VHA Office of Integrated Veteran Care
Clinical Determination and Indication
Prostate-Specific Membrane Antigen Positron Emission Tomography Scan for Prostate Cancer

CDI Number: 00028

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 Prostate-Specific Membrane Antigen Positron Emission Tomography Imaging

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans use targeted radioactive diagnostic agents to detect antigen over-expressing positive lesions in Veterans with prostate cancer. A PSMA PET scan is considered **medically necessary** for any of the following:

- Initial staging for Veteran with newly diagnosed, biopsy proven prostate cancer who is at risk for metastatic disease
- Veterans with suspected metastasis who are candidates for initial definitive therapy
- Veteran with suspected recurrence of prostate cancer based on elevated serum prostate-specific antigen (PSA) levels

A PSMA PET scan is also indicated for selection of patients with metastatic prostate cancer for whom Lu177-PSMA radioligand directed therapy is indicated.

- Please refer to the Clinical Determination and Indication for 00017 Lutetium Lu177-PSMA (vipivotide tetraxetan) Pluvicto for additional information and clinical indications for PSMA-directed therapy.

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 Clinical Pathway and find the 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 imaging facility must have radiation safety precautions in place to keep radiation exposures to Veterans, employees, and the public as low as reasonably achievable (ALARA). The facility PET/CT program should be accredited by either the ACR or IAC and accreditation practice standards should be followed

b. Limitations/Exclusions

Conditions/indications for which PSMA PET is **not medically necessary** include, but are not limited to, the following:

- Low risk of metastatic disease such as very low, low, and favorable intermediate risk groups for prostate cancer using National Comprehensive Cancer Network (NCCN) risk stratification system

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

c. Description of Procedure

A PSMA PET/computed tomography (CT) exam is an imaging test used to detect prostate cancer throughout the body. The radioactive agents target a protein called PSMA that is expressed by prostate cancer cells. Imaging must be performed with a PET/CT machine that uses digital silicon photomultiplier technology. The PSMA tracer agent is administered intravenously and there are no other special preparation requirements prior to image acquisition.

Dosage and Administration

FDA approved imaging agents include Ga68 and F18-based PSMA radiotracers. Please refer to the package inserts or FDA labels for Illuccix, Pylarify, Locametz, or Posluma for additional information on dosage and administration.

Image Acquisition

The recommended start time for image acquisition is 60 minutes after intravenous administration of the PSMA imaging agent. Depending upon the

radiopharmaceutical used and facility imaging protocol, the Veteran may be asked to void immediately prior to the procedure to assure the bladder is empty. The Veteran is typically positioned supine - lying on their back with arms extended above their head. The scan will typically start from the mid-thigh and proceed up through the skull vertex.

Post Procedure Care

There are no clinical restrictions post PSMA PET scan and Veterans are encouraged to resume normal activities. The PSMA radiotracer is naturally excreted within hours of injection, and the Veteran will likely be encouraged to drink water and urinate as often as possible post procedure to reduce radiation dose.

Safety Precautions

- Risk of radiation exposure: Ensure safe drug handling to protect Veterans and health care workers from unintentional radiation exposure
- For additional safety precautions please refer to the package inserts or FDA labels for Illuccix, Pylarify, Locametz, or Posluma

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 determinations for medical necessity and alignment with generally accepted standards of medical practice.

a. Background of Prostate Cancer and PSMA PET

Prostate cancer is the second most common type of cancer, for individuals with a prostate gland, in the United States. An estimated 1 in 8 people with a prostate will be diagnosed with prostate cancer during their lifetime. The average age of initial diagnosis is approximately 66 years old. The American Cancer Society predicts 5-year overall survival rates are greater than 99% when the cancer is localized to the prostate gland or has regional spread just outside the prostate gland, and only 34% 5-year overall survival when the cancer has spread to more distant parts of the body, such as the bones, lungs, or liver.

Prostate specific membrane antigen (PSMA) is a protein normally found in healthy prostate cells. When prostate cancer is present PSMA is expressed 100 to 1000 times more than normal. The high expression of PSMA on prostate cancer cells provides a means for diagnostic nuclear medicine agents to identify the presence of prostate cancer cells within the body.

Screening and Diagnosis

Accurate assessment of the extent of disease and identifying if the cancer is localized to the prostate gland or metastasized to other locations within the body, is essential for guiding treatment decisions. There are several tests and procedures that may be used to assist in the diagnosis of prostate cancer.

- **History and Physical exam:** An exam of the body to assess general signs of health, including checking for signs of disease, such as localized pain or anything else that seems unusual.
- **Digital rectal exam:** An exam of the rectum where a medical professional inserts a lubricated, gloved finger into the rectum and assesses the prostate gland through the rectal wall for lumps or abnormal areas.
- **Prostate-specific antigen (PSA) blood test:** A test that measures the level of PSA in the blood. PSA is a substance made by the prostate that may be found in higher-than-normal amounts in the blood of those who have abnormal prostate cells/tissue.
- **Prostate biopsy:** A prostate biopsy is a procedure in which a small sample of prostate tissue is removed and evaluated to identify potential cancerous cells.
- **PSMA PET:** A noninvasive diagnostic nuclear medicine imaging procedure that is used to identify prostate cancer cells in the prostate gland and that have spread outside of the prostate, into bone, lymph nodes, or other organs.

