaxel, cabazitaxel) **AND** • Has received prior taxane-based chemotherapy OR it is considered appropriate to delay taxane-based chemotherapy
Xofigo (radium Ra 223 dichloride)	**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).**

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

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews and all other reviews for Lutathera may be approved up to 12 months and up to a total of 4 doses.** **Non-formulary exception reviews and all other reviews for Pluvicto may be approved up to 12 months and up to a total of 6 doses (administered once every 6 weeks; see Related Information for dosage modifications).** **Non-formulary exception reviews and all other reviews for Xofigo may be approved up to 12 months and up to a total of 6 doses (typically administered every 4 weeks).**

Length of Approval	
Approval	**Criteria**
Re-authorization criteria	**Lutathera treatment greater than a total of 4 doses is considered investigational.** **Pluvicto treatment greater than a total of 6 doses (administered once every 6 weeks) is considered investigational.** **Xofigo treatment greater than a total of 6 doses, typically delivered at 4-week intervals, is considered investigational.**

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 (^{68}Ga-dotate, 64Cu-Dotatate, or 68Ga-Dotatoc positron emission tomography or computed tomography, which is preferred) or somatostatin receptor scintigraphy confirming somatostatin receptor expression of a neuroendocrine tumor
- Documentation that disease has progressed while on octreotide long-acting release therapy or lanreotide therapy.
- 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
- Documented **Karnofsky Performance Status** score of 60 or greater

For continuation of treatment, documentation of the following:

Documentation Requirements

- 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)
- 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) and a taxane-based (e.g., paclitaxel docetaxel) 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
HCPCS	
A9513	Lutetium lu 177, dotatate, therapeutic, 1 mC (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
	40	Disabled; requires special care and assistance

Karnofsky Performance Status Scale Definitions	Rating (%)	Criteria
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	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://npcrc.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 be or chair

Source: **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.[2] 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.[3]

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.[4]

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.[5] In many cases, diagnosis is incidental to imaging for other unrelated causes. Most gastroenteropancreatic neuroendocrine tumors express somatostatin receptors that can be imaged using a radiolabeled form of the somatostatin analogue octreotide (e.g.,^{111}In-pentetreotide)

Treatment Approach

There is a general lack of prospective data to guide the treatment of neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors are chemotherapy-responsive neoplasms, and platinum-based chemotherapy represents the backbone of treatment for both early and advanced-stage tumors.[6] 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[7] while the median overall survival for small bowel neuroendocrine tumors has been reported as 7.9 years.[8]

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. [9] However, the role of somatostatin analogues in individuals with nonfunctioning neuroendocrine tumors is unclear.[10]

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.[11,12]

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.[13] 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).[14] and lung and gastrointestinal neuroendocrine tumors nonfunctional (RADIANT-4 trial).[15] 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.[16]

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.[13] 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.[17] 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.[18]

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.[19] 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.[20] 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.[21] In addition, the medical overall and disease-specific survival were 24.6 and 33.7 years for pheochromocytoma and paraganglioma, respectively.[22]

Diagnosis

The initial diagnosis of pheochromocytomas and paragangliomas includes biochemical testing, such as blood tests and urinalysis which measure the levels of metanephrine, a catecholamine metabolite in blood and urine. Imaging may be used to detect the location and size of tumors within the organs or tissues. Other advanced diagnostic procedures, such as ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, octreotide scan, and fluorodeoxyglucose- PET scan is used to further determine whether the tumors are malignant and metastatic.[19]

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

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.[24]

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.[25,26] Tyrosine kinase receptor inhibitors such as sunitinib (Sutent) have also been used.[27]

