

Therapeutic Radiopharmaceuticals in Oncology

Medicare Advantage Medical Policy #MA-138

Original Effective Date: 11/01/2025

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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider lutetium 177 dotatate (Lutathera[®])[‡] or lutetium lu 177 vipivotide tetraxetan (Pluvicto[™])[‡] for the treatment of appropriate locally advanced or metastatic tumors to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of lutetium 177 dotatate (Lutathera), or lutetium lu 177 vipivotide tetraxetan (Pluvicto) will be considered when ALL of the specific drug's criteria are met:

- For **Lutathera** requests:
 - Patient is greater than or equal to 12 years of age; AND
 - Patient has documented gastroenteropancreatic (including foregut, midgut, and hindgut) or bronchopulmonary or thymus neuroendocrine tumor; AND
 - Disease meets one of the following:
 - Locoregional advanced and/or distant metastases, well-differentiated, grade 1/2, Ki-67 $\geq 10\%$ with clinically significant tumor burden; OR
 - Well-differentiated, grade 3 tumors that are unresectable, locally advanced/metastatic, Ki-67 $< 55\%$, and slow growing with clinically significant tumor burden or evidence of disease progression; AND
 - Patient has documented somatostatin receptor expression of a neuroendocrine tumor as detected by somatostatin receptor-based imaging or somatostatin receptor scintigraphy; AND
 - Patient is not receiving long-acting somatostatin analogues for at least 4 weeks prior to initiating Lutathera; AND
 - The patient does not have severe renal impairment [defined as a creatinine clearance < 30 milliliters per minute (mL/min)]; AND
 - The patient has adequate bone marrow and hepatic function as determined by the treating physician; AND
 - Patient has documented Karnofsky Performance Status score of 60 or greater OR an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; AND
 - The dose will not exceed 7.4 gigabecquerels (GBq) [200 millicuries (mCi)] per dose for a total of 4 doses; AND
 - Patient is not pregnant or breast-feeding; AND

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- If patient is of reproductive potential, patient agrees to use effective contraception during and after treatment according to recommendations in package insert.
- For **Pluvicto** requests:
 - Patient has a diagnosis of metastatic castrate resistant prostate cancer; AND
 - Patient is 18 years of age or older; AND
 - Patient has prostate specific membrane antigen (PSMA) positive disease as detected by a positron emission tomography (PET)/computed tomography (CT) scan using an FDA-approved diagnostic imaging agent; AND
 - Patient meets BOTH of the following criteria:
 - Patient has been treated with at least one androgen receptor pathway inhibitor (e.g., abiraterone, Zytiga[®], Yonsa[®], Xtandi[®], Erleada[®], or Nubeqa[®])[‡]; AND
 - Patient has been treated with at least one taxane-based chemotherapy regimen (e.g., docetaxel or Jevtana[®])[‡] or are considered appropriate to delay taxane-based chemotherapy; AND
 - The dose of Pluvicto will not exceed 7.4 GBq (200 mCi) every 6 weeks for up to 6 doses.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers use of lutetium 177 dotatate (Lutathera) when the patient does not meet the below criteria to be **not medically necessary**.**

- Disease meets ONE of the following:
 - Locoregional advanced and/or distant metastases, well-differentiated, grade 1/2, Ki-67 $\geq 10\%$ with clinically significant tumor burden; OR
 - Well-differentiated, grade 3 tumors that are unresectable, locally advanced/metastatic, Ki-67 $< 55\%$, and slow growing with clinically significant tumor burden or evidence of disease progression; OR
- Patient has documented Karnofsky Performance Status score of 60 or greater OR an ECOG performance status of 0-2.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers lutetium 177 dotatate (Lutathera), or lutetium lu 177 vipivotide tetraxetan (Pluvicto) to be **investigational*** when the patient selection criteria (other than those considered to be **not medically necessary****) are not met.

Background/Overview

Therapeutic radiopharmaceuticals are a new class of drugs that combine a radioisotope with an organic molecule which targets the radioisotope to specific organs, tissues, or cells. Currently

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available radiopharmaceuticals include the radiolabeled somatostatin analogue, Lutathera and the prostate specific membrane antigen (PSMA)-targeted radioligand, Pluvicto.

Lutathera binds to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors. It is then internalized and beta particle emission from the drug induces cellular damage by formation of free radicals in somatostatin receptor-positive and neighboring cells. It is dosed at 7.4 GBq (200 mCi) every 8 weeks (± 1 week) for a total of 4 doses. Each dose should be preceded by an infusion of amino acids to protect the patient's kidneys and the infusion should continue during and for at least 3 hours after Lutathera infusion. Because there are theoretical concerns regarding the competition between somatostatin analogues and Lutathera for somatostatin receptor binding, long-acting somatostatin analogues should not be administered for 4 to 6 weeks prior to each Lutathera treatment. In addition, short-acting somatostatin analogues should be stopped 24 hours before each Lutathera treatment. Both long-acting and short-acting somatostatin analogues can be resumed 4 to 24 hours after each Lutathera treatment.

