A PYLARIFY® PET/CT SCAN MAY

HELP YOUR DOCTOR SEE MORE. CLEARLY.

Approved Use

PYLARIFY® (piflufolastat F 18) Injection is a radioactive diagnostic agent. PYLARIFY is used along with positron emission tomography (PET) imaging for men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum levels of prostate-specific antigen (PSA) level.

PYLARIFY Injection is designed to detect prostate-specific membrane antigen (PSMA) positive lesions when used with PET imaging (scans).

IMPORTANT SAFETY INFORMATION

Radiation exposure:

- PYLARIFY is a radioactive diagnostic agent and adds to your long-term overall amount of radiation exposure, which could lead to an increased risk of cancer. You should stay well hydrated before, during, and after you are given PYLARIFY and urinate frequently to reduce radiation exposure.

CT=computed tomography; PET=positron emission tomography.

PYLARIFY®
Piflufolastat F 18 Injection

Please see Important Safety Information and the accompanying Prescribing information.

UNDERSTANDING PROSTATE CANCER. CLEARLY.

If you have prostate cancer, you're not alone. In fact, more than 3.1 million American men are currently living with the disease. While this may be an uncertain time, the information in this brochure can help you and your loved ones understand what's ahead to help make informed choices.

Initial prostate cancer diagnosis

As part of your initial diagnosis, your doctor determines your risk group, which helps inform an appropriate treatment plan. There are 5 prostate cancer risk groups to be aware of: **very low, low, intermediate, high,** and **very high**.

Approximately 288,300 new prostate cancer cases will be diagnosed in 2023.

Recurrent prostate cancer

Even though initial treatment for prostate cancer can be curative, up to **50%** of patients experience a return of the disease within 10 years, also known as a recurrence.

If you've received treatment for prostate cancer—such as surgery, radiation, or hormone therapy—your doctor will monitor your overall health and run a variety of tests, including one that checks your prostate-specific antigen, or PSA level. If the test confirms an elevated PSA level, this means the cancer may have returned, or recurred.

Your doctor may schedule an imaging scan to help determine where the prostate cancer is and if it has spread. Imaging scans are important even when PSA levels are still very low.

DEFINITIONS

Initial Diagnosis
This is the first prostate cancer diagnosis you receive.

Recurrent Prostate Cancer
If your prostate cancer came back after you've received treatment such as surgery, radiation, or hormone therapy, you now have recurrent prostate cancer.

Metastatic Prostate Cancer
If cancer spreads beyond the prostate to other parts of your body, it's considered to have metastasized and is now metastatic prostate cancer.

Prostate-Specific Antigen (PSA)
PSA is a protein produced by the prostate cells and mostly found in semen, with a small amount released into the bloodstream. When there is a problem with the prostate—such as prostate cancer—PSA is detected in the blood.

- A PSA test is one of the important steps to help determine an initial diagnosis
- Follow-up PSA tests are performed to determine if a treatment has been successful or if the cancer has come back (recurred)

Prostate-Specific Membrane Antigen (PSMA)
PSMA is a protein found on the surface of most—more than 90%—prostate cancer cells.

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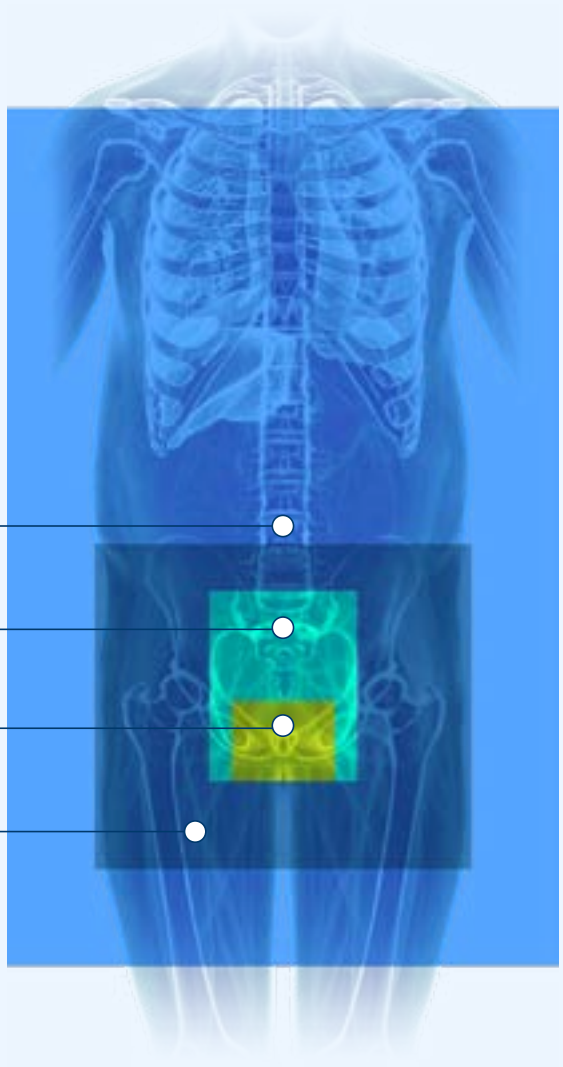
PROSTATE CANCER ASSESSMENT

