KAISER PERMANENTE® Mid-Atlantic States	**Pluvicto for Treatment of Metastatic Castrate-Resistant Prostate Cancer Medical Coverage Policy**

UTILIZATION * ALERT*

- Prior to use of this MCP for evaluation of medical necessity, benefit coverage MUST be verified in the member's EOC or benefit document.
- For Medicare members, please consult the Medicare Coverage Database.
- Medicare does not have a National Coverage Determination (NCD) for Pluvicto.
- Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) do not exist at this time.
- Note: After searching the Medicare Coverage Database, if no NCD/LCD/LCA is found, then use the policy referenced above for coverage guidelines

I. Procedure: **Lutetium Lu 177 vipivotide tetraxetan (Pluvicto)** for treatment of Metastatic Castrate-Resistant Prostate Cancer

II. Specialties: **Urology, Medical Oncology, Radiation Oncology, Nuclear Medicine**

III. **Clinical Indications for Referral**

PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan or Lu-177-PSMA-617) is medically necessary 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 (AR) pathway inhibition and taxane-based chemotherapy.

IV. Eligibility Criteria for ^{177} Lutetium PSMA therapy (Pluvicto)

Pluvicto treatment is considered medically necessary if the patient meets **ALL** of the following criteria:

A. The patient must meet **ALL** of the following:
1. Age 18 or older**; and**
2. Has prostate-specific membrane antigen (PSMA)-positive disease or castrate-resistant, metastatic prostate cancer**; and**
3. Prostate-specific membrane antigen (PSMA)-positive disease demonstrated by a positive PSMA-11 based PET scan**; and**
4. Prior treatment with **both** of the following:
   a. Previous treatment with taxane-based chemotherapy regimen (such as docetaxel or Jevtana

cabazitaxel intravenous infusion)**; and**

b. Previous treatment with **any** of the following androgen receptor (AR) pathway inhibitors:
   i. Abiraterone acetate; or
   ii. Apalutamide; or
   iii. Enzalutamide; or
   iv. Darolutamide

5. Treatment is prescribed by or in consultation with the Oncologist or Radiation Oncologist.

B. Clinical Requirements:

1. ECOG PS 0-2; **and**
2. Life expectancy of at least 6 months; **and**
3. Previously received at least 1 androgen targeted therapy (e.g., abiraterone, enzalutamide, etc.); **and**
4. Previously received at least one taxane-based chemotherapy (docetaxel, cabazitaxel) for metastatic castration-resistant prostate cancer, at least two cycles are required; **and**
5. At least 30 days out from starting bisphosphonate or denosumab (if on it); **and**
6. No radium-223 within last 6 months; **and**
7. No chemotherapy, immunotherapy, or biologics within 28 days of treatment; **and**
8. No impending cord compression; **and**
9. Prior CNS metastases are acceptable if stable. Prior treatment for metastases is acceptable but the patient cannot currently be on steroids for this treatment, and they must be neurologically intact; **and**
10. No NYHA class 3-4 heart failure, active Hepatitis B/C or uncontrolled infection; **and**
11. Must utilize birth control if partner has child-bearing potential

C. Imaging Study requirements:

1. Baseline CT C/A/P and bone scan within 1 month of therapy; **and**
2. PSMA PET/CT with PSMA-avid within 4 months of therapy; **and**
3. PSMA PET/CT with PSMA-avid (tracer uptake greater than normal liver activity) metastatic disease of any size in any organ system; **and**
4. Treatment for patients with non-PSMA-avid lesions thought to be consistent with prostate cancer metastasis will be reviewed by subject matter experts on a case-by-case basis; **and**
5. At least one metastatic lesion must be visible on CT, bone scan or MRI (note that lesions visible only on PSMA imaging, without anatomic correlate, are not sufficient); **and**
6. Metastatic Castrate Resistant Prostate Cancer (mCRPC) disease progression documented by imaging;
   a. Unequivocal progression of soft tissue lesions; **or**
   b. Development of >1 new bone lesions (note that increased uptake in pre-existing lesions on a bone scan does not constitute progressive disease)

