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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Radiopharmaceuticals

- Dotatate (Lutathera) – used for neuroendocrine tumors
- Vipivotide Tetraxetan (Pluvicto™, formerly 177Lu-PSMA) – used for metastatic prostate cancer

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Vipivotide Tetraxetan (Pluvicto™, formerly 177Lu-PSMA)" and "Dotatate (Lutathera") ,*** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Service	Criteria
Dotatate (Lutathera)	**Candidates must meet ALL of the following:** 1. Presence of metastasized or locally advanced, unresectable (with curative intent) gastroenteropancreatic neuroendocrine tumors (GEP-NET) **and** 2. Ki-67 protein ≤ 20% (patients with higher-grade disease need to be evaluated on case-by-case basis) **and** 3. Progressive disease under somatostatin analog therapy (SSA) **and** 4. At least 18 years of age **and** 5. Target lesions overexpressing somatostatin receptors as demonstrated on ^{68}Ga-DOTATATE PET/CT scan within last 3 months **and** 6. Monitoring labs must be conducted within the first 4 weeks of injection (baseline); 4-6 weeks after each Lutathera injection and 2 days prior to subsequent Lutathera injections **Contraindications:** 1. Women who are or may be pregnant, as this agent can cause fetal harm when administered to a pregnant woman (pregnancy category X) **or** 2. Women who are breast feeding **or** 3. Pediatric patients (<18 years of age)

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	4. Lutathera Therapy is not covered when: 5. Recent surgery, radioembolization, chemoembolization, radiofrequency ablation or chemotherapy within 4 weeks prior to initiation of Lutathera treatment. 6. Known brain metastases unless these metastases have been treated and stabilized. 7. Uncontrolled congestive heart failure (NYHA II, III, IV) 8. Treatment with *short-acting* somatostatin analog therapy (SSA) that cannot be interrupted for 24 hours before Lutathera administration, or treatment with *long-acting* (LAR) somatostatin analog therapy SSA that cannot be interrupted for at least 4 weeks before initiation of Lutathera a. Patient may go on short acting somatostatin analog therapy (SSA) as a bridge between LAR injection and Lutathera treatment, but this must be stopped 24 hrs. before Lutathera treatment. 9. Prior external beam radiation therapy to >25% of the bone marrow. 10. Current spontaneous urinary incontinence making it unsafe to administer Lutathera Please click here to view clinical criteria for PET Scan: Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)
Vipivotide Tetraxetan (Pluvicto™, *formerly* 177Lu-PSMA)	Lutetium Lu 177 Vipivotide Tetraxetan (Pluvicto™, formerly 177Lu-PSMA) given every 6 weeks for 4-6 cycles is considered medically necessary for individuals with progressive metastatic castration-resistant prostate cancer who meet **ALL of the following** conditions: 1. Patient must be age 18 or older 2. Must have baseline CT/bone scan within the prior 2 months of chest/abdomen/pelvis with at least one visible lesion 3. Have been treated with 1 or more androgen-receptor pathway inhibitors (ie, enzalutamide and/or abiraterone) 4. Previously received at least 1 taxane-based chemotherapy regimens (docetaxel, cabazitaxel) for metastatic castration-resistant prostate cancer, for at least 2 cycles 5. Must have PSMA-positive mCRPC defined as having at least one tumor lesion with uptake greater than normal liver within the past 3 months 6. Does NOT have any PSMA-negative (defined as FDA approved PSMA tracer uptake less than or equal to uptake in normal liver) prostate cancer lesions exceeding the below size criteria: a. Visceral metastases ≥1cm b. Lymph node metastases ≥2.5cm c. Bone metastases ≥1cm 7. At least 30 days out from starting bisphosphonate or denosumab (if applicable) 8. No radium-223 within last 6 months 9. No chemotherapy, immunotherapy, or biologics within 28 days of treatment 10. No impending cord compression 11. Prior CNS metastases okay if stable; must not be on steroids for treatment of CNS metastases, OK if has received prior treatment for metastases (e.g., radiation, surgery), and must be neurologically intact

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	12. No NYHA 3-4 heart failure, active hep B/C, uncontrolled infection 13. Birth control if partner has child-bearing potential 14. Meets **ALL** of the following Diagnosis/Drug specific criteria below: a. WBC at least 2.5K/uL and/or ANC at least 1.5 K/uL b. Hgb > 9mg/dL (no transfusion within 30 days) c. Platelets > 100 K/uL d. T.bili < 1.5x ULN (3x for Gilbert's) e. AST/ALT < 3x ULN (5x if liver metastases) f. Serum creatinine < 1.5x ULN and creatinine clearance > 50 mL/min (using Cockcroft-Gault equation with actual body weight) g. Albumin > 3.0g/L h. ECOG* PS 0-2 (consider patients with PS2 very carefully; only 7% of patients on VISION had a PS of 2 so these patients were not well represented in the trial) If initial criteria are met, approve x4 doses. If initial criteria are not met, do not approve. **RENEWAL CRITERIA**: Must meet **ALL of the following**: *(Describe specific criteria that would warrant continuation of the drug)* 1. Patient has tolerated medication 2. Patient has shown evidence of response, defined as one of the following: a. PSA response b. Radiologic response c. Clinical benefit per treating physician If renewal criteria are met, approve x2 doses. If renewal criteria are not met, do not approve. **Pluvicto™ treatment greater than a total of 6 doses as per the Food and Drug Administration-approved regimen is considered investigational.**