If your doctor is concerned that the prostate cancer has spread, they may schedule an imaging scan. Your doctor will then assess if the cancer has: remained in the **prostate and pelvic area**, spread into **nearby lymph nodes**, or reached **other parts of the body**. This information will help guide your doctor in the selection of an appropriate treatment.



When detected early, 5-year survival rates for prostate cancer found in the prostate area can be as high as 100%, which is why ongoing screenings are important. Having more information about the different imaging options and steps may help relieve any concerns you have about what's involved.

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Please see Important Safety Information and the accompanying Prescribing information.

DETECTING PROSTATE CANCER. CLEARLY.

Prostate cancer imaging plays a vital role in helping to detect and monitor prostate cancer progression. There are several types of imaging tests, however, not all imaging scans are the same.

A PET scan is often combined with a CT scan for better diagnostic accuracy. Compared to conventional imaging–such as bone, CT, and MRI scans–a PET/CT scan with PYLARIFY® (piflufolastat F 18) injection provides you and your doctor a clearer image of where the prostate cancer is and helps your doctor make more informed treatment choices.

What is a PET scan?

A PET scan is an imaging test that helps doctors look for disease sites in the body. A PET scan uses an imaging agent—like PYLARIFY®—that contains a small amount of radioactive tracer, which targets cancer cells. Once there, the imaging agent lights up, helping the reader of the PET scan find the disease location, usually before tumors appear on other types of imaging scans.

What is PYLARIFY®?

PYLARIFY® is an advanced diagnostic imaging agent used with PET/CT scans to find tumors in the prostate, lymph nodes, bones, and other organs, typically better than other types of imaging scans.

How does PYLARIFY® work?

PYLARIFY® attaches to prostate-specific membrane antigen (PSMA), a protein found on the surface of most—more than 90%—prostate cancer cells. By targeting PSMA, PYLARIFY® can give your doctor a clear image and additional information on the location and the extent of the cancer.

PYLARIFY® helps create clearer images for your doctor

PYLARIFY® uses a radioactive tracer called fluorine-18, or ^{18}F, which helps create a clear and more detailed PET/CT scan image for your doctor. A clearer image also provides improved insights, which can lead to more informed treatment choices.

CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography.

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PYLARIFY® PET/CT SCAN vs OTHER CONVENTIONAL IMAGING

IMAGING TYPE How it works	PYLARIFY® PET/CT SCAN Uses imaging agent that contains radioactive tracer. This agent accumulates in prostate cancer tumor(s), enabling earlier and clearer detection than other scans	CONVENTIONAL IMAGING CT SCAN Uses X-rays to create pictures of a cross-sectional view of the body that can not only show shape, size, and location of the organs, but also abnormalities like cancer	MRI SCAN Uses strong magnets for a cross-sectional view of the soft tissue of the body, and can also locate cancer. Cannot be used in people with pacemakers or artificial joints	BONE SCAN Uses radioactive tracer. This tracer is taken up by abnormal cells, like cancer in the bone that can be detected by scan
DETECTION OF CANCER				
IN BONES	●	●	●	●
IN SOFT TISSUE	●	●	●	NA
WHEN IT IS SMALL	●*	●	●	NA
WHEN PSA LEVELS ARE LOW†	●	●	●	●

● Yes ● Yes, but with some limitations ● No

*Although a PET scan has some limitations when detecting microscopic metastases, it can detect smaller metastases compared to CT or MRI.
†PSA <2 ng/mL.
CT=computed tomography; MRI=magnetic resonance imaging; NA=not applicable, can only detect cancer in bones; PET=positron emission tomography; PSA=prostate-specific antigen.

Talk with your doctor

to see if a PET/CT scan with PYLARIFY® (piflufolastat F 18) injection is right for you.

Not an actual patient.