D. Laboratory Requirements:

1. WBC at least 2.5 K/uL and ANC at least 1.5 K/uL; **and**
2. Hgb > 9 mg/dL (no transfusion within 30 days); **and**
3. Platelets > 100 K/uL; **and**
4. T. bilirubin < 1.5x ULN (3x for Gilbert's); **and**
5. AST/ALT < 3x ULN (5x if liver metastases); **and**
6. Serum creatinine < 1.5x ULN and creatinine clearance > 50 mL/min (using Cockcroft-Gault equation with actual body weight); **and**
7. Albumin > 3.0 g/dL;

V. Precautionary Measures with Treatment

A. Adverse Reactions

Treatment with Pluvicto mainly affects the lacrimal glands, salivary glands, left and right colon, kidneys, and bladder wall. To reduce the risk of adverse events, the following measures should be taken prior to and during treatment.

1. **Risk from radiation exposure**
   a. Encourage patients to increase oral fluid intake and ensure they are well hydrated;
   b. Advise patients to void as often as possible to reduce bladder radiation;
   c. Minimize radiation exposure during and after treatment consistent with institutional good radiation safety practices and patient treatment procedures.
      i. Limit close contact (<3 feet) with household contacts for 2 days or with children/pregnant women x 7 days **and**
      ii. Sleep in a separate bedroom from household contacts x 3 days, children x 7 days, pregnant women x 15 days

2. **Myelosuppression**
   a. Perform complete blood count before and during treatment; and
   b. Withhold, reduce dose, or permanently discontinue treatment and clinically treat complications based on severity.

3. **Renal toxicity**
   The treatment can induce renal toxicity. Those patients with mild or moderate renal impairment are at greater risk.
   a. Maintain adequate hydration in the days around and during treatment;
   b. Encourage patient to urinate frequently post treatment;
   c. Perform kidney function laboratory tests before and during treatment; and
   d. Withhold, reduce dose, or permanently discontinue treatment based on severity of renal toxicity.

4. **Embryo-fetal toxicity**
   The treatment can cause fetal harm based on its mechanism of action.
   Male patients with female partners of childbearing age should be advised to use effective contraception during treatment up to 14 weeks after the last dose.

5. **Infertility**
   The recommended cumulative dose of 44.4 GBq of treatment can induce temporary or permanent infertility due to absorption of radiation in the testes.

B. Continuation of Treatment, Dose Modification or Discontinue Treatment in Adverse Events

The recommended dose of Lu-177-PSMA-617 (PluvictoTM) is 7.4 GBq (200 mCi) intravenously every 6 weeks up to a maximum of 6 doses in total. Management of adverse reactions during treatment may require temporary dose interruption (such as extending the dosing interval from every 6 weeks up to every 10 weeks), dose reduction or to permanently discontinue the treatment.

1. Dose Modification
   a. A one-time dose reduction of 20% to 5.9 GBq (160 mCi) is allowed to reduce toxicity.
   b. The dose should NOT be re-escalated.
   c. Discontinue treatment if further adverse events occur requiring additional dose reduction.

   Note: Please refer to Lu-177-PSMA-617 prescribing information for recommended dosage modifications.

2. Discontinue Treatment
   Treatment with PLUVICTO must be **discontinued** in the presence of **any** of the following:
   a. There is treatment delay due to adverse events that persists for > 4 weeks; **or**
   b. Further adverse reactions occur that would require additional dose reduction, after initial dose reduction for toxicity of 20% has already been made (with no re-escalation of dose).

3. Lu-177-PSMA-617 must be **permanently discontinued** if the patient develops **any** of the following:
   a. Recurrent Grade ≥ 3 myelosuppression after one dose reduction**; or**
   b. Grade ≥ 3 renal toxicity**; or**
   c. Recurrent renal toxicity after one dose reduction**; or**
   d. Recurrent Grade 3 dry mouth after one dose reduction**; or**
   e. Recurrent Grade ≥ 3 gastrointestinal toxicity after one dose reduction**; or**
   f. Aspartate aminotransferase or alanine aminotransferase > 5 times the upper limit of normal in the absence of liver metastases**; or**
   g. Any unacceptable toxicity**; or**

h. Any serious adverse reaction that requires treatment delay of > 4 weeks**; or**
i. Any recurrent Grade 3 or 4 or persistent and intolerable Grade 2 adverse reaction after one dose reduction

VI. Exclusions and Limitations

A. Exclusions

Pluvicto is not medically necessary and considered experimental /investigational if the patient does not meet **all** of the following criteria:

1. For other uses or indication except the FDA-approved clinical indication cited in section III; **and**
2. If the patient does not meet all of the eligibility criteria cited in section IV.

