

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PLUVICTO® (lutetium Lu 177 vipivotide tetraxetan) injection, for intravenous use

Initial U.S. Approval: 2022

RECENT MAJOR CHANGES

Indications and Usage (1.1)	x/2026
Dosage and Administration, Patient Selection (2.2)	x/2026
Dosage and Administration, Recommended Dosage (2.3)	x/2026
Dosage and Administration, Radiation Dosimetry (2.6)	4/2026
Warnings and Precautions, Myelosuppression (5.2)	x/2026
Warnings and Precautions, Renal Toxicity (5.3)	x/2026

INDICATIONS AND USAGE

PLUVICTO is a radioligand therapeutic agent indicated:

Metastatic Androgen Pathway Modulation-Naïve or -Sensitive (mAPMN/S) Prostate Cancer

- in combination with androgen receptor pathway inhibitor (ARPI) therapy for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic androgen pathway modulation-naïve or -sensitive (mAPMN/S) prostate cancer. (1.1)

Metastatic Androgen Pathway Modulation-Resistant (mAPMR) Prostate Cancer

- for the treatment of adult patients with PSMA-positive metastatic androgen pathway modulation-resistant (mAPMR) prostate cancer who have been treated with ARPI therapy, and
 - are considered appropriate to delay taxane-based chemotherapy, or
 - have received prior taxane-based chemotherapy. (1.2)

DOSAGE AND ADMINISTRATION

- Select patients for treatment using LOCAMETZ® or another approved PSMA positron emission tomography (PET) product based on PSMA expression in tumors. (2.2)
- mAPMN/S Prostate Cancer: The recommended dosage of PLUVICTO in combination with ARPI is 7.4 GBq (200 mCi) every 6 weeks for 6 doses, or until disease progression or unacceptable toxicity. (2.3)
- mAPMR Prostate Cancer: The recommended dosage of PLUVICTO is 7.4 GBq (200 mCi) every 6 weeks for 6 doses, or until disease progression or unacceptable toxicity. (2.3)

- Dose interruption, reduction, or permanent discontinuation may be required due to adverse reactions. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 1,000 MBq/mL (27 mCi/mL) at calibration time in a single-dose vial containing 7.4 GBq (200 mCi) ± 10% at administration time. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Risk From Radiation Exposure: Minimize radiation exposure during and after treatment with PLUVICTO consistent with institutional good radiation safety practices and patient treatment procedures. Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation. (5.1)
- Myelosuppression: Perform complete blood counts. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity. (2.4, 5.2)
- Renal Toxicity: Advise patients to remain well hydrated and to urinate frequently. Perform kidney function laboratory tests. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity. (2.4, 5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise males with female partners of reproductive potential to use effective contraception. (5.4, 8.1, 8.3)
- Infertility: PLUVICTO may cause temporary or permanent infertility. (5.5, 8.3)

ADVERSE REACTIONS

Most common (≥ 20%) adverse reactions, including laboratory abnormalities, were decreased lymphocytes, decreased hemoglobin, fatigue, dry mouth, decreased neutrophils, nausea, decreased platelets, decreased estimated glomerular filtration rate, increased aspartate aminotransferase, decreased sodium, increased magnesium, increased potassium, decreased calcium, and increased alkaline phosphatase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Metastatic Androgen Pathway Modulation-Naïve or -Sensitive Prostate Cancer
- 1.2 Metastatic Androgen Pathway Modulation-Resistant Prostate Cancer

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Safety Instructions
- 2.2 Patient Selection
- 2.3 Recommended Dosage
- 2.4 Dosage Modifications for Adverse Reactions
- 2.5 Preparation and Administration
- 2.6 Radiation Dosimetry

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Risk From Radiation Exposure
- 5.2 Myelosuppression
- 5.3 Renal Toxicity
- 5.4 Embryo-Fetal Toxicity
- 5.5 Infertility

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation

- 8.3 Females and Males of Reproductive Potential

- 8.4 Pediatric Use

- 8.5 Geriatric Use

- 8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

- 11.1 Physical Characteristics

- 11.2 External Radiation

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

- 12.2 Pharmacodynamics

- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Metastatic Androgen Pathway Modulation-Naïve or -Sensitive Prostate Cancer

- 14.2 Metastatic Androgen Pathway Modulation-Resistant Prostate Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Androgen Pathway Modulation-Naïve or -Sensitive Prostate Cancer

PLUVICTO is indicated in combination with androgen receptor pathway inhibitor (ARPI) therapy for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic androgen pathway modulation-naïve or -sensitive (mAPMN/S) prostate cancer.

1.2 Metastatic Androgen Pathway Modulation-Resistant Prostate Cancer

PLUVICTO is indicated for the treatment of adult patients with PSMA-positive metastatic androgen pathway modulation-resistant (mAPMR) prostate cancer who have been treated with ARPI therapy, and

- are considered appropriate to delay taxane-based chemotherapy, or
- have received prior taxane-based chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Instructions

PLUVICTO is a radiopharmaceutical; handle with appropriate safety measures to minimize radiation exposure [*see Warnings and Precautions (5.1)*]. Use waterproof gloves and effective radiation shielding when handling PLUVICTO.

Radiopharmaceuticals, including PLUVICTO, should be used by or under the control of healthcare providers 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.

2.2 Patient Selection

Select patients with metastatic prostate cancer for treatment with PLUVICTO using LOCAMETZ or another approved PSMA positron emission tomography (PET) product based on PSMA expression in tumors. Additional selection criteria were used in clinical studies [*see Clinical Studies (14)*].

2.3 Recommended Dosage

Metastatic Androgen Pathway Modulation-Naïve or -Sensitive Prostate Cancer

The recommended dosage of PLUVICTO in combination with ARPI is 7.4 GBq (200 mCi) every 6 weeks for 6 doses, or until disease progression or unacceptable toxicity.

Refer to the Prescribing Information for ARPI for recommended dosing information.

Metastatic Androgen Pathway Modulation-Resistant Prostate Cancer

The recommended dosage of PLUVICTO is 7.4 GBq (200 mCi) every 6 weeks for 6 doses, or until disease progression or unacceptable toxicity.