PYLARIFY®
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Please see Important Safety Information and the accompanying Prescribing information.

HOW TO PREP FOR A PET/CT SCAN WITH PYLARIFY®

Drink fluids before and after your scan. Staying properly hydrated and going to the bathroom are important pre- and post-scan

With PYLARIFY®, fasting might not be required. Although fasting before a PYLARIFY® PET/CT scan is not required, your doctor might ask you to

If your doctor thinks a PET/CT scan with PYLARIFY® (piflufolastat F 18) injection is appropriate for you, here are a few things to help you understand the procedure:

Upon arrival

- Your weight and height will be measured and recorded
- An intravenous (IV) catheter line will be placed in your arm or similar vein
- You'll receive an injection of PYLARIFY® 1 hour prior to your PET/CT scan
- It'll take approximately 1 hour for PYLARIFY® to circulate through your bloodstream and into any cancer cells that may be present
- You may be asked to use the restroom after your injection of PYLARIFY® and prior to starting your scan

During the procedure

- After you've received your injection of PYLARIFY®, you'll lie on your back on the scanner bed with your arms raised above your head; a trained PET/CT technologist or nurse will be there to help
- The scanner bed will move slowly into the scanner and the scan will begin. The scan will be painless
- The scan will typically start at your mid-thigh and go all the way up to your head
- The scan could last up to 40 minutes and you may be asked to change body positions

After your scan

- The results will be sent to your doctor
- Be sure to continue to hydrate and go to the bathroom for the first few hours
- Schedule a follow-up appointment with your doctor so together you can see and review the results and discuss a treatment plan

In clinical trials, side effects of PYLARIFY® were minor and rare. The most common side effects were headache (2% of patients), unusual taste (2% of patients), and fatigue (1% of patients). In addition, a hypersensitivity reaction was reported in 1 patient (0.2%) with a history of allergic reactions.

CT=computed tomography; PET=positron emission tomography.

PYLARIFY®
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IMPORTANT SAFETY INFORMATION

How well does PYLARIFY work?

- As with all diagnostic imaging tests such as x-rays, bone scans, and computed tomography (CT) scans, it is possible that the physician (a radiologist or nuclear medicine physician) that reviews your PYLARIFY PET/CT scan could interpret your results incorrectly. This means that a negative PYLARIFY PET/CT scan does not rule out that you have prostate cancer, and a positive PYLARIFY PET/CT scan does not confirm that you have prostate cancer.
- PYLARIFY seems to be affected by the amount (level) of PSA in your blood. As the levels of PSA in your blood go up, a PYLARIFY PET/CT scan is better able to identify prostate cancer.

Hypersensitivity reactions:

- Patients should be monitored for hypersensitivity reactions, especially those with a history of allergy to other drugs and foods. Reactions may be delayed. Always have trained staff and resuscitation equipment available.

Radiation exposure:

- PYLARIFY is a radioactive diagnostic agent and adds to your long-term overall amount of radiation exposure, which could lead to an increased risk of cancer. You should stay well hydrated before, during, and after you are given PYLARIFY and urinate frequently to reduce radiation exposure.

What are the possible side effects of PYLARIFY?

- There were no serious reactions reported in patients who received scans in clinical trials with PYLARIFY, but some patients did report side effects associated with the use of PYLARIFY.
- The most commonly reported adverse reactions are headache, fatigue and unusual taste in the mouth. An allergic reaction to PYLARIFY was reported in one patient with a significant history of allergic reactions.

Tell your doctor if you have any side effect that bothers you or does not go away.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-888-INFO-FDA (1-888-463-6332).

For more information, please see Full Prescribing information for PYLARIFY.

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TALKING ABOUT PROSTATE CANCER AND PYLARIFY®. CLEARLY.

Ongoing checkups and screenings are important steps you and your doctor can take to monitor prostate cancer. Here are a few questions to help you start or continue the conversation with your doctor:

- Based on the initial diagnosis assessment, or if the prostate cancer has come back (recurred) or spread (metastasized), how can imaging options help determine the extent of the cancer?
- Is a PET/CT scan with PYLARIFY® an option for me?
- Can you talk to me about PET/CT scans and how safe they are?

Scheduling your scan and follow-up appointment

After your PET/CT scan with PYLARIFY® (piflufolastat F 18) injection, be sure to schedule a follow-up appointment with your doctor so together you can see and review the results and discuss a treatment plan. For your convenience, you can print this page and record your scheduled appointments below.

