VHA Office of Integrated Veteran Care

Clinical Determination and Indication

Lutetium-177 (Lu177) PSMA-617, Vipivotide Tetraxetan (Pluvicto)

CDI Number: 00017

Original Effective Date: January 1, 2025

Last Review Date: January 1, 2025

I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgment when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Lutetium-177 (Lu177) PSMA-617, Vipivotide Tetraxetan (Pluvicto)

Lu177 PSMA-617, vipivotide tetraxetan (Pluvicto) is a U.S. Food and Drug Administration (FDA) approved radiopharmaceutical and is indicated for the treatment of prostate-specific membrane antigen (PSMA)-positive metastatic castrate-resistant prostate cancer (mCRPC). It is considered **medically necessary** when **ALL** the following criteria are met:

- Adult Veteran with PSMA-positive mCRPC castrate-resistant prostate cancer
  - PSMA expression in tumors is identified using an FDA-approved PSMA positron emission tomography (PET) imaging agent
- Veterans with PSMA-positive mCRPC must have progressed on first line and second line therapy treatments unless other medical considerations* are a priority. The patient must meet **both** of the following criteria:
  - Veteran has received and progressed through at least one androgen receptor (AR) pathway inhibitor
  - Veteran has progressed or is intolerant to at least one taxane-based chemotherapy agent Limitations/Exclusions

***Note**: Medical considerations may include Veterans who are intolerant to chemotherapy or clinically reasonable patient refusal.

Note: This Clinical Determination and Indication (CDI) is in alignment with the "VA Oncology Prostate Cancer Clinical Pathway". For additional information

on clinical management, please refer to the Prostate Cancer – Castrate Resistant Prostate Cancer (CRPC) M1 clinical pathway.

Quality of Care Recommendations:

- The VA Oncology Clinical Pathways are standardized, evidence-based decision support tools and recommended resources when determining the treatment plan for Veterans in the community; these resources are not intended to replace clinical judgement
- The treating facility must have radiation safety precautions in place to keep radiation exposure to patients, employees, and the public as low as reasonably achievable (ALARA)
- Prior to the initial cycle of therapy (<30 days), the Veteran must meet with the treating physician for an initial assessment that includes the following: history and physical, review of relevant labs and PET imaging results, patient education, and review of radiation safety guidelines
- Documentation of initial visit, inter-cycle assessments, and completion evaluation with treatment summary must be provided to the referring VA Medical Center for inclusion in the patient's VA Electronic Health Record
- After each cycle of therapy, the Veteran must be assessed for side effects of the therapy, as well as treatment effectiveness and relevant biomarkers
- Post-therapy administration SPECT imaging and dosimetry is considered a best practice; however, planar imaging to confirm radiopharmaceutical distribution is a minimum recommendation
- It is strongly recommended that at a minimum after the 4th cycle of Pluvicto, a follow-up PSMA-PET scan is obtained for sites not performing post-treatment SPECT, and a follow-up visit with the treating physician is conducted to determine treatment effectiveness

b. Limitations/Exclusions

For all conditions/indications not listed in section II.a. of this document, Lu177 PSMA-617, vipivotide tetraxetan is considered **not medically necessary** due to insufficient evidence of efficacy and safety.

c. Dosage Limitations

Lu177-PSMA-617, vipivotide tetraxetan (Pluvicto) is considered **medically necessary** for treatment up to six (6) total doses/treatment cycles.

d. Description of Treatment

Pluvicto is a therapeutic radioactive drug used for the treatment of patients with PSMA-positive mCRPC who have been previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy. Pluvicto uses radiation to shrink prostate tumor tissue, while minimizing damage to other parts of the body.

In order to be treated with Pluvicto, high levels of PSMA expression must be shown on a PSMA PET scan. The PSMA PET scan uses a diagnostic radioactive agent to target PSMA positive cells, a prostate-specific membrane antigen expressed by prostate cancer. The radioactive agent is injected into a vein before the patient goes through the PET scanner, which captures three-dimensional images of the inside of the body. The PSMA levels identified on the PET scan will inform providers and patients whether they are eligible for Pluvicto. After each treatment administration the patient may be imaged with a SPECT scanner to confirm the distribution of radiopharmaceutical. The SPECT scan data may be used for radiation dose determination (dosimetry).

Dose interruption, reduction, or permanent discontinuation may be required due to adverse reactions. The most common adverse reactions include fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation.