Patients receiving PLUVICTO for metastatic prostate cancer should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

2.4 Dosage Modifications for Adverse Reactions

Recommended dosage modifications of PLUVICTO for adverse reactions are provided in Table 1. Management of adverse reactions may require temporary dose interruption, dose reduction, or permanent discontinuation of treatment with PLUVICTO. If a treatment delay due to an adverse reaction persists for > 4 weeks, consider permanent discontinuation of PLUVICTO. The dose of PLUVICTO may be reduced by 20% to 5.9 GBq (160 mCi) once; do not re-escalate dose. If a patient has further adverse reactions that would require an additional dose reduction, treatment with PLUVICTO must be discontinued.

Table 1: Recommended Dosage Modifications of PLUVICTO for Adverse Reactions

Adverse reaction	Severity	Dosage modification
Myelosuppression (Anemia, thrombocytopenia, leukopenia, or neutropenia) <i>[see Warnings and Precautions (5.2)]</i>	Grade 2	Withhold PLUVICTO until improvement to Grade 1 or baseline.
	Grade ≥ 3	Withhold PLUVICTO until improvement to Grade 1 or baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Recurrent Grade ≥ 3 myelosuppression after one dose reduction	Permanently discontinue PLUVICTO.
Renal toxicity <i>[see Warnings and Precautions (5.3)]</i>	Defined as: - Confirmed serum creatinine increase (Grade ≥ 2) - Confirmed CLcr < 30 mL/min; calculate using Cockcroft-Gault with actual body weight	Withhold PLUVICTO until improvement.
	Defined as: - Confirmed $\geq 40\%$ increase from baseline serum creatinine <u>and</u> - Confirmed $> 40\%$ decrease from baseline CLcr; calculate using Cockcroft-Gault with actual body weight	Withhold PLUVICTO until improvement or return to baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Grade ≥ 3 renal toxicity	Permanently discontinue PLUVICTO.
	Recurrent renal toxicity after one dose reduction	Permanently discontinue PLUVICTO.
Dry mouth <i>[see Adverse Reactions (6.1)]</i>	Grade 2	Withhold PLUVICTO until improvement or return to baseline. Consider reducing PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Grade 3	Withhold PLUVICTO until improvement or return to baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Recurrent Grade 3 dry mouth after one dose reduction	Permanently discontinue PLUVICTO.
Gastrointestinal toxicity <i>[see Adverse Reactions (6.1)]</i>	Grade ≥ 3 (not amenable to medical intervention)	Withhold PLUVICTO until improvement to Grade 2 or baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Recurrent Grade ≥ 3 gastrointestinal toxicity after one dose reduction	Permanently discontinue PLUVICTO.
Fatigue <i>[see Adverse Reactions (6.1)]</i>	Grade ≥ 3	Withhold PLUVICTO until improvement to Grade 2 or baseline.
Electrolyte or metabolic abnormalities <i>[see Adverse Reactions (6.1)]</i>	Grade ≥ 2	Withhold PLUVICTO until improvement to Grade 1 or baseline.

Adverse reaction	Severity	Dosage modification
Other non-hematologic toxicity [see Adverse Reactions (6.1)]	Any unacceptable toxicity	Permanently discontinue PLUVICTO.
	Any adverse reaction that requires treatment delay of > 4 weeks	Permanently discontinue PLUVICTO.
	Any recurrent Grade 3 or 4 or persistent and intolerable Grade 2 adverse reaction after one dose reduction	Permanently discontinue PLUVICTO.

Abbreviations: CLcr, creatinine clearance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal. Grading according to most current Common Terminology Criteria for Adverse Events (CTCAE).

2.5 Preparation and Administration

Preparation Instructions

- Use aseptic technique and radiation shielding when handling or administering PLUVICTO, using tongs as needed to minimize radiation exposure.
- Inspect the product visually under a shielded screen for particulate matter and discoloration prior to administration. Discard the vial if particulates and/or discoloration are present.
- Do not inject the PLUVICTO solution directly into any other intravenous solution.
- Confirm the amount of radioactivity of PLUVICTO delivered to the patient with an appropriately calibrated dose calibrator prior to and after each PLUVICTO administration.
- Dispose of any unused medicinal product or waste material in accordance with local and federal laws.

Administration Instructions

Prior to administration, flush the intravenous catheter used exclusively for PLUVICTO administration with ≥ 10 mL of 0.9% Sodium Chloride Injection, USP to ensure patency and to minimize the risk of extravasation. Manage cases of extravasation as per institutional guidelines.

The recommended dosage of PLUVICTO may be administered intravenously as an injection using the syringe method, as an infusion using the gravity method, or as an infusion using the peristaltic pump method.

When using the gravity or peristaltic pump method, infuse PLUVICTO directly from its original container.

Use the syringe method or the peristaltic pump method when administering a reduced dose of PLUVICTO following a dosage modification for an adverse reaction. When using the gravity method for a reduced dose, adjust the PLUVICTO dose before the administration to avoid the delivery of an incorrect volume of PLUVICTO.

Intravenous Methods of Administration

Instructions for the Syringe Method

- Withdraw an appropriate volume of PLUVICTO solution to deliver the desired radioactivity by using a disposable syringe fitted with a syringe shield and a disposable sterile needle that is 9 cm, 18 gauge (long needle). To aid the withdrawal of the solution, a filtered 2.5 cm, 20 gauge needle (short venting needle) can be used to reduce the resistance from the pressurized vial. Ensure that the short needle does not touch the PLUVICTO solution in the vial.
- Administer PLUVICTO to the patient by slow intravenous push within approximately 1 to 10 minutes (either with a syringe pump or manually without a syringe pump) via an intravenous catheter that is primed with 0.9% Sodium Chloride Injection, USP and that is used exclusively for PLUVICTO administration to the patient.
- If using a syringe pump, fit the syringe into the shielded pump and include a 3-way stopcock valve between the syringe and an intravenous catheter primed with 0.9% Sodium Chloride Injection, USP and used for PLUVICTO administration to the patient.
- When the desired PLUVICTO radioactivity has been delivered, stop the syringe pump and then change the position of the 3-way stopcock valve to flush the syringe with 25 mL of 0.9% Sodium Chloride Injection, USP. Restart the syringe pump.

- After the flush of the syringe has been completed, perform an intravenous flush of ≥ 10 mL of 0.9% Sodium Chloride Injection, USP through the intravenous catheter to the patient.