Scheduled Scan Visit

Date

Time

Imaging center

Address

Phone number

Follow-up Visit

Date

Time

Visit PYLARIFY.com/patient for more information.

CT=computed tomography; PET=positron emission tomography.

This information is intended for US residents only.

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DISCHARGE PLAN

This page is a resource provided to you to help you keep your treatment information close by. Please print and complete this card and carry it with you to all of your appointments.

Discharge Card

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Patient: _____

Hospital: _____

City, State: _____

Hospital 24-hour contact name and number:

_____

This patient has been administered PYLARIFY®

Procedure date and time: _____

Activity administered: _____

PYLARIFY®
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PyLARIFY® safely and effectively. See full prescribing information for PyLARIFY.

PYLARIFY® (piflufolastat F 18) injection, for intravenous use

Initial U.S. Approval: 2021

---------- INDICATIONS AND USAGE ----------

PYLARIFY is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Recommended dose is 333 MBq (9 mCi) with an acceptable range of 296 MBq to 370 MBq (8 mCi to 10 mCi), administered as a bolus intravenous injection. (2.2)
- Initiate imaging approximately 60 minutes after PYLARIFY administration. The patient should void immediately prior to initiation of imaging. Image acquisition should start from mid-thigh and proceed to the skull vertex. (2.3, 2.4)
- See full prescribing information for additional preparation, handling, administration, imaging, and radiation dosimetry information. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Injection: clear, colorless solution in a multiple-dose vial containing 37 MBq/mL to 2,960 MBq/mL (1 mCi/mL to 80 mCi/mL) of piflufolastat F 18 at calibration date and time. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Image Misinterpretation: PYLARIFY uptake can be seen in a variety of tumor types as well as in non-malignant processes and normal tissues. Image interpretation errors can occur with PYLARIFY imaging. (5.1)
- Hypersensitivity Reactions: Monitor patients for hypersensitivity reactions, particularly patients with a history of allergy to other drugs and foods. (5.2)
- Radiation Risk: Ensure safe drug handling to protect patients and health care workers from unintentional radiation exposure. (5.3)

---------- ADVERSE REACTIONS ----------

The most common reported adverse reactions are headache, dysgeusia, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Progenics Pharmaceuticals, Inc. at 1-800-362-2668 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PYLARIFY is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety – Drug Handling

PYLARIFY is a radioactive drug. Only authorized persons qualified by training and experience should receive, use, and administer PYLARIFY. Handle PYLARIFY with appropriate safety measures to minimize radiation exposure during administration *[see Warnings and Precautions (5.3)]*. Use waterproof gloves and effective radiation shielding, including syringe shields, when preparing and handling PYLARIFY.

2.2 Recommended Dosage and Administration Instructions

Recommended Dose

The recommended amount of radioactivity to be administered for PET imaging is 333 MBq (9 mCi) with an acceptable range of 296 MBq to 370 MBq (8 mCi to 10 mCi) administered as a single bolus intravenous injection.

Preparation and Administration

- Use aseptic technique and radiation shielding when preparing and administering PYLARIFY.
- Visually inspect the radiopharmaceutical solution. Do not use if it contains particulate matter or if it is discolored (PYLARIFY is a clear, colorless solution).
- Calculate the necessary volume to administer based on calibration time and required dose. PYLARIFY may be diluted with 0.9% Sodium Chloride Injection, USP.
- Assay the dose in a suitable dose calibrator prior to administration.

Post Administration Instructions

- Follow the PYLARIFY injection with an intravenous flush of 0.9% Sodium Chloride Injection USP.
- Dispose of any unused PYLARIFY in compliance with applicable regulations.

2.3 Patient Preparation

Instruct patients to drink water to ensure adequate hydration prior to administration of PYLARIFY and to continue drinking and voiding frequently for the first few hours following administration to reduce radiation exposure *[see Warnings and Precautions (5.3)]*.

2.4 Image Acquisition

The recommended start time for image acquisition is 60 minutes after PYLARIFY injection. Starting image acquisition more than 90 minutes after injection may adversely impact imaging performance. Patients should void immediately prior to image acquisition. Position the patient supine with arms above the head. Image acquisition should start from mid-thigh and proceed to the skull vertex. Scan duration is 12 minutes to 40 minutes depending on the number of bed positions (typically 6 to 8) and acquisition time per bed position (typically 2 minutes to 5 minutes).