Pluvicto is administered intravenously approximately every six weeks, for up to six doses. Pluvicto, a radiopharmaceutical agent, must be administered and handled by a certified nuclear medicine technologist with appropriate radiation safety precautions in place to keep radiation exposure to patients, employees, and the public as low as reasonably achievable (ALARA). Administration of Pluvicto should be performed in a radiopharmaceutical therapy center accredited by the Intersocietal Accreditation Commission (IAC) or in a designated Society of Nuclear Medicine and Molecular Imaging (SNMMI) Clinical or Comprehensive Therapy Center of Excellence.Background and Supporting Information

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38 (b). Each subsection supports VA's determination for medical necessity and is in alignment with generally accepted standards of medical practice.

a. Background of Prostate Cancer

Prostate cancer is the second most common type of cancer for people with prostates in the United States. An estimated 1 in 8 people with prostates will be diagnosed with prostate cancer during their lifetime. Prostate cancer is

more prominent in older and non-Hispanic people with prostates. The average age of initial diagnosis is approximately 66 years old. The American Cancer Society predicts 5-year survival rates are greater than 99% when the cancer is localized to the prostate or has spread just outside the prostate, and 32% when the cancer has spread to further parts of the body, such as the lungs or liver.

A majority of prostate cancers are initially found as a result of routine screening, as symptoms are not usually present in early-stage prostate cancer. More advanced prostate cancer may cause symptoms such as problems with urination, blood present in the urine or semen, erectile dysfunction, bone pain (such as hips, spine, or ribs), and weakness or numbness in the lower extremities.

Screening and Diagnosis

A prostate-specific antigen (PSA) blood test can be used as both a screening tool for patients experiencing symptoms of prostate cancer, and as an ongoing test for those who have already been diagnosed. The PSA blood test measures the amount of PSA in the body, which is a protein created by both healthy and cancerous prostate gland cells. While there is no set cutoff point to make the determination of a cancer diagnosis, most physicians use 4 ng/ml or higher as the threshold for determining if the patient may require further testing. If the results from a PSA blood test, digital rectal exam (DRE), or other test is suggestive of prostate cancer, a prostate biopsy is performed to make a confirmative diagnosis.

Management and Treatment

Androgen deprivation therapy (ADT) is the typical first line treatment option for those with advanced prostate cancer, however disease progression may still occur while undergoing ADT therapy. When prostate cancer is resistant to ADT, this disease state is called castrate-resistant prostate cancer (CRPC). As CRPC is a type of cancer that continues to grow, even when testosterone levels are low, it can advance to metastatic castrate-resistant prostate cancer (mCRPC), meaning the cancer has spread to lymph nodes or other parts of the body. Once mCRPC has developed, treatment options advance to chemotherapy, second-line hormone therapies, targeted therapy, and radiation therapy. Pluvicto, a radiopharmaceutical that was approved by the FDA in March 2022, is used for the treatment of PSMA-positive mCRPC. For a detailed treatment guideline, please refer to the VA Oncology Prostate Cancer Clinical Pathway “Prostate Cancer – Castrate Resistant Prostate Cancer (CRPC) M1.”

b. Research, Clinical Trials, and Evidence Summaries

In 2021, Lu177 PSMA-617, also known as Pluvicto, was granted priority review by the FDA as a new drug application (NDA) for investigational targeted radioligand therapy. This priority review was granted based on encouraging data from a phase III multicenter study – the VISION Trial. The VISION study determined that Pluvicto is both safe and effective for the treatment of PSMA-positive mCRPC. The following outlines the VISION study.

Sartor et al. (2021) conducted an international, open-label, multi-center, phase three trial evaluating Lu177-PSMA-617 in patients who had mCRPC previously treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regimens, and who had PSMA-positive gallium-68-labeled PSMA-11 positron-emission tomographic-computed (CT) tomographic scans. Patients (n=831) were randomly assigned with a 2:1 ratio to receive either Lu-PSMA-617 plus protocol-permitted standard care or standard care alone. The trial showed that Lu177-PSMA-617 plus standard care significantly prolonged both imaging-based progression-free survival and overall survival. Additionally, all secondary end points (objective response, disease control, and time to symptomatic skeletal events) favored Lu177-PSMA-617 over standard care alone.

Additionally, another phase III clinical study, entitled PSMAfore, is actively being conducted to evaluate the efficacy and safety of Pluvicto versus a change in androgen-receptor pathway inhibitor (ARPI) in patients with PSMA-positive mCRPC.

c. U.S. Food & Drug Administration (FDA) Information

Pluvicto has received NDA approval by the FDA for treatment of adult patients with PSMA-positive metastatic castrate-resistant prostate cancer.

To search for more FDA-approved drugs, please visit the FDA-approved drugs website.

Information	Description
NDA Number	215833
Drug Name	Pluvicto
Active Ingredients	Lutetium Lu-177 Vipivotide Tetraxetan
Company Name	Advanced Accelerator Applications USA, Inc., A Novartis Company
Address	8910 Purdue Road, Suite 250 Indianapolis, IN 46268

Information	Description
Approval Date	03/23/2022
FDA Website	FDA Approval Info

d. Medicare Coverage Determinations

There are no available Medicare coverage determinations for this pharmaceutical agent. This does not indicate VA exclusively follows CMS coverage determinations.