Instructions for the Gravity Method

- Insert a 2.5 cm, 20 gauge needle (short needle) into the PLUVICTO vial and connect via a catheter to 500 mL 0.9% Sodium Chloride Injection, USP (used to transport the PLUVICTO solution during the infusion). Ensure that the short needle does not touch the PLUVICTO solution in the vial and do not connect the short needle directly to the patient. Do not allow the 0.9% Sodium Chloride Injection, USP to flow into the PLUVICTO vial prior to the initiation of the PLUVICTO infusion and do not inject the PLUVICTO solution directly into the 0.9% Sodium Chloride Injection, USP.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the PLUVICTO vial, ensuring that the long needle touches and is secured to the bottom of the PLUVICTO vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is primed with 0.9% Sodium Chloride Injection, USP and that is used exclusively for the PLUVICTO infusion into the patient.
- Use a clamp or an infusion pump to regulate the flow of the 0.9% Sodium Chloride Injection, USP via the short needle into the PLUVICTO vial (the 0.9% Sodium Chloride Injection, USP entering the vial through the short needle will carry the PLUVICTO solution from the vial to the patient via the intravenous catheter connected to the long needle within approximately 30 minutes).
- During the infusion, ensure that the level of solution in the PLUVICTO vial remains constant.
- Disconnect the vial from the long needle line and clamp the 0.9% Sodium Chloride Injection, USP line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an intravenous flush of ≥ 10 mL of 0.9% Sodium Chloride Injection, USP through the intravenous catheter to the patient.

Instructions for the Peristaltic Pump Method

- Insert a filtered 2.5 cm, 20 gauge needle (short venting needle) into the PLUVICTO vial. Ensure that the short needle does not touch the PLUVICTO solution in the vial and do not connect the short needle directly to the patient or to the peristaltic pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the PLUVICTO vial, ensuring that the long needle touches and is secured to the bottom of the PLUVICTO vial during the entire infusion. Connect the long needle and a 0.9% Sodium Chloride Injection, USP to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic pump according to manufacturer's instructions.
- Prime the line by opening the 3-way stopcock valve and pumping the PLUVICTO solution through the tubing until it reaches the exit of the valve.
- Prime the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% Sodium Chloride Injection, USP and pumping the 0.9% Sodium Chloride Injection, USP until it exits the end of the catheter tubing.
- Connect the primed intravenous catheter to the patient and set the 3-way stopcock valve such that the PLUVICTO solution is in line with the peristaltic pump.
- Infuse an appropriate volume of PLUVICTO solution at approximately 25 mL/h to deliver the desired radioactivity.
- When the desired PLUVICTO radioactivity has been delivered, stop the peristaltic pump and then change the position of the 3-way stopcock valve so that the peristaltic pump is in line with the 0.9% Sodium Chloride Injection, USP. Restart the peristaltic pump and infuse an intravenous flush of ≥ 10 mL of 0.9% Sodium Chloride Injection, USP through the intravenous catheter to the patient.

2.6 Radiation Dosimetry

Dosimetry of lutetium Lu 177 vipivotide tetraxetan was collected in 29 patients in the VISION sub-study, in order to calculate whole body and organ radiation dosimetry. The mean and standard deviation (SD) of the estimated radiation

absorbed doses to different organs for adults receiving PLUVICTO are shown in Table 2. The organs with the highest radiation absorbed doses are lacrimal glands, salivary glands, large intestine (left and right colon), kidneys, and urinary bladder wall. The maximum penetration of lutetium-177 in tissue is approximately 2 mm and the mean penetration is 0.67 mm.

Table 2: Estimated Radiation Absorbed Dose^a for PLUVICTO in VISION

Organ	Absorbed dose per unit activity (Gy/GBq) N = 29		Calculated absorbed dose for 7.4 GBq administration (Gy)		Calculated absorbed dose for 6 × 7.4 GBq (44.4 GBq cumulative activity) (Gy)	
	Mean	SD	Mean	SD	Mean	SD
Adrenals	0.033	0.026	0.25	0.19	1.5	1.1
Brain	0.0069	0.0051	0.051	0.038	0.30	0.23
Esophagus	0.025	0.026	0.18	0.19	1.1	1.2
Eyes	0.022	0.025	0.16	0.18	0.98	1.1
Gallbladder wall	0.028	0.026	0.21	0.19	1.3	1.2
Heart wall	0.17	0.12	1.3	0.88	7.8	5.3
Kidneys	0.42	0.19	3.1	1.4	19	8.4
Lacrimal glands	2.1	0.48	15	3.6	92	21
Left colon	0.58	0.14	4.3	1.0	26	6.1
Liver	0.093	0.050	0.69	0.37	4.1	2.2
Lungs	0.11	0.11	0.78	0.83	4.7	5.0
Osteogenic cells: -blood-based*	0.036	0.029	0.26	0.21	1.6	1.3
-image-based**	0.048	0.038	0.36	0.28	2.1	1.7
Pancreas	0.027	0.026	0.20	0.19	1.2	1.2
Prostate	0.027	0.026	0.20	0.19	1.2	1.2
Rectum	0.56	0.14	4.1	1.1	25	6.3
Red marrow: -blood-based*	0.035	0.020	0.26	0.15	1.5	0.91
-image-based**	0.055	0.046	0.41	0.34	2.5	2.1
Right colon	0.32	0.079	2.4	0.58	14	3.5
Salivary glands	0.63	0.37	4.6	2.7	28	16
Small intestine	0.071	0.031	0.52	0.23	3.1	1.4
Spleen	0.061	0.028	0.45	0.21	2.7	1.2
Stomach wall	0.025	0.026	0.19	0.19	1.1	1.2
Testes	0.023	0.025	0.17	0.19	1.0	1.1
Thymus	0.024	0.026	0.18	0.19	1.1	1.2
Thyroid	0.26	0.37	1.9	2.8	11	17
Total body	0.037	0.027	0.28	0.20	1.7	1.2
Urinary bladder wall	0.32	0.025	2.4	0.19	14	1.1

^aRadiation absorbed dose estimates were derived using OLINDA v2.4 radiation dosimetry software, using measured time-activity data from patient imaging as input. Specific methods and software used for bone marrow and osteogenic cells dosimetry estimates are included below:

*Estimated radiation absorbed dose based on activity measured in blood samples collected from patients, and dosimetry calculations using OLINDA v2.4.