2.5 Image Display and Interpretation

PYLARIFY binds to prostate-specific membrane antigen (PSMA). Based on the intensity of the signals, PET images obtained using PYLARIFY indicate the presence of PSMA in tissues. Lesions should be considered suspicious if uptake is greater than physiologic uptake in that tissue or greater than adjacent background if no physiologic uptake is expected. Tumors that do not express PSMA will not be visualized. Increased uptake in tumors is not specific for prostate cancer *[see Warnings and Precautions (5.1)]*.

2.6 Radiation Dosimetry

Radiation absorbed dose estimates are shown in Table 1 for organs and tissues of adult male patients from intravenous administration of PYLARIFY. The radiation effective dose resulting from administration of 370 MBq (10 mCi) of PYLARIFY to an adult weighing 70 kg is estimated to be 4.3 mSv. The radiation doses for this administered dose to the critical organs, which are the kidneys, liver, and spleen, are 45.5 mGy, 13.7 mGy, and 10 mGy respectively. When PET/CT is performed, exposure to radiation will increase by an amount dependent on the settings used in the CT acquisition.

Table 1. Estimated Radiation Absorbed Doses in Organs/Tissues in Adults who Received PYLARIFY

Organ/Tissue	Mean Absorbed dose per Unit Administered Activity (mGy/MBq)	
	Mean	Standard Deviation
Adrenal glands	0.0131	0.0013
Brain	0.0021	0.0003
Breasts	0.0058	0.0007
Gallbladder wall	0.0141	0.0012
Lower large intestine wall	0.0073	0.001
Small intestine	0.0089	0.0009
Stomach wall	0.0092	0.0008
Upper large intestine wall	0.0091	0.0009
Heart wall	0.0171	0.0022
Kidneys	0.123	0.0434
Liver	0.037	0.0058
Lungs	0.0102	0.0016
Muscle	0.0069	0.0008
Pancreas	0.0124	0.0011
Red bone marrow	0.0071	0.0007
Osteogenic cells	0.0099	0.0012
Skin	0.0052	0.0006
Spleen	0.0271	0.0115
Testes	0.0059	0.0008
Thymus gland	0.007	0.0008
Thyroid	0.0062	0.0009
Urinary bladder wall	0.0072	0.001
Effective dose	**0.0116 (mSv/MBq)**	**0.0022 mSv/MBq**

(continues next column)

3 DOSAGE AND STRENGTHS

Injection: clear, colorless solution in a multiple-dose vial containing 37 MBq/mL to 2,960 MBq/mL (1 mCi/mL to 80 mCi/mL) of piflufolastat F 18 at calibration date and time.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Image Misinterpretation

Imaging interpretation errors can occur with PYLARIFY imaging. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of PYLARIFY for imaging of patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels *[see Clinical Studies (14)]*. The performance of PYLARIFY for imaging of metastatic pelvic lymph nodes prior to initial definitive therapy seems to be affected by risk factors such as Gleason score and tumor stage *[see Clinical Studies (14)]*. PYLARIFY uptake is not specific for prostate cancer and may occur with other types of cancer as well as non-malignant processes and in normal tissues. Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, is recommended.

5.2 Hypersensitivity Reactions

Monitor patients for hypersensitivity reactions, particularly patients with a history of allergy to other drugs and foods. Reactions may not be immediate. Always have trained staff and resuscitation equipment available.

5.3 Radiation Risks

Diagnostic radiopharmaceuticals, including PYLARIFY, expose patients to radiation *[see Dosage and Administration (2.6)]*. Radiation exposure is associated with a dose-dependent increased risk of cancer. Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. Advise patients to hydrate before and after administration and to void frequently after administration *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PYLARIFY was evaluated in 593 patients, each receiving one dose of PYLARIFY. The average injected activity was 340 ± 26 MBq (9.2 ± 0.7 mCi).

The adverse reactions reported in >0.5% of patients within the studies are shown in Table 2. In addition, a hypersensitivity reaction was reported in one patient (0.2%) with a history of allergic reaction.

Table 2 Adverse Reactions with a Frequency >0.5% in Patients Who Received PYLARIFY* (n = 593)

Adverse Reaction	n (%)
Headache	13 (2%)
Dysgeusia	10 (2%)
Fatigue	7 (1%)

7 DRUG INTERACTIONS

Androgen deprivation therapy and other therapies targeting the androgen pathway

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, may result in changes in uptake of PYLARIFY in prostate cancer. The effect of these therapies on performance of PYLARIFY PET has not been established.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

PYLARIFY is not indicated for use in females. There is no information on the risk of adverse developmental outcomes in pregnant women or animals with the use of piflufolastat F 18. All radiopharmaceuticals, including PYLARIFY, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose.

