OVERVIEW
Radiopharmaceuticals are composed of a radioisotope (i.e., a radioactive particle) bond to an organic molecule and are used for diagnostic and therapeutic purposes. The organic molecule acts as a targeting compound (ligand) that conveys the radioisotope to specific organs, tissues, or cells. Lutetium Lu 177 vipivotide tetraxetan (Pluvicto™), commonly abbreviated as Lu-177-PSMA-617, is a radioligand therapy that targets prostate-specific membrane antigen (PSMA), which is highly expressed on prostate cancer cells. Lu-177-PSMA-617 is indicated for use in adults with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have already been treated with other anticancer treatments, including androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

MEDICAL CRITERIA
Medicare Advantage Plans and Commercial Products
Therapeutic radiopharmaceuticals for prostate cancer using Lu-177-PSMA-617 (Pluvicto™), may be considered medically necessary for the treatment of adults with PSMA-positive mCRPC when both of the following criteria are met:
- Patients with ≥1 PSMA-positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions,
- Patients who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy.

PRIOR AUTHORIZATION
Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers.

POLICY STATEMENT
Medicare Advantage Plans and Commercial Products
Therapeutic radiopharmaceuticals for prostate cancer using Lu-177-PSMA-617 (Pluvicto™) is considered medically necessary when the above criteria are met.

Therapeutic radiopharmaceuticals for prostate cancer using Lu-177-PSMA-617 (Pluvicto™) is considered investigational when the above criteria are not met.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for therapeutic radiology coverage/benefits.

BACKGROUND
Prostate cancer is the second leading cause of cancer-related deaths among American men with 268,490 new cases and 34,500 disease-related deaths estimated for 2022. About 6 in 10 cases of prostate cancer are diagnosed in men who are ≥ 65 years of age, and the disease is rare in men < 40 years of age. Furthermore, prostate cancer disproportionately affects non-Hispanic Black men versus white men. Prostate cancer is typically suspected due to increased levels of prostate-specific antigen (PSA) upon screening.

Clinical staging is based on the digital rectal exam and biopsy results. T1 lesions are not palpable while T2 lesions are palpable but appear to be confined to the prostate. T3 lesions extend through the prostatic capsule, and T4 lesions are fixed to or invade adjacent structures. The most widely used grading scheme for a
prostate biopsy is the Gleason system. It is an architectural grading system ranging from 1 (well-differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is a high-grade cancer that grows more quickly.

**Treatment**

Early localized disease can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose prostate cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In patients with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. Androgen deprivation therapy (ADT) is generally the initial treatment for patients with advanced prostate cancer. Unfortunately, while ADT is effective at producing tumor response and improving quality of life, most patients’ disease will eventually progress on ADT.

**Castration-Resistant Prostate Cancer**

Prostate cancer that progresses while the patient is on ADT is referred to as castration-resistant prostate cancer (CRPC). Androgen pathways are important in the progression of CRPC, therefore, even after progression, continued ADT is generally used in conjunction with other treatments. Several drugs have been developed that either inhibit enzymes involved in androgen production or inhibit the androgen receptor, such as abiraterone and enzalutamide. Taxane chemotherapy with docetaxel or cabazitaxel may also be used after progression. Immunotherapy (sipuleucel-T) or radium 223 are additional options for select men.

**Prostate-Specific Membrane Antigen–Positive Metastatic Castration-Resistant Prostate Cancer**

Prostate-specific membrane antigen (PSMA) is a transmembrane glutamate carboxypeptidase that is highly expressed on prostate cancer cells and high PSMA expression is an independent biomarker of poor prognosis. Metastatic lesions are PSMA-positive in most patients with mCRPC and high expression has been independently associated with reduced survival. More recently, radioligand therapies such as Lu-177-PSMA-617 have demonstrated the ability to selectively target prostate cancer cells in patients who have PSMA-positive mCRPC.