Pluvicto binds to PSMA positive cells, including prostate cancer cells. It is then internalized into the cell and the beta particle emission from the drug causes single- and double-stranded DNA breaks in the targeted and surrounding cells to cause cell death. It is dosed at 7.4 GBq (200 mCi) intravenously every 6 weeks for up to 6 doses or until disease progression or unacceptable toxicity. It should be noted that Pluvicto is only approved by the Food and Drug Administration (FDA) for use when the patient's cancer is determined to be PSMA-positive using a Ga 68 gozetotide PSMA-11 test (Locametz[®])[‡]. However, clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) note that both Ga 68 PSMA-11 or F-18 piflufolastat PSMA imaging (Pylarify[®])[‡] can be used to determine eligibility for treatment with Pluvicto.

All radiopharmaceuticals can cause fetal harm and should not be used in pregnant or breastfeeding females. In addition, females of reproductive potential should be advised to use effective contraception during treatment and for 7 months after the final dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for 4 months after the final dose.

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. Approximately 61% of all neuroendocrine tumors originate from the gastrointestinal system or pancreas and are referred to as gastroenteropancreatic neuroendocrine tumors. Lung neuroendocrine tumors may also be referred to as pulmonary neuroendocrine tumors, pulmonary carcinoids, or bronchopulmonary neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors may further be characterized as functional or nonfunctional based on whether they secrete hormones that result in clinical symptoms, particularly serotonin which results in "carcinoid syndrome" characterized by flushing and diarrhea.

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Diagnosis of neuroendocrine tumors is difficult due to the rarity of the condition and the fact that symptoms are often nonspecific and mimic other disorders such as irritable bowel syndrome or asthma. For this reason, the average diagnosis delay is 5-7 years after symptom onset. Most of these tumors express somatostatin receptors that can be imaged using a radiolabeled form of the somatostatin analogue, octreotide. Neuroendocrine tumors are often staged with the Ki-67 index, and only patients with a Ki-67 index of 20% or less were included in the randomized trial of Lutathera. However, current guidelines from the National Comprehensive Cancer Network (NCCN) recommend Lutathera as a first line option for treatment of grade 1 or 2 tumors with a Ki-67 index $\geq 10\%$ or grade 3 tumors with a Ki-67 index $< 55\%$.

There is a general lack of prospective data to guide 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 disease is highly variable. The median overall survival from diagnosis for patients with metastatic pancreatic neuroendocrine tumors has been reported to range from 2 to 4.8 years while the median overall survival for small bowel neuroendocrine tumors has been reported as 7.9 years. Somatostatin analogues (e.g., octreotide, lanreotide) were initially developed to manage the hormonal symptoms related to neuroendocrine tumors, and they are a first-line treatment option for these patients. They were also found to exert antiproliferative activity and result in prolonged progression-free survival in patients with neuroendocrine tumors. However, the role of somatostatin analogues in patients with nonfunctioning neuroendocrine tumors is unclear. Currently, there are no data to support a specific sequence of second-line therapies and only streptozocin, everolimus, and sunitinib are FDA approved for treatment of pancreatic neuroendocrine tumors.

Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Prostate cancer is the second most common cancer among men in the United States but can often be treated successfully with radical prostatectomy or primary radiotherapy. In patients who fail this initial curative therapy, treatment involves androgen deprivation therapy (ADT) followed by chemotherapy. However, in many cases, the metastatic spread and disease progression continues even after ADT, leading to the more lethal metastatic castration-resistant prostate cancer (mCRPC).

Despite recent advances in the treatment of mCRPC, metastatic prostate cancer has a 5-year survival rate of less than 30%, and only limited treatment options are available for patients with mCRPC who progress on multiple lines of therapy. These options include agents such as abiraterone acetate (Zytiga, Yonsa), enzalutamide (Xtandi), olaparib (Lynparza[®])[‡], cabazitaxel (Jevtana), and rucaparib (Rubraca[®])[‡]. Targeted radionuclide therapies such as Pluvicto appear to be a viable third-line option in men with metastatic prostate cancer based on recent clinical studies. Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein expressed at low levels in normal human prostate epithelium and is overexpressed in virtually all types of prostate cancers. The most recent guidelines

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from the National Comprehensive Cancer Network (NCCN) now recommend Pluvicto as an option with category 1 evidence for patients with at least 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 (unless considered appropriate to delay taxane-based chemotherapy).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

On January 26, 2018, Lutathera was approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors, including foregut, midgut, and hindgut neuroendocrine tumors in adults. In April 2024 this indication was expanded to include patients 12 years of age and older.