Please click here to view clinical criteria for PET Scan: Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Neuroendocrine Tumors

Gastroenteropancreatic neuroendocrine tumors are rare. It is estimated that approximately one out of 27,000 people are diagnosed with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) per year (Voelker, 2018). However, their incidence has increased in the last thirty years (Cives & Strosberg, 2018). Neuroendocrine tumors of the midgut represent the most common malignant gastrointestinal neuroendocrine tumors. Overall survival rate is less than 50% especially in patients with metastatic disease (Modlin, Lye, & Kidd, 2003; Yao et al., 2008). Initial therapy includes somatostatin analogue (Caplin, Pavel, & Ruszniewski, 2014). However, there exists a lack of second-line treatment for neuroendocrine tumors (except for everolimus for nonfunctional neuroendocrine tumors (Yao et al., 2016)) if first-line treatment fails. Radiolabeled somatostatin analogue, Lutetium-177, has been the center of attention and it may be promising for the management of advanced neuroendocrine tumors (NETs).

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Lutathera or Lutetium Lu 177 dotatate is a radioactive targeted therapy. The medication binds to somatostatin receptors which are present on certain tumors. Once Lutathera binds to the receptor, it enters the cell and uses radiation to cause damage. However, it does not impact normal cells. Lutathera delivers beta- and gamma radionuclides to cancerous cells with a maximum particle range of 2 mm and a half-life of 160 hours (van der Zwan et al., 2015). It is administered as four infusions separated by eight weeks interval.

On January 29, 2018, the Food and Drug Administration approved lutetium Lu 177 dotatate (LUTATHERA, Advanced Accelerator Applications USA, Inc.) a radiolabeled somatostatin analog, for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Prostate Cancer
Source: Verbatim from Juzeniene A, Stenberg VY, Bruland ØS, Larsen RH. Preclinical and Clinical Status of PSMA-Targeted Alpha Therapy for Metastatic Castration-Resistant Prostate Cancer. Cancers (Basel). 2021 Feb 13;13(4):779. doi: 10.3390/cancers13040779. PMID: 33668474; PMCID: PMC7918517.)
"Prostate cancer is the second most common cancer in men worldwide, with an estimated 1.3 million new cases and 359,000 deaths in 2018 [1]. The tumors of 10–20% of prostate cancer patients become refractory to androgen deprivation therapy and progress as metastatic castration-resistant prostate cancer (mCRPC) [2,3]. Bone metastases dominate, but lymph node and visceral metastases are also frequent in mCRPC patients [4–6]."

Medical Technology Assessment Committee (MTAC)

Lutetium Lu 177 Dotatate (Lutathera) for Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
01/14/2019: MTAC Review
Evidence Conclusion:

- There is limited evidence comparing Lu-Dotatate and octreotide
  - Based on one RCT with moderate risk of bias, Lu-Dotatate may be more effective than octreotide LAR in adult population with predominantly low grade, higher level of expression of somatostatin receptors gastroenteropancreatic NETs who failed initial therapy.
  - However, Octreotide results in lower adverse events than Lu-Dotatate.
- In non-comparative studies, low evidence suggests that Lu-Dotatate may be effective and safe in patients with advanced gastroenteropancreatic neuroendocrine tumors.

Articles: PubMed was searched through October 19, 2018. Search terms include ((Lutathera OR lutetium Lu 177 dotatate OR lutetium 177 dotatate OR Lu-177 OR 177Lu-DOTATATE)) AND (Neuroendocrine tumors OR pancreatic neuroendocrine tumors OR gastrointestinal neuroendocrine tumors). The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Several articles were identified but only one RCT (NETTER-1 trial) met the inclusion criteria. Clinicaltrial.gov was also searched on October 11, 2018 and identified several ongoing studies with no available results. See Evidence Table**.**

The use of Lutetium Lu 177 Dotatate (Lutathera) for Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Prostate-Specific Membrane Antigen Radioligand Therapy for the Treatment of Metastatic Castration-Resistant Prostate Cancer
07/14/2022: Medical Technology Assessment Team (MTAT)
Evidence Conclusion:
177-Lu PRLT
Overall Conclusion(s)
Efficacy

- Overall, moderate-certainty evidence from 3 RCTs with a total of 821 mCRPC patients, with disease progression after various therapies including androgen-receptor pathway inhibitors, taxane chemotherapy, and palliative radiotherapy, demonstrates that 177-Lu PRLT had a statistically significant decrease in PSA levels, increase in response rates (i.e., objective or overall response, disease control rate), prolonged OS and/or PFS, and/or improvement in quality of life outcomes compared to cabazitaxel, standard care, or docetaxel. An additional 2

