MEDICAL POLICY

POLICY TITLE	THERAPEUTIC RADIOPHARMACEUTICALS FOR NEUROENDOCRINE TUMORS
POLICY NUMBER	MP 2.371

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 2/1/2026**

I. POLICY

Lutetium (Lu 177) dotatate (Lutathera®)

Initial Treatment
Lutetium (Lu 177) dotatate (Lutathera®) treatment may be considered **medically necessary** when **ALL** of the following are met:

- Individual Is an adult (18 years of age or older); **and**
- Individual has documented low or intermediate grade (Ki-67 index ≤20%), locally advanced or metastatic, gastroenteropancreatic (including foregut, midgut, and hindgut) or metastatic bronchopulmonary or thymus neuroendocrine tumor; **and**
- Individual has documented somatostatin receptor expression of a neuroendocrine tumor as detected by somatostatin receptor-based imaging (see Policy Guidelines); **and**
- Individual has documented disease progression while on octreotide long-acting release or lanreotide therapy; **and**
- 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; **and**
- Individual does not have severe renal impairment (creatinine clearance <30 mL/min); **and**
- Individual has adequate bone marrow and hepatic function as determined by the treating physician; **and**
- Individual has documented Karnofsky Performance Status score of 60 or greater

Continuation of Treatment
Continuation of Lu 177 dotatate (Lutathera®) may be considered **medically necessary** when **ALL** of the following are met:

- No recurrent grade 2, 3, or 4 thrombocytopenia (see Table PG1); **and**

- No recurrent grade 3 or 4 anemia and neutropenia (see Table PG1); **and**
- No recurrent hepatotoxicity (see definition of hepatotoxicity in the Policy Guidelines section); **and**
- No recurrent grade 3 or 4 nonhematologic toxicity (see Table PG1); **and**
- No renal toxicity requiring a treatment delay of 16 weeks or longer (see definition of renal toxicity in the Policy Guidelines section).

Lu 177 dotatate treatment is considered **investigational** in all other indications and situations in which the above criteria are not met, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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

Lu 177 dotatate treatment is considered investigational for all other indications including pheochromocytoma and paraganglioma.

POLICY GUIDELINES

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.

Lutetium Lu 177 dotatate (Lutathera®)

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

There are theoretical concerns regarding the competition between somatostatin analogues and Lu 177 dotatate for somatostatin receptor binding. Therefore, the following is recommended:

- Do not administer long-acting somatostatin analogues for 4 to 6 weeks prior to each Lu 177 dotatate treatment
- Stop short-acting somatostatin analogues 24 hours before each Lu 177 dotatate treatment
- Both long-acting and short-acting somatostatin analogues can be resumed 4 to 24 hours after each Lu 177 dotatate treatment.

Lu 177 dotatate is a radiopharmaceutical and should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of

radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

Lu 177 dotatate should be discontinued permanently if the patient develops hepatotoxicity defined as bilirubinemia greater than 3 times the upper limit of normal (grade 3 or 4), or hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.

Lu 177 dotatate should be discontinued permanently if patient develops renal toxicity defined as a creatinine clearance of less than 40 mL/min calculated using Cockcroft-Gault equation with actual body weight, or 40% increase in baseline serum creatinine, or 40% decrease in baseline creatinine clearance calculated using Cockcroft-Gault equation with actual body weight.

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

Table PG1. Common Toxicity Criteria for Adverse Events

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.

Cross-References:

MP 2.373 Step Therapy Treatment of Stage Four, Advanced Metastatic Cancer, and Severe Related Health Conditions
MP 5.022 Radioimmunoscintigraphy Imaging Monoclonal Antibody Imaging w-Indium-111 Capromab Pendetide for Prostate Cancer

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

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FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

TOP

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.

Neuroendocrine tumors

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

Neuroendocrine tumors are classified as orphan diseases by the U.S. Food and Drug Administration (FDA). Based on an analysis of Surveillance, Epidemiology, and End Results Program registry data from 1973 to 2012, the overall incidence of neuroendocrine tumors has been reported to be in the range of 6.98 per 100000 people per year.

Diagnosis

Neuroendocrine tumors are not easy to diagnose because of the rarity of the condition. Symptoms are often nonspecific or mimic other disorders such as irritable bowel syndrome (in the case of gastroenteropancreatic neuroendocrine tumors) or asthma (in the case of a lung neuroendocrine tumors) resulting in an average diagnosis delay of five to seven years after symptom onset. In many cases, diagnosis is incidental to imaging for other unrelated cause.