**Estimated radiation absorbed dose based on activity measured in patient imaging (voxelized analysis of measured activity in bone marrow regions approximately 1 cm adjacent to bone metastasis activity within the vertebrae T8-L5) from 81 individual volume of interest (VOI) collected from 28 patients, and dosimetry calculations using Hermia Voxel Dosimetry v3.1.0.

3 DOSAGE FORMS AND STRENGTHS

Injection: 1,000 MBq/mL (27 mCi/mL) of lutetium Lu 177 vipivotide tetraxetan at calibration time as a clear and colorless to slightly yellow solution in a single-dose vial containing 7.4 GBq (200 mCi) ± 10% at administration time.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk From Radiation Exposure

PLUVICTO contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and others during and after treatment with PLUVICTO consistent with institutional good radiation safety practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.

Before the patient is released, inform patients about the necessary radioprotection precautions to follow to minimize radiation exposure to others [*see Patient Counseling Information (17)*].

After each administration of PLUVICTO, advise patients to:

- Limit close contact (less than 3 feet) with others for 2 days or with children and pregnant women for 7 days.
- Refrain from sexual activity for 7 days.
- Sleep in a separate room from others for 3 days, from children for 7 days, or from pregnant women for 15 days.

5.2 Myelosuppression

PLUVICTO can cause severe and life-threatening myelosuppression, including anemia, thrombocytopenia, leukopenia, and neutropenia.

In the PSMAAddition study, Grade 3 or 4 decreased leukocytes (7%), decreased neutrophils (4.4%), decreased hemoglobin (4.3%), and decreased platelets (1.1%) occurred in patients treated with PLUVICTO.

In the PSMAfore study, Grade 3 or 4 decreased hemoglobin (7%), decreased leukocytes (4.4%), decreased neutrophils (3.5%), and decreased platelets (2.7%) occurred in patients treated with PLUVICTO. One death occurred due to bone marrow failure during long-term follow-up in a patient who received PLUVICTO.

In the VISION study, Grade 3 or 4 decreased hemoglobin (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade ≥ 3 pancytopenia occurred in 1.1% (which includes two fatal events) of patients treated with PLUVICTO. Two deaths (0.4%) occurred due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia, one death (0.2%) occurred due to sepsis and concurrent neutropenia, and one death (0.2%) occurred due to bone marrow failure in patients treated with PLUVICTO.

Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO based on the severity of myelosuppression [*see Dosage and Administration (2.4)*].

5.3 Renal Toxicity

PLUVICTO can cause severe renal toxicity.

In the PSMAAddition study, Grade 3 or 4 acute kidney injury (1.6%) occurred in patients treated with PLUVICTO.

In the PSMAfore study, Grade 3 or 4 acute kidney injury (1.3%) occurred in patients treated with PLUVICTO.

In the VISION study, Grade 3 or 4 acute kidney injury (3.4%) occurred in patients treated with PLUVICTO.

Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Perform kidney function laboratory tests, including serum creatinine and calculated creatinine clearance (CL_{cr}), before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO based on the severity of renal toxicity [*see Dosage and Administration (2.4)*].

5.4 Embryo-Fetal Toxicity

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm [*see Clinical Pharmacology (12.1)*]. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, radioactive emissions, including those from PLUVICTO, can cause fetal harm. Advise males with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [*see Use in Specific Populations (8.1, 8.3)*].

5.5 Infertility

PLUVICTO may cause infertility in males. The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility [see *Use in Specific Populations* (8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression [see *Warnings and Precautions* (5.2)]
- Renal Toxicity [see *Warnings and Precautions* (5.3)]

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.

In the pooled safety population for the PSMAddition, PSMAfore and VISION studies (N = 1320), the most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased lymphocytes (86%), decreased hemoglobin (68%), fatigue (51%), dry mouth (46%), decreased neutrophils (35%), nausea (35%), decreased platelets (33%), decreased estimated glomerular filtration rate (28%), increased aspartate aminotransferase (25%), decreased sodium (22%), increased magnesium (22%), increased potassium (21%), decreased calcium (21%), and increased alkaline phosphatase (20%).

Metastatic Androgen Pathway Modulation-Naïve or -Sensitive Prostate Cancer

PSMAddition

The safety of PLUVICTO in combination with ARPI was evaluated in the PSMAddition study in patients with PSMA-positive mAPMN/S prostate cancer [see *Clinical Studies* (14.1)]. Patients could have been treated with ARPI in the metastatic setting for up to 45 days prior to consent. Patients received at least one dose of either PLUVICTO 7.4 GBq (200 mCi) administered every 6 weeks in combination with ARPI (N = 564) or ARPI alone (N = 565). Among patients who received PLUVICTO in combination with ARPI, the median duration of exposure to PLUVICTO was 8.3 months (range, 1.3 to 11.2) and the median number of doses of PLUVICTO received was 6 (range, 1 to 6). The median cumulative administered activity of PLUVICTO was 43.4 GBq (range, 7.1 to 47.3).

Serious adverse reactions occurred in 32% of patients who received PLUVICTO in combination with ARPI. Serious adverse reactions in $> 1\%$ of patients included acute kidney injury (1.6%), pneumonia and sepsis (1.4% each), anemia, basal cell carcinoma, general physical health deterioration, and syncope (1.1% each).

Fatal adverse reactions occurred in 2.7% of patients who received PLUVICTO in combination with ARPI, including general physical health deterioration (0.5%), respiratory failure and sudden death (0.4% each), arrhythmia, cardiac arrest, congestive heart failure, cholangiocarcinoma, COVID-19, malignant neoplasm of unknown primary site, multiple organ dysfunction syndrome, and subdural hemorrhage (0.2% each).

PLUVICTO was permanently discontinued due to adverse reactions in 8% of patients who received PLUVICTO in combination with ARPI. The most frequent ($\geq 1\%$) adverse reaction leading to permanent discontinuation of PLUVICTO was anemia (1.1%).

Adverse reactions leading to a dose interruption of PLUVICTO occurred in 12% of patients who received PLUVICTO in combination with ARPI. The most frequent ($\geq 1\%$) adverse reactions leading to a dose interruption of PLUVICTO were neutropenia (2%), leukopenia, and COVID-19 (1.2% each).

Adverse reactions leading to a dose reduction of PLUVICTO occurred in 3.9% of patients who received PLUVICTO in combination with ARPI. The most frequent ($\geq 1\%$) adverse reaction leading to a dose reduction of PLUVICTO was dry mouth (1.1%).