IV. Definitions

Term	Definition
Androgen Receptor	A protein that binds sex hormones called androgens
Androgen Deprivation	Treatment to suppress or block the production or action of the androgen sex hormone. This is done by having the testicles removed, by taking female sex hormones, or by taking drugs called antiandrogens
Antigen	Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, or other substances that come from outside the body. Body tissues and cells, including cancer cells, also have antigens on them that can cause an immune response
Castration	Removal or destruction of the testicles or ovaries using radiation, surgery, or drugs. Medical castration refers to the use of drugs to suppress the function of the ovaries or testicles
Metastatic	Describing metastasis, which is the spread of cancer from the primary site (place where it started) to other parts of the body
Myelosuppression	A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. When myelosuppression is severe, it is called myeloablation
Radioligand Therapy	Targeted form of cancer treatment that delivers radiation directly to cancer cells
Radiopharmaceutical	A drug that contains a radioactive substance and is used to diagnose or treat disease, including cancer
Time to Symptomatic Skeletal Event	Time from randomization to first new pathological bone fracture, spinal cord compression, tumor-related orthopedic surgery, radiation therapy for bone pain, or death

V. References

American Cancer Society. (2019, August). Can prostate cancer be found early? Retrieved on September 5, 2023, from https://www.cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/detection.html

Canadian Cancer Society. (2021, February). Treatments for castration-resistant prostate cancer. Retrieved on September 5, 2023, from https://cancer.ca/en/cancer-information/cancer-types/prostate/treatment/castration-resistant-prostate-cancer#:~:text=Castration%2Dresistant%20prostate%20cancer%20(CRPC,or%20hormone%2Dresistant%20prostate%20cancer

Dawson, N., & Leger, P. (2023). Overview of the treatment of castration-resistant prostate cancer (CRPC). UpToDate. Retrieved September 5, 2023, from https://www.uptodate.com/contents/overview-of-the-treatment-of-castration-resistant-prostate-cancer-crpc#

Hupe, M. C., Philippi, C., Roth, D., Kümpers, C., Ribbat-Idel, J., Becker, F., Joerg, V., Duensing, S., Lubczyk, V. H., Kirfel, J., Sailer, V., Kuefer, R., Merseburger, A. S., Perner, S., & Offermann, A. (2018). Expression of prostate-specific membrane antigen (PSMA) on biopsies is an independent risk stratifier of prostate cancer patients at time of initial diagnosis. Frontiers in Oncology, 8, 623. https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2018.00623/full

Kwon, D.H., Velazquez A., de Kouchkovsky, I. (2022). PSMA PET scan. JAMA, 8(12), 1860. https://jamanetwork.com/journals/jamaoncology/fullarticle/2797264

Medicare Coverage Database (n.d.) Retrieved September 13, 2023, from https://www.cms.gov/medicare-coverage-database/search.aspx

National Cancer Institute. (n.d.). NCI dictionaries. Retrieved September 5, 2023, from https://www.cancer.gov/publications/dictionaries

National Comprehensive Cancer Network. (2023). NCCN guidelines: Prostate cancer. Retrieved September 5, 2023, from https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459

Novartis Pharmaceuticals Corporation. (2023, May). Utility of PSMA PET/CT imaging. Retrieved September 5, 2023, from https://www.hcp.novartis.com/products/locametz/psma-pet-ct/utility-of-psma-pet-ct/#metastatic-pc-patient-selection-for-psma-directed-therapy

Sartor, O., de Bono, J., Chi, K.N., Fizazi, K., Herrmann, K., Rahbar, K., Tagawa, S.T., Nordquist, L.T., Vaishampayan, N., El-Haddad, G., Park, C.H., Beer, T.M., Armour, A., Pérez-Contreras, W.J., DeSilvio, M., Kpamegan, E., Gericke, G., Messmann, R.A., Morris, M.J., & Krause, B.J. (2021). Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. The New England Journal of Medicine, 385(12), 1091-1103. https://www.nejm.org/doi/full/10.1056/NEJMoa2107322

U.S. Department of Veterans Affairs. (2023, June). Oncology clinical pathways: Pancreatic cancer. National Oncology Program. Retrieved September 5, 2023, from https://www.cancer.va.gov/CANCER/clinical-pathways.html

U.S. Food & Drug Administration. (n.d.). Drugs@FDA: FDA-approved drugs. Retrieved September 5, 2023, from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

U.S. Food & Drug Administration (2022). FDA D.I.S.C.O.: Burst Edition: FDA approval of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) for the treatment of adult patients with prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. Retrieved September 5, 2023, from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-pluvicto-lutetium-lu-177-vipivotide-tetraxetan-treatment-adult

VI. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI
	MM/DD/YYYY	
	MM/DD/YYYY	