Most gastroenteropancreatic neuroendocrine tumors express somatostatin receptors that can be imaged using a radiolabeled form of the somatostatin analogue octreotide (e.g., ^{111}In pentetreotide).

Treatment Approach

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

Pharmacologic Treatment

First-Line Treatment Options

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

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

Second-Line Treatment Options

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

Mechanistic Target of Rapamycin Inhibitors
The mechanistic target of rapamycin is an enzyme that regulates cell metabolism and proliferation in response to environmental stimuli. It is upregulated in a variety of malignancies in response to stimulation by growth factors and cytokines. Whole-exome genomic analysis has shown that approximately 15% of pancreatic neuroendocrine tumors are associated with somatic variants in genes associated with the mechanistic target of rapamycin pathway.

Everolimus, an oral mechanistic target of rapamycin inhibitor, has been shown to significantly prolong PFS versus placebo in patients with pancreatic neuroendocrine tumors (RADIANT-3 trial), and lung and gastrointestinal neuroendocrine tumors nonfunctional (RADIANT-4 trial). Note that everolimus is approved by the FDA for adults with progressive neuroendocrine tumors of pancreatic origin and adults with progressive, well-differentiated, nonfunctional neuroendocrine tumors of gastrointestinal or lung origin that are unresectable, locally advanced, or metastatic. The RADIANT-2 trial, conducted in patients with progressive advanced neuroendocrine tumors associated with carcinoid syndrome failed to show a statistically significant improvement in the primary endpoint of PFS.

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

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

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

Pheochromocytoma and Paraganglioma

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

are malignant (metastatic) which can spread to other parts of the body, such as the liver, lungs, bone, or distant lymph nodes.

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

Diagnosis

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

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

Treatment Approach

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

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

Regulatory Status

On January 26, 2018, Lutathera® (lutetium 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 May 5, 2022, Novartis announced that it had temporarily suspended production of Lutathera® at production sites in Ivrea, Italy and Millburn, New Jersey out of an abundance of caution as a result of potential quality issues identified in its manufacturing processes. This production suspension will impact both commercial and clinical trial supply in the US and Canada. At the time of the 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 patients from doses previously produced at these sites but has notified treatment sites to closely monitor patients.

On July 30, 2018, AZEDRA (iobenguane I 131) injection was approved by the FDA for the treatment of adult and pediatric patient'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 patients through Q1 2024. The decision was not related to safety or efficacy concerns. Azedra is not further addressed in this review.

An 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.

IV. RATIONALE

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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. Relevant outcomes are overall survival (OS), disease-specific survival, quality of life, and treatment-related mortality and morbidity. The randomized controlled trial results showed a consistent statistically significant and clinically meaningful effect on overall response rate, progression-free survival (PFS), and OS among patients 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 provided additional support for a clinical benefit of Lu 177 dotatate in patients with a gastroenteropancreatic neuroendocrine tumor. The evidence is sufficient to determine that the technology results in an 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. 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 patients with bronchopulmonary (n=23) or thymus (n=2) neuroendocrine tumors. Among the 23 patients with bronchopulmonary neuroendocrine tumor, the median progression-free survival was 20 months, the median time to

progression was 25 months, and median overall survival was 52 months. Stratified results of 2 patients with thymus neuroendocrine tumors were not reported. The U.S. Food and Drug Administration in its review of the ERASMUS study for patients with gastroenteropancreatic neuroendocrine tumor concluded that time to event analyses such as time to progression, progression-free survival, and overall survival were not interpretable in the context of the single-arm ERASMUS study because of missing data at baseline, high dropout rates and open-label design of the study. The multicenter registry included 58 patients with bronchopulmonary tumors and reported 0 complete responses, 14 partial responses, a median PFS of 17.6 months, and a median overall survival of 44.8 months. The case series evaluated 48 patients with predominantly atypical carcinoid bronchopulmonary tumors, finding a median progression-free survival and overall survival 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 2 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% CI, 18% to 35%). Another meta-analysis found improved PFS with Lu 177 dotatate compared to iobenguane I 131 among studies enriched with pheochromocytomas. One retrospective case series reported that 8/13 patients were able to reduce dosages of antihypertensive treatment at 3 months. Disease regression was reported in 5/14 patients with available CT imaging. Out of 16 patients with available iobenguane scans, 10 patients had mild or negative uptake. However, patient outcomes were not stratified by iobenguane uptake status. No prospective studies directly comparing Lu 177 dotatate to iobenguane I 131 or assessing Lu 177 dotatate response in a fully non-iobenguane avid population were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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RADIOPHARMACEUTICALS: Radiopharmaceutical agents are used to diagnose or treat various malignancies, endocrinopathies, metabolopathies, and perfusion abnormalities.