Table 3 and Table 4 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in PSMAddition.

Table 3: Adverse Reactions ($\geq 10\%$) in Patients With PSMA-Positive mAPMN/S Prostate Cancer Who Received PLUVICTO in Combination With ARPI or ARPI in PSMAddition

Adverse reactions	PLUVICTO in combination with ARPI (N = 564)		ARPI (N = 565)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
General disorders				
Fatigue ^a	51	1.4	41	1.8
Decreased appetite	14	0.9	7	0.2
Gastrointestinal disorders				
Dry mouth ^a	46	0	3.7	0
Nausea	34	0.2	9	0
Constipation	18	0	16	0
Vomiting ^a	14	0.7	3.7	0
Diarrhea	12	0.2	10	0
Nervous system disorders				
Dysgeusia ^a	13	0	4.1	0
Headache	12	0	9	0.4

Abbreviation: ARPI, androgen receptor pathway inhibitors.

^aIncludes multiple similar terms.

Clinically relevant adverse reactions in $< 10\%$ of patients who received PLUVICTO in combination with ARPI included abdominal pain, dizziness, acute kidney injury, dry eye, dry skin, stomatitis, gastroesophageal reflux disease, vertigo, eye irritation, oral fungal infection, dysphagia, and esophagitis.

Table 4: Select Laboratory Abnormalities ($\geq 10\%$) That Worsened From Baseline in Patients With PSMA-Positive mAPMN/S Prostate Cancer Who Received PLUVICTO in Combination With ARPI or ARPI (Between Arm Difference of $\geq 5\%$ All Grades) in PSMAddition

Laboratory abnormalities	PLUVICTO in combination with ARPI ^a		ARPI ^b	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Decreased lymphocytes	91	24	61	10
Decreased hemoglobin	72	4.3 ^c	46	2.5 ^c
Decreased neutrophils	41	4.4	30	3
Decreased platelets	23	1.1	9	1.1
Chemistry				
Decreased estimated glomerular filtration rate (eGFR) ^d	43	1.8	44	1.1

Abbreviation: ARPI, androgen receptor pathway inhibitors.

^aThe denominator used to calculate the rate for each laboratory parameter varied from 563 to 564 based on the number of patients with a baseline value and at least one post-treatment value.

^bThe denominator used to calculate the rate for each laboratory parameter varied from 557 to 558 based on the number of patients with a baseline value and at least one post-treatment value.

^cNo Grade 4 laboratory abnormalities worsening from baseline were reported.

^d“All grades” column represents patients having any worsened eGFR category of < 90 mL/min/1.73 m² and “Grade 3 or 4” column represents patients having any worsened eGFR category of < 30 mL/min/1.73 m² calculated using the CKD-EPI formula.

Metastatic Androgen Pathway Modulation-Resistant Prostate Cancer

PSMAfore

The safety of PLUVICTO was evaluated in the PSMAfore study in patients with progressive, PSMA-positive mAPMR prostate cancer previously treated with ARPI therapy, for whom it was considered appropriate to delay taxane-based chemotherapy by the investigator [see *Clinical Studies (14.2)*]. Patients received at least one dose of either PLUVICTO 7.4 GBq (200 mCi) administered every 6 weeks (N = 227) or a change in ARPI (N = 232). The median duration of exposure to PLUVICTO was 8.4 months (range, 0.4 to 11.6) and the median number of doses of PLUVICTO received was 6 (range, 1 to 6). The median cumulative administered activity of PLUVICTO was 42.4 GBq (range, 7.0 to 45.4).

Serious adverse reactions occurred in 20% of patients who received PLUVICTO. Serious adverse reactions in > 1% of patients included anemia (1.8%), urinary tract infection (1.8%), hemorrhage (1.3%), and sepsis (1.3%).

Fatal adverse reactions occurred in 1.8% of patients who received PLUVICTO, including COVID-19 pneumonia, cardiac arrest, intestinal ischemia, and sepsis (0.4% each).

PLUVICTO was permanently discontinued due to adverse reactions in 6% of patients who received PLUVICTO. The most frequent ($\geq 1\%$) adverse reactions leading to permanent discontinuation of PLUVICTO were thrombocytopenia (1.8%) and dry mouth (1.3%).

Adverse reactions leading to a dose interruption of PLUVICTO occurred in 12% of patients who received PLUVICTO. The most frequent ($\geq 1\%$) adverse reactions leading to a dose interruption of PLUVICTO were COVID-19 (3.1%) and anemia (1.8%).

Adverse reactions leading to a dose reduction of PLUVICTO occurred in 3.5% of patients who received PLUVICTO. The most frequent ($\geq 0.5\%$) adverse reaction leading to a dose reduction of PLUVICTO was dry mouth (0.9%).

Table 5 and Table 6 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in PSMAfore.

Table 5: Adverse Reactions ($\geq 10\%$) in Patients With PSMA-Positive mAPMR Prostate Cancer Who Received PLUVICTO or Change in ARPI in PSMAfore

Adverse reactions	PLUVICTO (N = 227)		ARPI (N = 232)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal disorders				
Dry mouth ^a	61	0.9	2.6	0
Nausea	32	0	12	0.4
Constipation	22	0.4	14	0
Diarrhea	17	0	9	0.4
Vomiting	11	0	4.7	0
General disorders				
Fatigue ^a	53	1.3	53	5
Metabolism and nutrition disorders				
Decreased appetite	22	0	19	0.4
Musculoskeletal and connective tissue disorders				
Arthralgia	20	0	23	0.4
Back pain	14	1.3	20	2.6

Abbreviation: ARPI, androgen receptor pathway inhibitor.

^aIncludes multiple similar terms.

Clinically relevant adverse reactions in < 10% of patients who received PLUVICTO included abdominal pain, dysgeusia, peripheral edema, headache, acute kidney injury, weight decreased, dry eye, urinary tract infection, dizziness, dry skin, oral fungal infection, gastroesophageal reflux disease, pyrexia, vertigo, stomatitis, dysphagia, esophagitis, pancytopenia, and bone marrow failure.