8.2 Lactation

Risk Summary

PYLARIFY is not indicated for use in females. There is no information on the presence of piflufolastat F 18 in human milk, the effect on the breastfed infant, or the effect on milk production.

8.4 Pediatric Use

The safety and effectiveness of PYLARIFY in pediatric patients have not been established.

8.5 Geriatric Use

Of the 593 patients in completed clinical studies of PYLARIFY, 355 (60%) were ≥65 years old, while 76 (12.8%) were ≥75 years old. The efficacy and safety of PYLARIFY appear similar in adult and geriatric patients with prostate cancer, although the number of patients in the trials was not large enough to allow definitive comparison.

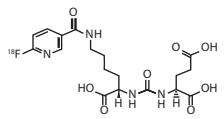
10 OVERDOSAGE

In the event of an overdose of PYLARIFY, reduce the radiation absorbed dose to the patient where possible by increasing the elimination of the drug from the body using hydration and frequent bladder voiding. A diuretic might also be considered. If possible, an estimate of the radiation effective dose administered to the patient should be made.

11 DESCRIPTION

11.1 Chemical Characteristics

PYLARIFY contains fluorine 18 (F 18), radiolabeled prostate-specific membrane antigen inhibitor imaging agent. Chemically piflufolastat F 18 is 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl} ureido)-pentanedioic acid. The molecular weight is 441.4 and the structural formula is:



The chiral purity of the unlabeled piflufolastat F 18 precursor is greater than 99% (S,S).

PYLARIFY is a sterile, non-pyrogenic, clear, colorless solution for intravenous injection. Each milliliter contains 37 to 2,960 MBq (1 to 80 mCi) piflufolastat F 18 with ≤0.01 µg/mCi of piflufolastat at calibration time and date, and ≤ 78.9 mg ethanol in 0.9% sodium chloride injection USP. The pH of the solution is 4.5 to 7.0.

PYLARIFY has a radiochemical purity of at least 95% up to 10 hours following end of synthesis, and specific activity of at least 1000 mCi/µmol at the time of administration.

11.2 Physical Characteristics

PYLARIFY is radiolabeled with fluorine 18 (F 18), a cyclotron produced radionuclide that decays by positron emission to stable oxygen 18 with a half-life of 109.8 minutes. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 3).

Table 3. Principal Radiation Produced from Decay of Fluorine 18 Radiation

	Radiation Energy (keV)	Abundance (%)
Positron	249.8	96.9
Gamma	511	193.5

11.3 External Radiation

The point source air-kerma coefficient for F 18 is 3.75 x 10^{-17} Gy m^2/(Bq s). The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by F 18 that results from various thicknesses of lead shielding is shown in Table 4. The use of 8 cm Pb decreases the radiation transmission (i.e. exposure) by a factor of about 10,000.

Table 4. Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shield Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Piflufolastat F 18 binds to cells that express PSMA, including malignant prostate cancer cells, which usually overexpress PSMA. Fluorine-18 (F 18) is a β+ emitting radionuclide that enables positron emission tomography.

12.2 Pharmacodynamics

The relationship between piflufolastat F 18 plasma concentrations and image interpretation has not been studied.

12.3 Pharmacokinetics

Distribution

Following intravenous administration of piflufolastat F 18, blood levels decline in a biphasic fashion. The distribution half-life is 0.17 ± 0.044 hours and the elimination half-life is 3.47 ± 0.49 hours.

Piflufolastat F 18 distributes to the kidneys (16.5% of administered activity), liver (9.3%), and lung (2.9%), within 60 minutes of intravenous administration.

Elimination

Elimination is by urinary excretion. In the first 8 hours post-injection, approximately 50% of administered radioactivity is excreted in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies to assess the carcinogenicity or mutagenic potential of piflufolastat have not been conducted. However, piflufolastat has the potential to be mutagenic because of the F 18 radioisotope.

No animal studies with piflufolastat have been performed to evaluate the potential impairment of fertility in males or females.

14 CLINICAL STUDIES

The safety and efficacy of PYLARIFY were evaluated in two prospective, open-label, multi-center clinical studies in men with prostate cancer: OSPREY (NCT02981368) and CONDOR (NCT03739684).

OSPREY

OSPREY enrolled a cohort of 268 men with biopsy-proven prostate cancer who were considered candidates for radical prostatectomy and pelvic lymph node dissection. These patients were all considered to have high risk disease based on criteria such as Gleason score, PSA level, and tumor stage. Each patient received a single PYLARIFY PET/CT from mid-thigh to skull vertex.