Metastatic Castration-Resistant Prostate Cancer

Prostate cancer is the second leading cause of cancer-related deaths among American men with 299,010 new cases and 35,250 disease-related deaths estimated for 2024.[46] 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 disproportionally 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.[47] 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.[48] 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.[46] 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).[46] 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.[49] 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.[50] 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 randomized controlled trial results showed a consistent statistically significant and clinically meaningful effect on overall response rate, progression-free survival (PFS), and OS among individuals treated with Lu 177 dotatate compared to those treated with long-acting octreotide. The results of the retrospective 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 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
Ongoing			
NCT03206060	Lu-177-DOTATATE (Lutathera) in Therapy of Inoperable Pheochromocytoma/ Paraganglioma	90	Jan 2027
NCT04665739	Testing Lutetium Lu 177 Dotatate in Patients with Somatostatin Receptor Positive Advanced Bronchial Neuroendocrine Tumors	108	Aug 2024
NCT04086485	Lu-177-DOTATATE (Lutathera) in Combination with Olaparib in Inoperable Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)	42	Jan 2026
NCT03691064	Post-Authorization Long-Term Safety Study of Lutathera (SALUS)	1014	Jun 2028
NCT03972488[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
NCT04954820	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	Sep 2029
NCT01876771	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 2033
NCT06121271	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
NCT06320067	A Randomised Controlled Platform Trial Testing Treatments in Metastatic Hormone Sensitive Prostate Cancer (STAMPEDE2)	8000	Mar 2034
NCT06496581	Standard of Care +/- 177Lu-PSMA-617 In de Novo mHSPC Patients With Poor PSA Response (PEACE6-Poor Responders)	500	Aug 2039
NCT04720157[a]	An International Prospective Open-label, Randomized, Phase III Study Comparing 177Lu-PSMA-617 in	1126	Feb 2026

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Combination with SoC, Versus SoC Alone, in Adult Male Patients with mHSPC (PSMAddition)		
NCT04689828[a]	177Lu-PSMA-617 vs. Androgen Receptor-directed Therapy in the Treatment of Progressive Metastatic Castrate Resistant Prostate Cancer (PSMAfore)	450	Sep 2025
NCT04663997	A Randomized Phase II Study of 177 LuPSMA-617 vs Docetaxel in Patients With Metastatic Castration-Resistant Prostate Cancer and PSMA-Positive Disease	200	Jul 2025
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)	110	Dec 2024

NCT: national clinical trial.

[a] 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).[42] 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.

National Comprehensive Cancer Network Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines (v.2.2024) 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.

Table 6 summarizes the NCCN guidelines for neuroendocrine and adrenal tumors.[43]

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

Treatment Category	Recommendation Category
Mid-gut recurrent, locoregional advanced or distant metastases gastrointestinal neuroendocrine tumors after disease progression on somatostatin analogues	1
Bronchopulmonary/thymic distant metastases neuroendocrine tumors if there is clinically significant tumor burden and low grade (typical) or evidence of progression or intermediate grade (atypical) tumor or symptomatic disease	2A

Treatment Category	Recommendation Category
Locoregional or recurrent advanced or distant metastases gastrointestinal neuroendocrine tumors after disease progression on somatostatin analogues	2A
Locoregional or recurrent advanced or distant metastases pancreatic neuroendocrine tumors after disease progression on somatostatin analogues	2A
Locally unresectable or distant metastases paraganglioma/pheochromocytoma (consider use if somatostatin receptor-positive)	2A

The NCCN guidelines also provide a category 2A recommendation to consider the use of lutetium 177 dotatate for treatment of individuals with locally unresectable bronchopulmonary or thymus neuroendocrine tumors and locally unresectable or distant metastatic pheochromocytoma or paraganglioma. For pheochromocytoma and paraganglioma, the guidelines additionally note that data are limited for use in this setting. 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.

The NCCN guidelines (v.2.2024) 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.

The NCCN guideline for prostate cancer (v4.2024) provides the following relevant recommendations with regard to the use of lutetiumLu 177 vipivotide tetraxetan (Lu-177-PSMA-617):[59]

"The NCCN Panel recommends Lu-177-PSMA-617 as a category 1, useful in certain circumstances treatment option for individuals with ≥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 ≥1.0 cm, lymph nodes ≥2.5 cm in short axis, and solid organ metastases ≥1.0 cm in size. The NCCN Panel believes that both Ga-68 PSMA-11 or F-18 piflufolastat PSMA imaging can be used to determine eligibility."

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.[44] 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.[45] 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.[1] The decision was not related to safety or efficacy concerns. Azedra is not further addressed in this policy.

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

On December 17, 2021, Illuccix (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.[52] [53] 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.[50]

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.[5051]

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.[28] 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.[29]

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.[51, 52]

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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 Iobenguane 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.

Date	Comments
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 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.

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.