**Radionuclide Therapy: Lutetium Lu 177 vipivotide tetraxetan**

Lu-177-PSMA-617 is a radiopharmaceutical agent with 2 components: a drug that delivers the therapy to cancer cells and a radioactive particle. In the case of Lu-177-PSMA-617, the delivery vehicle is PSMA-617 and the radioactive component is lutetium-177. Upon binding of Lu-177-PSMA-617 to PSMA-expressing cells, the beta-minus emission from lutetium-177 delivers radiation to PSMA-expressing cells, as well as to surrounding cells, and induces DNA damage which can lead to cell death. Patients should be selected for treatment with Lu-177-PSMA-617 using gallium Ga 68gozetotide or an approved PSMA-11 imaging agent based on PSMA expression in tumors.

Lu-177-PSMA-617 should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

The recommended dose of Lu-177-PSMA-617 is 7.4 GBq (200 mCi) every 6 weeks for up to 6 doses.

Patients should be well-hydrated during treatment.

Refer to the prescribing information for Lu-177-PSMA-617 for recommended dosage modifications for adverse reactions. The management of adverse reactions may require temporary dose interruption (extending the dosing interval from every 6 weeks up to every 10 weeks), dose reduction, or permanent discontinuation of treatment with Lu-177-PSMA-617. The dose of Lu-177-PSMA-617 may be reduced by 20% to 5.9 GBq (160 mCi) once; the dose should not be re-escalated.

Lu-177-PSMA-617 should be discontinued permanently if the patient develops any of the following:
• Recurrent Grade ≥ 3 myelosuppression after one dose reduction
• Grade ≥ 3 renal toxicity
• Recurrent renal toxicity after one dose reduction
• Recurrent Grade 3 dry mouth after one dose reduction
• Recurrent Grade ≥ 3 gastrointestinal toxicity after one dose reduction
• Aspartate aminotransferase or alanine aminotransferase > 5 times the upper limit of normal in the absence of liver metastases
• Any unacceptable toxicity
• Any serious adverse reaction that requires treatment delay of > 4 weeks
• Any recurrent Grade 3 or 4 or persistent and intolerable Grade 2 adverse reaction after one dose reduction

For individuals with PSMA-positive mCRPC who have failed other anticancer therapies, including androgen receptor pathway inhibition and taxane-based chemotherapy, who receive Lu-177-PSMA-617, the evidence includes a systematic review and 2 randomized controlled trials (RCTs). Relevant outcomes are overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related mortality and morbidity. The systematic review, which included a heterogeneous population of patients with mCRPC, demonstrated a higher proportion of patients responding to PSMA-targeted radionucleotide therapy based on a prostate-specific antigen (PSA) decrease of ≥50% compared to controls; the review was also limited by the inclusion of mostly retrospective studies with small numbers of patients. The VISION RCT compared Lu-177-PSMA-617 plus investigator-determined standard of care (SOC) therapy to SOC therapy alone in patients with PSMA-positive mCRPC who had been treated with AR pathway inhibitors and taxane-based chemotherapy. Results demonstrated that Lu-177-PSMA-617 plus SOC significantly prolonged the median OS (15.3 vs. 11.3 months) and radiographic progression-free survival (8.7 vs. 3.4 months). The incidence of Grade ≥3 adverse events was higher with Lu-177-PSMA-617 than without (52.7% vs. 38.0%). The phase 2 TheraP RCT compared Lu-177-PSMA-617 to cabazitaxel. Unlike the VISION trial, in TheraP, previous treatment with AR pathway inhibitors was not necessary for participants. Also, the TheraP trial used 2 PET/CT scans to identify PSMA-positive status and excluded patients with discordant findings using gallium-68-labeled PSMA-11 and 2-flourine-18[18F]fluoro-2-deoxy-D-glucose (FDG). The primary endpoint of PSA response, defined by a reduction of at least 50% from baseline, was achieved more often by patients who received Lu-177-PSMA-617 (66%) compared to cabazitaxel (37%). In this RCT, the incidence of Grade ≥3 adverse events was higher with cabazitaxel (53%) compared to Lu-177-PSMA-617 (33%). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING
Medicare Advantage Plans and Commercial Products
The following HCPCS code is medically necessary when criteria, above, are met:
A9607  Lutetium Lu 177 vipivotide tetraxetan, therapeutic, 1 mCi (New Code Effective 10/01/2022)

RELATED POLICIES
Not applicable

PUBLISHED
Provider Update, November 2022

REFERENCES