PSMA PET Imaging Agents

Prostate-specific membrane antigen (PSMA) radiotracers are radioactive imaging agents that bind to PSMA on prostate cancer cells. These agents are used to assist in staging, re-staging, and developing treatment plans for patients diagnosed with prostate cancer.

Once intravenously administered, the radioactive tracer travels through the blood and attaches to the PSMA protein that is found on the surface of prostate cells. Prostate cancer cells express large amounts of PSMA which allows a PET scan to detect high concentrations of the radioactive PSMA imaging agent. The resulting PET scan provides a visualization of where the prostate cancer cells are located, including if they have metastasized in the body.

Some prostate cancers do not express PSMA and will not be detected during the scan. Additionally, PSMA may be expressed by other types of cancers or noncancerous conditions. There are minor radiation risks associated with PSMA radiotracers as they contribute to a patient’s overall long-term

cumulative radiation exposure, which is associated with an overall lifetime increased risk for cancer.

b. Research, Clinical Trials, and Evidence Summaries

The clinical use of radioactive PSMA diagnostic agents is based upon growing scientific evidence that supports their favorable imaging performance. The FDA approved PSMA imaging agents have shown an excellent safety profile, as well as diagnostic accuracy greater than conventional imaging, in clinical trials.

Fendler et al. (2020) conducted a prospective single arm clinical trial at the University of California, Los Angeles and the University of California, San Francisco. The goal of the study was to identify the impact of 68Ga-PSMA-11 PET (68Ga-PSMA PET) (Illuccix) on the management of recurrent prostate cancer. Patients included had biochemical recurrent histopathology confirmed prostate adenocarcinoma. Biochemical recurrence was defined as a PSA of 0.2 ng/mL or higher, measured more than six weeks after prostatectomy or a PSA rise of 2 ng/mL or higher after radiation therapy. All patients underwent either a 68Ga-PSMA PET/CT or PET/MRI. Images were interpreted by local clinical readers and three masked readers. Areas of recurrent prostate cancer were prostate, prostate bed, and seminal vesicle remnants, pelvic lymph nodes, extrapelvic lymph nodes (retroperitoneal, inguinal, chest, and other), bone, and visceral organs. To assess the change in intended management after 68Ga-PSMA PET, referring physicians received a pre-PET, post-PET, and a post-treatment questionnaire. The pre-PET questionnaire assessed which diagnostic tests they would order and their intended management prior to having the 68Ga-PSMA PET results. The post-PET questionnaire asked their intended management based on the Ga-PSMA PET results, and the post-treatment questionnaire assessed whether the intended management identified post-PET was implemented. A total of 382 patients were included in the pre- and post-PET questionnaire and 206 patients were included in the post-treatment questionnaire. Results showed an intended change in treatment occurred in 260 patients (68%) and of these changes, 176 (46%) were identified as major changes. Authors concluded that sites of recurrent prostate cancer were clarified by 68Ga-PSMA PET and resulted in disease management changes in more than half of patients with biochemical recurrent prostate cancer.

Pienta et al. (2021) conducted a multicenter, prospective, open-label clinical trial called OSPREY, that focused on determining the diagnostic performance of Pylarify for detecting sites of metastatic prostate cancer. Eligible patients were divided into two cohorts: cohort A (n = 268) included high-risk prostate cancer patients and cohort B (n = 117) included patients with evidence of local recurrence or metastatic disease. Three blinded central nuclear

medicine physicians read and evaluated the Pylarify PET/CT scans. In cohort A, Pylarify PET demonstrated improved diagnostic performance over conventional imaging modalities with comparable sensitivity, but threefold higher positive predictive value (PPV) for detecting pelvic nodal metastasis. In cohort B, Pylarify PET detected presumptive metastatic disease in 57.6% of patients (19/33) who had no evidence of distant disease on conventional imaging. The study concluded that in both clinical settings, Pylarify PET provides reliable information to help improve staging of prostate cancer compared to conventional imaging.

Jani et al. (2023) conducted a phase 3, multicenter imaging study called SPOTLIGHT to evaluate the diagnostic performance and safety of 18F-rhPSMA-7.3 (Posluma). The study included 389 people with recurrent prostate cancer. Each participant received PET/CT 50-70 minutes after intravenous administration of Posluma. Three blinded readers evaluated the scans to assess the coprimary endpoints of verified detection rate (overall detection rate x positive predictive value). Statistical thresholds (lower bounds of the confidence intervals) of 36.5% and 62.5% were used for verified detection rate and combined region-level positive predictive value. Results showed Posluma overall detection rate was 83% and verified detection rate ranged from 51% to 54%. Combined region-level positive predictive value ranged from 46% to 60%, which was slightly less than the preidentified threshold. No significant safety concerns were identified. The authors concluded Posluma provides clinically meaningful verified detection rates for localization of recurrent prostate cancer.