Three central readers independently interpreted each PET scan for the presence of abnormal PYLARIFY uptake in pelvic lymph nodes in multiple subregions, including the common iliac lymph nodes. The readers were blinded to all clinical information. While readers also recorded the presence of PYLARIFY PET-positive lesions in the prostate gland and outside the pelvis, those results were not included in the primary efficacy analysis.

A total of 252 patients (94%) underwent standard-of-care prostatectomy and template pelvic lymph node dissection and had sufficient histopathology data for evaluation of the pelvic lymph nodes. Surgical specimens were separated into three regions: left hemipelvis, right hemipelvis, and other. For each patient, PYLARIFY PET results and histopathology results obtained from dissected pelvic lymph nodes were compared by surgical region. PET results in locations that were not dissected were excluded from analysis.

For the 252 evaluable patients, the mean age was 64 years (range 46 to 84 years), and 87% were white. The median serum PSA was 9.3 ng/mL. The total Gleason score was 7 for 19%, 8 for 46%, and 9 for 34% of the patients, with the remainder of the patients having Gleason scores of 6 or 10.

Table 5 shows PYLARIFY PET performance by reader through comparison to pelvic lymph node histopathology at the patient-level with region matching, such that at least one true positive region defines a true positive patient. Approximately 24% of the evaluable patients had pelvic lymph node metastases based on histopathology (95% confidence interval: 19%, 29%).

Table 5: Patient-Level, Region-Matched Performance of PYLARIFY PET for Detection of Pelvic Lymph Node Metastasis in OSPREY (n=252)

	Reader 1	Reader 2	Reader 3
True Positive	23	17	23
False Positive	7	4	9
False Negative	36	43	37
True Negative	186	188	183
Sensitivity, % (95% CI)	39 (27, 51)	28 (17, 40)	38 (26, 51)
Specificity, % (95% CI)	96 (94, 99)	98 (95, 99)	95 (92, 98)
PPV, % (95% CI)	77 (62, 92)	81 (59, 93)	72 (56, 87)
NPV, % (95% CI)	84 (79, 89)	81 (76, 86)	83 (78, 88)

Abbreviations: CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value

In exploratory analyses, there were numerical trends towards more true positive results among patients with total Gleason score of 8 or higher and among patients with tumor stage of T2c or higher relative to those patients with lower Gleason score or tumor stage.

CONDOR

CONDOR enrolled 208 patients with biochemical evidence of recurrent prostate cancer, defined by serum PSA of at least 0.2 ng/mL after radical prostatectomy (with confirmatory PSA level also at least 0.2 ng/mL) or by an increase in serum PSA of at least 2 ng/mL above the nadir after other therapies. The mean age was 68 years (range 43 to 91 years), and 90% of patients were white. The median serum PSA was 0.82 ng/mL. Prior treatment included radical prostatectomy in 85% of the patients.

All enrolled patients had conventional imaging evaluation (for most patients, CT or MRI) within 60 days prior to receiving PYLARIFY PET, and this evaluation was negative or equivocal for prostate cancer. All patients received a single PYLARIFY PET/CT from mid-thigh to skull vertex with optional imaging of the lower extremities.

Three central readers independently evaluated each PYLARIFY PET scan for the presence and location of positive lesions. Location of each lesion was categorized in one of 19 subregions that were grouped into 5 regions (prostate/prostate bed, pelvic lymph nodes, other lymph nodes, soft tissue, bone). The readers were blinded to all clinical information.

Depending on the reader, a total of 123 to 137 patients (59% to 66%) had at least one lesion that was identified as PYLARIFY PET-positive (Table 6, TP + FP + PET-Positive Without Reference Standard). The region most commonly observed to have a PYLARIFY PET-positive finding was pelvic lymph nodes (40% to 42% of all PET-positive regions) and the least common region was soft tissue (6% to 7%).

Depending on the reader, 99 to 104 patients with a PYLARIFY PET-positive region had location-matched composite reference standard information available (Evaluable Set, Table 6, TP + FP) that consisted of histopathology, imaging (CT, MRI, ultrasound, fluciclovine PET, choline PET, or bone scan) obtained within 60 days of the PYLARIFY PET scan, or response of serum PSA level to targeted radiotherapy. Reference standard information for PET-negative regions was not systematically collected in this study.