Table 6: Select Laboratory Abnormalities (≥ 10%) That Worsened From Baseline in Patients With PSMA-Positive mAPMR Prostate Cancer Who Received PLUVICTO or Change in ARPI (Between Arm Difference of ≥ 5% All Grades) in PSMAfore

Laboratory abnormalities	PLUVICTO ^a		ARPI ^b	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Decreased lymphocytes	78	27	57	12
Decreased hemoglobin	67	7 ^c	50	7 ^c
Decreased neutrophils	38	3.5	18	1.3
Decreased platelets	30	2.7	11	1.7
Chemistry				
Decreased estimated glomerular filtration rate (eGFR) ^d	41	0.9 ^c	42	3
Increased alkaline phosphatase	31	8	50	10 ^c
Increased magnesium	19	0.9 ^c	28	0 ^c
Decreased calcium	18	0.9	11	0.9
Decreased sodium	11	0 ^c	18	0 ^c
Decreased potassium	6	0.9 ^c	18	2.6

Abbreviation: ARPI, androgen receptor pathway inhibitor.

^aThe denominator used to calculate the rate for each laboratory parameter was based on 226 patients with a baseline value and at least one post-treatment value.

^bThe denominator used to calculate the rate for each laboratory parameter varied from 231 to 232 based on the number of patients with a baseline value and at least one post-treatment value.

^cNo Grade 4 laboratory abnormalities worsening from baseline were reported.

^d“All grades” column represents patients having any worsened eGFR category of < 90 mL/min/1.73 m² and “Grade 3 or 4” column represents patients having any worsened eGFR category of < 30 mL/min/1.73 m² calculated using the CKD-EPI formula.

VISION

The safety of PLUVICTO was evaluated in the VISION study in patients with progressive, PSMA-positive mAPMR prostate cancer previously treated with ARPI therapy and taxane-based chemotherapy [see *Clinical Studies* (14.2)]. Patients received at least one dose of either PLUVICTO 7.4 GBq (200 mCi) administered every 6 weeks plus BSoC (N = 529) or BSoC alone (N = 205). The median duration of exposure to PLUVICTO plus BSoC was 7.8 months (range, 0.3 to 36.5). Among patients who received PLUVICTO plus BSoC, the median number of doses of PLUVICTO received was 5 (range, 1 to 6). The median cumulative administered activity of PLUVICTO was 37.5 GBq (range, 7.0 to 48.3).

Serious adverse reactions occurred in 37% of patients who received PLUVICTO plus BSoC. Serious adverse reactions in > 1% of patients included musculoskeletal pain (4%), hemorrhage (4%), sepsis (3.2%), urinary tract infection (3%), anemia (2.8%), acute kidney injury (1.9%), pneumonia (1.7%), pyrexia (1.5%), pancytopenia (1.3%), spinal cord compression (1.1%), and pulmonary embolism (1.1%).

Fatal adverse reactions occurred in 3% of patients who received PLUVICTO plus BSoC, including sepsis (0.9%), pancytopenia (0.6%), hepatic failure (0.4%), intracranial hemorrhage (0.2%), subdural hematoma (0.2%), ischemic stroke (0.2%), COVID-19 (0.2%), and aspiration pneumonia (0.2%).

PLUVICTO was permanently discontinued due to adverse reactions in 12% of patients who received PLUVICTO plus BSoC. The most frequent (≥ 1%) adverse reactions leading to permanent discontinuation of PLUVICTO were anemia (2.8%), thrombocytopenia (2.8%), and leukopenia (including neutropenia) (1.7%).

Adverse reactions leading to a dose interruption of PLUVICTO occurred in 16% of patients who received PLUVICTO plus BSoC. The most frequent (≥ 3%) adverse reactions leading to a dose interruption of PLUVICTO were anemia (5%) and thrombocytopenia (3.6%).

Adverse reactions leading to a dose reduction of PLUVICTO occurred in 6% of patients who received PLUVICTO plus BSoC. The most frequent ($\geq 1\%$) adverse reactions leading to a dose reduction of PLUVICTO were thrombocytopenia (1.9%) and anemia (1.3%).

Table 7 and Table 8 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in VISION.

Table 7: Adverse Reactions ($\geq 10\%$) in Patients With PSMA-Positive mAPMR Prostate Cancer Who Received PLUVICTO Plus BSoC or BSoC in VISION

Adverse reactions	PLUVICTO plus BSoC (N = 529)		BSoC (N = 205)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
General disorders				
Fatigue ^a	48	7	29	2.4
Decreased appetite	21	1.9	15	0.5
Weight decreased	11	0.4	10	0.5
Peripheral edema ^a	10	0.4	7	1
Gastrointestinal disorders				
Dry mouth ^a	39	0	1	0
Nausea	36	1.3	17	0.5
Constipation	20	1.1	11	0.5
Vomiting ^a	19	0.9	6	0.5
Diarrhea	19	0.8	2.9	0.5
Abdominal pain ^a	12	1.3	6	0.5
Musculoskeletal and connective tissue disorders				
Back pain	24	3.6	15	3.9
Arthralgia	22	1.1	13	0.5
Bone pain	11	2.5	8	2.4
Renal and urinary disorders				
Urinary tract infection ^a	12	3.8	1	0.5

Abbreviation: BSoC, best standard of care.

^aIncludes multiple similar terms.

Clinically relevant adverse reactions in $< 10\%$ of patients who received PLUVICTO plus BSoC included acute kidney injury, dizziness, dysgeusia, headache, pyrexia, dry eye, oral fungal infection, vertigo, gastroesophageal reflux disease, stomatitis, pancytopenia, dry skin, dysphagia, esophagitis, and bone marrow failure.

Table 8: Select Laboratory Abnormalities ($\geq 10\%$) That Worsened From Baseline in Patients With PSMA-Positive mAPMR Prostate Cancer Who Received PLUVICTO Plus BSoC or BSoC (Between Arm Difference of $\geq 5\%$ All Grades) in VISION

Laboratory abnormalities	PLUVICTO plus BSoC ^a		BSoC ^b	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Decreased lymphocytes	85	47	51	18
Decreased hemoglobin	64	15 ^c	34	7 ^c
Decreased platelets	45	9	20	2.5
Decreased neutrophils	28	4.7	9	0.5
Chemistry				

Laboratory abnormalities	PLUVICTO plus BSoC ^a		BSoC ^b	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Decreased estimated glomerular filtration rate (eGFR) ^d	42	3.4	31	2.5
Decreased sodium	34	0.6 ^c	23	1
Decreased calcium	34	1.9	18	1.5
Increased aspartate aminotransferase (AST)	29	1.1	18	1 ^c
Increased potassium	24	0.6	18	0.5 ^c
Increased sodium	11	0 ^c	5	0 ^c

Abbreviation: BSoC, best standard of care.