On March 23, 2022, Pluvicto was approved for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. In March 2025, the label was expanded to include patients who are considered appropriate to delay taxane-based chemotherapy.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Lutathera

Approval of Lutathera was based on an open-label study in patients with midgut carcinoid tumors (NETTER-1), and the portion of the retrospective ERASMUS study that evaluated patients with gastroenteropancreatic neuroendocrine tumors.

In the NETTER-1 trial, patients with a Ki-67 index of 20% or less, Karnofsky Performance Status score of 60 or greater, confirmed presence of somatostatin receptors on all lesions (octreoscan uptake $\geq$ normal liver) and creatinine clearance for 50 mL/min or greater were included. The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee. Additional efficacy outcome measures were overall response rate, duration of response, and overall survival. Results showed a consistent statistically significant and clinically meaningful effect on overall response rate, PFS, and overall survival among patients given Lutathera compared with those given high-dose long-acting octreotide. The median PFS was not reached in the Lutathera group and was 8.5 months in the control group (HR=0.21[0.13-0.32]).

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In the ERASMUS study, 1214 patients with heterogeneous etiologies in terms of primary tumor site received Lutathera as part of expanded access protocol at a single center in the Netherlands. From this cohort, 360 patients with foregut, midgut, or hindgut gastroenteropancreatic neuroendocrine tumors were respectively identified and analyzed. The major efficacy outcome was investigator-assessed overall response rate. 55% of patients received a concomitant somatostatin analogue. The investigator-assessed overall response rate was found to be 16% and the median duration of response was 35 months among 58 responders.

The ERASMUS study also included 25 individuals with treatment-refractory bronchopulmonary or thymus neuroendocrine tumors who received Lutathera. Among the 23 patients with bronchopulmonary neuroendocrine tumor, the median progression-free survival was 20 months, 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.

Approval of Lutathera in adolescent patients was based on the NETTER-P study, an international, multi-center, single-arm, open-label trial of 9 patients with somatostatin receptor-positive tumors. Patients received Lutathera 7.4 GBq (200 mCi) administered every 8 weeks concurrently with the recommended amino acid solution. Adverse reactions observed in NETTER-P were similar to those observed in adults treated with Lutathera.

Pluvicto

The efficacy of Pluvicto was evaluated in VISION, a randomized (2:1), multicenter, open-label trial that evaluated Pluvicto plus best standard of care (n=551) or best standard of care alone (n=280) in men with progressive, PSMA-positive mCRPC. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were required to have received at least one AR pathway inhibitor, and 1 or 2 prior taxane-based chemotherapy regimens. Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded if any lesions exceeding size criteria in short axis had uptake less than or equal to uptake in normal liver.

Patients received Pluvicto 7.4 GBq (200 mCi) every 6 weeks for up to a total of 6 doses plus best standard of care (BSoC) or BSoC alone. BSoC administered at the investigator's discretion included ketoconazole, radiation therapy to localized prostate cancer targets, bone-targeted agents, androgen-reducing agents, and androgen receptor pathway inhibitors. Patients continued treatment for up to 4-6 doses, or until disease progression or unacceptable toxicity. Patients with stable disease or partial response after 4 doses of Pluvicto plus BSoC received up to 2 additional doses per investigator's discretion.

The major efficacy outcome measures were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review. Statistically significant improvement was seen in both of these measures in the Pluvicto plus BSoC arm compared to the BSoC arm. Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from

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early drop out in the control arm. Overall survival in the Pluvicto plus BSoC arm was 38% compared to 33% in the BSoC arm ($p < 0.001$).

References

1. Lutathera [package insert]. Advanced Accelerator Applications USA. Millburn, NJ. October 2024.
2. Pluvicto [package insert]. Advanced Accelerator Applications USA. Millburn, NJ. March 2025.
3. Pluvicto (lutetium Lu 177 vipivotide tetraxetan) New Drug Review. IPD Analytics. Updated April 2022.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 2.2025.

Policy History

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08/19/2025 UM Committee review and approval. New policy.

Next Scheduled Review Date: 08/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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Code Type	Code
CPT	No codes
HCPCS	A9513, A9607
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: <https://www.cms.gov/medicare-coverage-database/search.aspx>. You may wish to review the Guide to the MCD Search here: <https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx>.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.