Table 6 shows patient-level performance results of PYLARIFY PET by reader, including location-matched positive predictive value [true positive / (true positive + false positive)], also known as Correct Localization Rate (CLR). For these results, a patient was considered true positive if they had at least one matching location positive on both PYLARIFY PET and the composite reference standard. In addition to calculating location-matched positive predictive value in the Evaluable Set (CLR), an exploratory analysis of positive predictive value in all scanned patients (Imputed CLR) was performed in which PYLARIFY PET-positive patients who lacked reference standard information were imputed using an estimated likelihood that at least one PET-positive lesion was reference standard positive, based on patient-specific factors.

Table 6. Patient-Level Performance of PYLARIFY PET in CONDOR (n=208)

	Reader 1	Reader 2	Reader 3
True Positive (TP)	89	87	84
False Positive (FP)	15	13	15
PET-Positive Without Reference Standard	33	24	24
PET-Negative	71	84	85
CLR % (95% CI)	86 (79, 92)	87 (80, 94)	85 (78, 92)
Imputed CLR % (95% CI)	78 (71, 85)	81 (74, 88)	79 (72, 86)

Abbreviations: TP = true positive, FP = false positive, CLR = location-matched positive predictive value in the Evaluable Set [TP/(TP + FP)], Imputed CLR = location-matched positive predictive value in all scanned patients using an imputation approach based on patient-specific factors for PET-Positive Without Reference Standard, CI = confidence interval

An exploratory analysis of region-level positive predictive value using only PET-positive regions that had sufficient composite reference standard information to determine true positive or false positive status demonstrated results of 67% to 70% with the lower bound of the 95% confidence interval ranging from 59% to 63%.

The percentage of patients categorized as true positive in a location-matched analysis out of all patients scanned with PYLARIFY was an additional exploratory endpoint. Using the same imputation approach for PET-positive patients who lacked reference standard information as in Table 6 above, this value was 47% to 51%, with the lower bound of the 95% confidence interval ranging from 40% to 45%.

Table 7 shows patient-level PYLARIFY PET results from the majority read stratified by serum PSA level. Percent PET positivity was calculated as the proportion of patients with a positive PYLARIFY PET out of all patients scanned. Percent PET positivity includes patients determined to be either true positive or false positive as well as those in whom such determination was not made due to lack of composite reference standard information. The likelihood of a patient having at least one PYLARIFY PET-positive lesion generally increased with higher serum PSA level.

Table 7: Patient-Level PYLARIFY PET Results and Percent PET Positivity* Stratified by Serum PSA Level in the CONDOR Study Using Majority Result Among Three Readers (n=199)**

PSA (ng/mL)		PET positive patients			PET negative patients	Percent PET positivity, (95% CI)
	Total	TP	FP	Without reference standard		
		With reference standard				
<0.5	24	11	4	9	45	35 (24, 46)
		15				
≥0.5 and <1	18	12	3	3	18	50 (34, 66)
		15				
≥1 and <2	21	15	3	3	10	68 (51, 84)
		18				
≥2	57	50	3	4	6	90 (83, 98)
		53				
Total	120	88	13	19	79	60 (54, 67)
		101				

* Percent PET positivity = PET positive patients/total patients scanned. PET positive patients include true positive and false positive patients as well as those who did not have reference standard information.

** Six patients were excluded from this table due to lack of baseline PSA level. Three patients were excluded from this table due to lack of majority result among the categories true positive, false positive, PET positive without reference standard, and PET negative.

Abbreviations: TP = true positive, FP = false positive, CI = confidence interval

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PYLARIFY injection is supplied in a 50 mL multiple-dose glass vial (NDC# 71258-022-01) containing a clear, colorless solution at a strength of 37 MBq/mL to 2,960 MBq/mL (1 mCi/mL to 80 mCi/mL) piflufolastat F 18 at calibration time and date.

16.2 Storage and Handling

Storage

Store PYLARIFY at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). PYLARIFY does not contain a preservative. Store PYLARIFY in the original container with radiation shielding. The expiration date and time are provided on the container label. Use PYLARIFY within 10 hours from the time of end of synthesis

Handling

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

17 PATIENT COUNSELING INFORMATION

Adequate Hydration

Instruct patients to drink a sufficient amount of water to ensure adequate hydration before their PET study and urge them to drink and urinate as often as possible during the first hours following the administration of PYLARIFY, in order to reduce radiation exposure *[see Dosage and Administration (2.3) and Warnings and Precautions (5.3)]*.

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Patent: http://www.lantheus.com/patents/index.html

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