^aThe denominator used to calculate the rate for each laboratory parameter varied from 506 to 529 based on the number of patients with a baseline value and at least one post-treatment value.

^bThe denominator used to calculate the rate for each laboratory parameter varied from 194 to 198 based on the number of patients with a baseline value and at least one post-treatment value.

^cNo Grade 4 laboratory abnormalities worsening from baseline were reported.

^d“All grades” column represents patients having any worsened eGFR category of < 90 mL/min/1.73 m² and “Grade 3 or 4” column represents patients having any worsened eGFR category of < 30 mL/min/1.73 m² calculated using the CKD-EPI formula.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm [see *Clinical Pharmacology (12.1)*]. There are no available data on PLUVICTO use in pregnant females. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radioactive emissions, including those from PLUVICTO, can cause fetal harm.

8.2 Lactation

Risk Summary

The safety and efficacy of PLUVICTO have not been established in females. There are no data on the presence of lutetium Lu 177 vipivotide tetraxetan in human milk or its effects on the breastfed child or on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see *Clinical Pharmacology (12.1)*, *Nonclinical Toxicology (13.1)*].

Infertility

The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 564 patients who received at least one dose of PLUVICTO in combination with ARPI in the PSMAddition study, 379 patients (67%) were 65 years of age or older and 115 patients (20%) were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥ 75 years of age and younger patients. Serious adverse

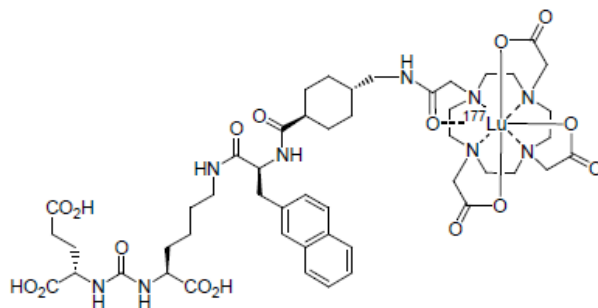
Of the 227 patients who received at least one dose of PLUVICTO in the PSMAfore study, 177 patients (78%) were 65 years of age or older and 83 patients (37%) were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥ 75 years of age and younger patients. Serious adverse reactions occurred in 20% of patients ≥ 75 years of age and in 20% of younger patients. Grade ≥ 3 adverse reactions occurred in 39% of patients ≥ 75 years of age and in 34% of younger patients.

8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

The chemical name is 2-[4-[2-[4-[[(2S)-1-[(5S)-5-carboxy-5-[(1S)-1,3-dicarboxypropyl]carbamoylamino]pentyl]amino]-3-naphthalen-2-yl]-1-oxopropan-2-yl]carbamoyl]cyclohexyl]methylamino]-2-oxoethyl]-4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetate; lutetium-177(3+). The molecular mass is 1216.06 g/mol and the molecular formula is $C_{49}H_{68}^{177}LuN_9O_{16}$. The chemical structure for lutetium Lu 177 vipivotide tetraxetan is shown below:



Reference ID: 5844808

11.1 Physical Characteristics

Lutetium-177 decays to a stable hafnium-177 with a physical half-life of 6.647 days by emitting beta-minus radiation with a maximum energy of 498 keV (79%) and photonic radiation (γ) of 208 keV (11%) and 113 keV (6.4%).

The main radiations of lutetium-177 are detailed in Table 9.

Table 9: Lutetium-177 Main Radiations

Radiation	Energy (keV)	I β -%	I γ -%
β^-	176.5	12.2	
β^-	248.1	0.05	
β^-	384.9	9.1	
β^-	497.8	78.6	
γ	71.6		0.15
γ	112.9		6.40
γ	136.7		0.05
γ	208.4		11.0
γ	249.7		0.21
γ	321.3		0.22

11.2 External Radiation

Table 10 summarizes the radioactive decay properties of lutetium-177.

Table 10: Physical Decay Chart: Lutetium-177 Physical Half-life = 6.647 days

Hours	Fraction remaining
0	1.000
1	0.996
2	0.991
5	0.979
10	0.958
24 (1 day)	0.901
48 (2 days)	0.812
72 (3 days)	0.731
120 (5 days)	0.594
168 (7 days)	0.482
336 (14 days)	0.232
720 (30 days)	0.044
1080 (45 days)	0.009

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lutetium Lu 177 vipivotide tetraxetan is a radioligand therapeutic agent. The active moiety of lutetium Lu 177 vipivotide tetraxetan is the radionuclide lutetium-177 which is linked to a moiety that binds to PSMA, a transmembrane protein that is expressed in prostate cancer. Upon binding of lutetium Lu 177 vipivotide tetraxetan 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.

12.2 Pharmacodynamics

Lutetium Lu 177 vipivotide tetraxetan exposure-efficacy relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

At the recommended dosage, PLUVICTO does not cause large mean increases (> 20 ms) in the QTc interval.

12.3 Pharmacokinetics

Pharmacokinetics of lutetium Lu 177 vipivotide tetraxetan are expressed as geometric mean (geometric mean coefficient of variation) unless otherwise specified.

The blood lutetium Lu 177 vipivotide tetraxetan area under the curve (AUC) is 52.3 ng.h/mL (31.4%) and the maximum blood concentration (C_{max}) is 6.58 ng/mL (43.5%) at the recommended dosage.

Distribution

Lutetium Lu 177 vipivotide tetraxetan volume of distribution is 123 L (78.1%).

Within 2.5 hours after administration, lutetium Lu 177 vipivotide tetraxetan distributes in gastrointestinal tract, liver, lungs, kidneys, heart wall, bone marrow, and salivary glands.

Vipivotide tetraxetan and non-radioactive lutetium vipivotide tetraxetan are 60% to 70% bound to human plasma proteins.

Elimination

The lutetium Lu 177 vipivotide tetraxetan terminal elimination half-life is 41.6 hours (68.8%) and the clearance (CL) is 2.04 L/h (31.5%).

Metabolism

Lutetium Lu 177 vipivotide tetraxetan does not undergo hepatic or renal metabolism.