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RCTs (71 patients) investigated 177-Lu PRLT dosing and reported inconsistent data for PSA decline and disease control rates. The overall certainty in the RCT evidence was downgraded to reflect inconsistency, indirectness, imprecision, as well as risk of bias. With respect to the quality of individual studies, risk of bias is moderate due to heterogeneity in patient populations and/or treatment protocols, lack of masking, as well as loss to follow-up in control groups. Industry sponsorship of studies was also common, although this funding source is common in cancerrelated drug trials. There is moderate confidence that the reported effect estimate is likely to be close to the true effect, but there is a possibility that it is substantially different. Additional RCTs with large sample sizes, consistent patient selection and treatment regimen, would contribute to the overall certainty in evidence.

- In addition to the RCTs, there were 95 observational studies (3 retrospective comparative, 22 prospective non-comparative, 70 retrospective non-comparative) with 5,291 mCRPC patients demonstrating that, after treatment with 177-Lu PRLT, 55.5% to 84.7% patients experienced PSA decline, 0% to 73% had partial response, 8.4% to 46% had stable disease, 4% to 46% had progressive disease, with OS ranging from median 6 to 18 months and PFS ranging from median 3.8 to 11 months. The evidence from the observational studies is rated with lowcertainty given the retrospective and/or non-comparative study design in the majority of the included studies and the inherent biases associated with this design, as well as small sample sizes.

Safety

- Overall, low-certainty evidence from 5 RCTs with 1,142 mCRPC patients reported mortality rates ranging from 0% to 87% (5 RCTs; 1,142 patients) and serious (grade ≥3) anemia, bone marrow suppression, pain, and thrombocytopenia AEs occurring in greater than 10% of patients (4 RCTs; 985 patients). One RCT with 40 patients reported no statistically significant difference in treatment-emergent grade 3-to-5 AEs (30% vs 50%) among 177-Lu PRLT and docetaxel treated patients. The evidence certainty was downgraded for heterogeneity in patient populations and treatment protocols, lack of masking, and loss to follow-up in control groups. Furthermore, the lack of analyses in 4 out of the 5 RCTs, to determine the statistical significance of the between-group difference in mortality and/or AEs, warranted further downgrading of the evidence to low-certainty.
- In addition to the RCTs, there were 44 observational studies (2 retrospective comparative, 16 prospective non-comparative, 26 retrospective non-comparative) with 2,244 mCRPC patients reporting additional AEs including: increases in aspartate aminotransferase and alanine transaminase; chronic kidney disease (grade 1 to 2); hemoglobin toxicity; and renal toxicity (grade 1). The evidence from the observational studies was rated with low certainty given the majority of included studies had small sample sizes and used a retrospective and/or noncomparative study design.

225-Actinium (Ac) PRLT

Evidence Summary and Overall Conclusion(s)

- There is very-low-certainty evidence from 1 retrospective, non-comparative study with 40 mCRPC patients demonstrating 225-Ac PRLT decreased PSA levels, had an OS greater than 12 months, radiologic PFS of 6 months, and resulted in xerostomia and/or loss of taste events. There is very-low confidence that the reported effect estimate reflects the true effect due to the small, retrospective, non-comparative design from the single study that also lacked well-defined inclusion/exclusion criteria, long-term follow-up, and comparative evidence.

131-Iodine (I)-MIP-1095 PRLT

Evidence Summary and Overall Conclusion(s)

- There is very-low-certainty evidence from 1 retrospective non-comparative study with 34 mCRPC patients demonstrating 131-I-MIP-1095 PRLT decreased PSA levels, had a median time to PSA progression of 75 days, median OS of 17 months, with patients experiencing fatigue, leukopenia, thrombopenia, and xerostomia events. There is very-low confidence that the reported effect estimate reflects the true effect due to the small, retrospective, non-comparative design from the single study that also lacked well-defined inclusion/exclusion criteria, long-term follow-up, and comparative evidence.

References

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Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
A9513	Lutetium Lu 177, dotatate, therapeutic, 1 mCi
A9607	Lutetium Lu 177 vipivotide tetraxetan, therapeutic, 1 mCi

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
01/06/2023	01/10/2023[MPC]	06/05/2023

[MPC] Medical Policy Committee

Revision History	Description
1/10/2023	MPC approved coverage criteria for Pluvicto (Luteteium Lu 177 vipivotide tetraxetan) for Prostate Cancer. Requires 60-day notice; Effective June 01, 2023.
1/23/2023	Merged Lutetium Lu 177, dotatate (Lutathera) criteria to this Radiopharmaceuticals page with Lutetium Lu 177 vipivotide tetraxetan (Pluvicto). Archiving Lutathera criteria page.
03/03/2023	Updated sources to include Vision and TheraP trials.
03/22/2023	Clarified language related to Medical Oncologist recommending this treatment.
06/05/2023	Removed language related to Medical Oncologist recommending Pluvicto treatment

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