THE COCKCROFT GAULT EQUATION: Developed prior to the use of standardized creatinine assays and has not been revised for use with creatinine values traceable to standardized reference materials.

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KARNOFSKY PERFORMANCE STATUS: The KPS ranges from values of 100, signifying normal functional status with no complaints nor evidence of disease, to 0, signifying death.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure codes							
A4641	A9513						

ICD-10-CM Diagnosis Code	Description
C7A.00	Malignant carcinoid tumor of unspecified site
C7A.010	Malignant carcinoid tumor of the duodenum
C7A.011	Malignant carcinoid tumor of the jejunum
C7A.012	Malignant carcinoid tumor of the ileum

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ICD-10-CM Diagnosis Code	Description
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
C7A.020	Malignant carcinoid tumor of the appendix
C7A.021	Malignant carcinoid tumor of the cecum
C7A.022	Malignant carcinoid tumor of the ascending colon
C7A.023	Malignant carcinoid tumor of the transverse colon
C7A.024	Malignant carcinoid tumor of the descending colon
C7A.025	Malignant carcinoid tumor of the sigmoid colon
C7A.026	Malignant carcinoid tumor of the rectum
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.090	Malignant carcinoid tumor of the bronchus and lung
C7A.091	Malignant carcinoid tumor of the thymus
C7A.092	Malignant carcinoid tumor of the stomach
C7A.093	Malignant carcinoid tumor of the kidney
C7A.094	Malignant carcinoid tumor of the foregut, unspecified
C7A.095	Malignant carcinoid tumor of the midgut, unspecified
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified
C7A.098	Malignant carcinoid tumors of other sites
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7A.8	Other malignant neuroendocrine tumors
C7B.00	Secondary carcinoid tumors, unspecified site
C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7B.02	Secondary carcinoid tumors of liver
C7B.03	Secondary carcinoid tumors of bone
C7B.04	Secondary carcinoid tumors of peritoneum
C7B.09	Secondary carcinoid tumors of other sites
C7B.8	Other secondary neuroendocrine tumors
C74.10	Malignant neoplasm of medulla of unspecified adrenal gland
C74.11	Malignant neoplasm of medulla of right adrenal gland
C74.12	Malignant neoplasm of medulla of left adrenal gland
C75.5	Malignant neoplasm of aortic body and other paraganglia
Z51.0	Encounter for antineoplastic radiation therapy

IX. REFERENCES

TOP

1. *Society of Nuclear Medicine and Molecular Imaging. Lantheus to Discontinue Production of Azedra. August 18, 2023*

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, Konig 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, Iniguez-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*
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, Chougnet 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*
29. *Novartis. Novartis resumes production and delivery of radioligand therapy medicines ahead of schedule. June 30, 2022*
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*
32. *Novartis Inc. Lutathera (lutetium Lu 177 dotatate) injection, for intravenous use administration of Lutathera (Prescribing Label). 2024*
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, Iravani A, Oleinikov K, et al. Efficacy and Safety of 177 Lu-DOTATATE in Lung Neuroendocrine Tumors: A Bicenter 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*
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*
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*
46. *Blue Cross Blue Shield Association Medical Policy Reference Manual, 6.01.60. Therapeutic Radiopharmaceuticals in Oncology. November 2024*

POLICY TITLE	THERAPEUTIC RADIOPHARMACEUTICALS FOR NEUROENDOCRINE TUMORS
POLICY NUMBER	MP 2.371

X. POLICY HISTORY

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MP 2.371	**12/12/2019 New Policy**. Lutetium Lu 177 dotatate (Lutathera®) and Iobenguane I 131 (Azedra®) treatment are considered **medically necessary** when criteria listed are met. All other indications will be considered investigational. Effective 07/01/2020.
	10/30/2020 Consensus Review. Policy statement unchanged. References updated. Removed HCPCS codes C9407 and C9408, added A9590, revised diagnosis codes.
	10/07/2021 Consensus Review. References updated. Coding reviewed.
	09/01/2022 Minor Review. Title changed. Criteria updated for clarification. Removal of Karnofsky Performance Status Score. References and rationale updated. Removed codes 78804, 79101, 77300 and 77790.
	11/14/2023 Consensus Review. No change to policy statement. Background, Rationale, Definitions and References updated.
	12/09/2024 Minor Review. Karnosky score criteria changed from 50 to 60. Removed criteria for iobenguane I 123 as the product has been withdrawn from the market by the manufacturer. CPT code A9590 removed. Background, Rationale and References updated.
	07/17/2025 Retirement.

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