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

Illuccix, Pylarify, Locametz, and Posluma have received New Drug Application (NDA) approval by the FDA for PET of PSMA positive lesions in people with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

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

Information	Description
NDA Number	214032
Drug Name	Illuccix
Active Ingredients	Gallium GA-68 Gozetotide
Company Name	Telix Pharmaceutical Inc

Information	Description
Address	12 Municipal Drive Suite 330 Fishers, Indiana 46038
Approval Date	December 17, 2021
FDA Website	ILLUCCIX (fda.gov)

Information	Description
NDA Number	214793
Drug Name	Pylarify
Active Ingredients	Piflufolastat F-18
Company Name	Progenics Pharmaceutical Inc (a Lantheus company)
Address	One World Trade Center 47th Floor Suite J New York, NY 1007
Approval Date	May 26, 2021
FDA Website	PYLARIFY (fda.gov)

Information	Description
NDA Number	215841
Drug Name	Locametz
Active Ingredients	Gozetotide
Company Name	Advanced Accelerator Applications USA, Inc., a Novartis Company
Address	8910 Purdue Road, Suite 250 Indianapolis, IN 46268
Approval Date	March 23, 2022
FDA Website	LOCAMETZ (fda.gov)

Information	Description
NDA Number	69932-002-50
Drug Name	Posluma
Active Ingredients	Flotufolastat F 18 gallium
Company Name	Blue Earth Diagnostics Ltd.

Information	Description
Address	100 Daingerfield Rd, Suite 400 Alexandria, VA 22314
Approval Date	May 25, 2023
FDA Website	Posluma (fda.gov)

d. Medicare Coverage Determinations

Available Medicare coverage determinations are listed below as a resource. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

NCD Number	Name	Effective Date
220.6.17	Positron Emission Tomography for Oncologic Conditions	06/11/2013

LCD Number	Contractor	Original/Revision Effective Date
None	N/A	N/A

- NCD: National Coverage Determination
- LCD: Local Coverage Determination

e. TRICARE Policy Manual

Available TRICARE coverage determinations are listed below as a resource. VA and TRICARE are governed by separate laws and regulations; thus, VA coverage determinations may be different.

TRICARE Policy Manual 6010.60-M, Chapter 05, Section 4.1

- PET* and PET/CT are proven diagnostics for the diagnosis, staging, restaging, and monitoring of oncologic indications, when supported by National Comprehensive Cancer Network (NCCN) clinical practice guidelines
- National Comprehensive Cancer Network (NCCN) clinical practice guidelines identifies PSMA PET use for initial risk stratification and staging workup

***Note:** VA requires PSMA PET Imaging be performed on a PET/CT or PET/MRI scanner. Scans using non-fusion PET Imaging technology are rarely appropriate for PSMA PET

IV. Definitions

Term	Definition
Adenocarcinoma	A type of cancer that develops in the glands that line the organs
Biochemical Function	Chemical processes that occur in cells
Endothelium	A thin membrane that lines the inside of blood vessels
Extrapelvic	External to the pelvis
Inguinal	Of, relating to, or situated in the region of the groin
Metastasis	Development of secondary malignant growths at a distance from a primary site of cancer
Neovasculature	Abnormal or excessive formation of new blood vessels typically in abnormal tissues such as a tumor
Position Emission Tomography (PET)	Type of nuclear medicine procedure that measures metabolic and expression activity of the cells of body tissues
Prostate	A gland in the male reproductive system found below the bladder and in front of the rectum
Prostate Bed	A structure in the male pelvis situated just beneath the bladder where the prostate gland rests
Prostate-Specific Membrane Antigen (PSMA)	A membrane-bound glycoprotein restricted to normal prostatic epithelial cells, prostate cancer, and the endothelium of the neovasculature of tumors
Retroperitoneal	The space behind the lining of the abdominal cavity
Serum Prostate-Specific Antigen (PSA) Level	A blood test used primarily to screen for prostate cancer
Seminal Vesicle	Pair of glandular pouches that lie on either side of the male reproductive tract
Skull Vertex	The highest point of the skull or calvaria (roof of the skull)

V. References

Defense Health Agency (2015) Radiology Nuclear Medicine TRICARE Policy Manual 6010.60-M. Chapter 05, Section 4.1. Retrieved November 30, 2023, from https://manuals.health.mil/pages/DisplayManual.aspx?SeriesId=TPT5

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National Comprehensive Cancer Network. (2023). NCCN Clinical Practice Guidelines: Prostate Cancer. Retrieved December 10, 2023, from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

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U.S. Food & Drug Administration NDA Approval, Posluma. Retrieved February 08, 2024, from https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/216023Orig1s000ltr.pdf

VA National Oncology Program (2023) Oncology clinical pathways - Prostate Cancer. V6.2023. Retrieved December 13, 2023, from https://www.cancer.va.gov/assets/pdf/clinical-pathways/ProstateCancerClinicalPathways.pdf

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	