B. Treatment Limitation

1. Course of treatment
   a. Quantity: 6 single dose vials given every 6 weeks
   b. Duration: up to 30 weeks
   c. Only one course of treatment is allowed per lifetime.
2. Renewal of treatment – none

VII. Definitions

1. Pluvicto (lutetium Lu 177 vipivotide tetraxetan) is a radioligand therapeutic agent for the treatment of adults with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. Lutetium Lu 177 vipivotide tetraxetan binds to PSMA-expressing cells resulting in the delivery of radiation to PSMA-expressing and surrounding cells causing DNA damage and eventual cell death.

Pluvicto was approved by the Food and Drug Administration on March 23, 2022. It was studied in Phase-3 VISION clinical trial, a randomized targeted RLT active-control study comparing PLUVICTO + BSOC vs BSOC alone. The VISION study investigators concluded that Pluvicto extended imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer. Adverse events during treatment were noted to have occurred no more than 30 days after the last dose and before subsequent anti-cancer treatment. Significant toxicities noted include:

- Grade 3-4 decreased hemoglobin 15%, decreased platelets 9%, decreased leukocytes 7%, decreased neutrophils 4.5% with 5 study related deaths (nearly 2%) related to bone marrow suppression
- Grade 3 or 4 acute kidney injury (3%) and increased creatinine (4%)

- Other significant potential toxicities include fatigue, dry mouth, nausea, anorexia, constipation, hyponatremia, hypocalcemia, infertility
- Overall differences in efficacy or toxicity were not noted in patients >75 years of age.

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Pluvicto is manufactured by Advanced Accelerator Applications, a Novartis company. It is available in a single-use 30 ml vial containing 1,000 MBq/mL (27 mCi/mL) of lutetium Lu 177 vipivotide tetraxetan to be administered once every 6 weeks between 4 up to 6 doses, or until disease progression or unacceptable toxicity.

2. **Prostate-specific membrane antigen (PSMA)** is a transmembrane protein, overexpressed in prostate cancer, including metastatic castration-resistant prostate cancer (mCRPC) and correlates with the aggressiveness of the disease.

3. **Positive metastatic castration-resistant prostate cancer (mCRPC**) is a form of advanced prostate cancer that no longer respond to hormone treatment and shows signs of disease progression including metastasis.

4. **Androgen receptor pathway inhibitors** are a class of drugs for treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) and non-metastatic castration-resistant prostate cancer (nmCRPC). The approved AR pathway inhibitors in the US are: 3 anti-androgens—apalutamide, enzalutamide, and darolutamide and androgen receptor pathway inhibitor, abiraterone acetate.

5. **Taxanes** are cytotoxic chemotherapy agents that affect cellular structures that are needed for cancer cells to divide - the microtubules. Taxane-based chemotherapy includes paclitaxel (Taxol), albumin paclitaxel (Abraxane) and docetaxel (Taxotere).

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Approval History

Effective June 01, 2016, state filing is no longer required per Maryland House Bill HB 798 – Health Insurance – Reporting

Date approved by RUMC	Date of Implementation
06/26/2023	06/26/2023
05/23/2024	05/23/2024

*The Regional Utilization Management Committee received delegated authority in 2011 to review and approve designated Utilization Management and Medical Coverage Policies by the Regional Quality Improvement Committee.

Note: Kaiser Permanente Mid-Atlantic States (KPMAS) include referral and authorization criteria to support primary care and specialty care practitioners, as appropriate, in caring for members with selected conditions. Medical Coverage Policies are not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by a practitioner in any particular set of circumstances for an individual member.