Excretion

Lutetium Lu 177 vipivotide tetraxetan is primarily eliminated renally.

Specific Populations

Exposure (AUC) of lutetium Lu 177 vipivotide tetraxetan increased with decreasing creatinine clearance (CL_{Cr}). The effect of baseline CL_{Cr} < 54 mL/min on lutetium Lu 177 vipivotide tetraxetan pharmacokinetics has not been studied.

Drug Interaction Studies

In Vitro Studies

CYP450 enzymes: Vipivotide tetraxetan is not a substrate of cytochrome P450 (CYP450) enzymes. Vipivotide tetraxetan did not induce CYP1A2, 2B6 or 3A4; and did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A in vitro.

Transporters: Vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2. Vipivotide tetraxetan did not inhibit BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with lutetium Lu 177 vipivotide tetraxetan; however, radiation is a carcinogen and mutagen.

No animal studies were conducted to determine the effects of lutetium Lu 177 vipivotide tetraxetan on fertility.

14 CLINICAL STUDIES

14.1 Metastatic Androgen Pathway Modulation-Naïve or -Sensitive Prostate Cancer

PSMAddition

The efficacy of PLUVICTO in combination with ARPI therapy was evaluated in PSMAddition (NCT04720157), a randomized, multicenter, open-label trial in patients with prostate-specific membrane antigen (PSMA)-positive metastatic androgen pathway modulation-naïve or -sensitive (mAPMN/S) prostate cancer. No systemic treatment was allowed apart from androgen deprivation therapy (ADT) in the neo-/adjuvant setting and/or up to 45 days of ADT, ARPI, or both in the metastatic setting prior to consent. Patients were required to have at least one metastatic lesion (soft tissue or bone) present by conventional imaging and at least one tumor lesion (soft tissue or bone) with gallium Ga 68 gozetotide uptake greater than in normal liver. Patients were excluded if all present liver metastases were gallium Ga 68 gozetotide negative.

Patients were randomized (1:1) to receive either PLUVICTO 7.4 GBq (200 mCi) every 6 weeks for a planned 6 doses in combination with ARPI (N = 572) or ARPI alone (N = 572). Treatment with ARPI in both arms could be continued until progressive disease, change of antineoplastic therapy, unacceptable toxicity, death, or withdrawal. The administered ARPI per investigator's choice included abiraterone (n = 424), apalutamide (n = 372), enzalutamide (n = 250), darolutamide

(n = 68), or another ARPI (n = 12). Patients received a gonadotropin-releasing hormone (GnRH) agonist or antagonist concurrently or had a bilateral orchiectomy. Randomization was stratified by disease volume (high vs low, as per CHAARTED criteria), age ≥ 70 years (yes vs no), and previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (yes vs no).

The major efficacy outcome measure was radiographic progression-free survival (rPFS) as determined by blinded independent central review (BICR) per Prostate Cancer Working Group 3 (PCWG3)-modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Overall survival (OS) was an additional efficacy outcome measure.

The median age was 68 years (range, 36 to 91); 61% were White; 4.8% Black or African American; 19% Asian; 3.8% were Hispanic or Latino; 78% not Hispanic or Latino; 19% ethnicity not reported/unknown/missing; 99% had ECOG PS0-1. Seventy percent (70%) of patients had high-volume disease and 30% had low-volume disease.

PSMAddition demonstrated a statistically significant improvement in rPFS by BICR for patients randomized to PLUVICTO in combination with ARPI compared to ARPI alone. The OS data were immature, and a total of 291 patients (25%) had died across both study arms.

Efficacy results for PSMAddition are presented in Table 11 and Figure 1.

Table 11: Efficacy Results in PSMAddition

	PLUVICTO in combination with ARPI	ARPI
Radiographic Progression-free Survival (rPFS)^a	N = 572	N = 572
Number of events (progression or death), n (%)	139 (24)	172 (30)
Median, months (95% CI) ^b	NE (NE, NE)	NE (29.7, NE)
Hazard ratio (95% CI) ^c	0.72 (0.58, 0.90)	
P-value ^d	0.002	

Abbreviations: ARPI, androgen receptor pathway inhibitor; NE, Not estimable.

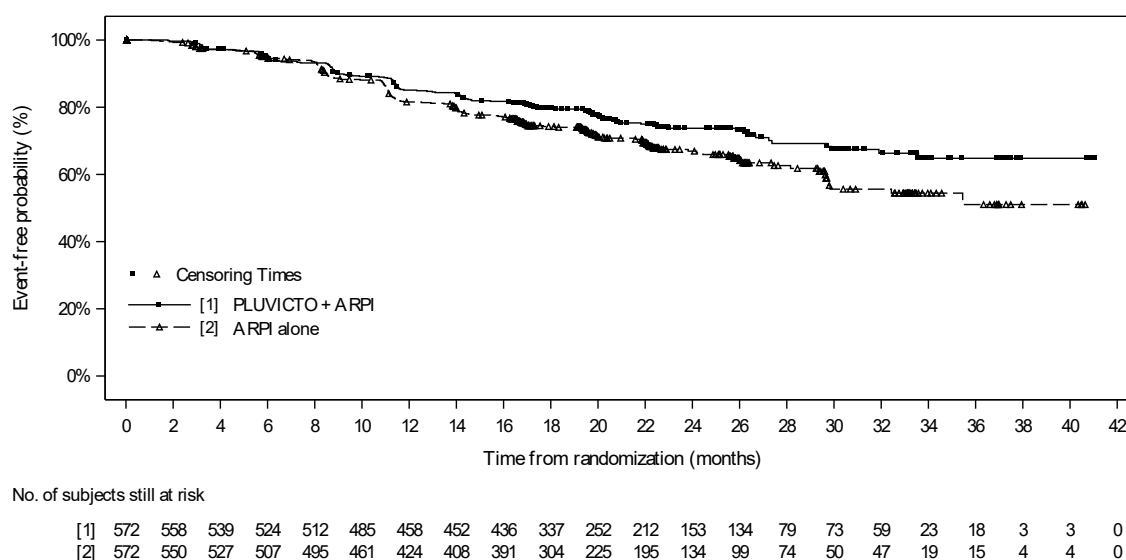
^aBy BICR per PCWG3-modified RECIST v1.1 criteria.

^bBased on Kaplan-Meier estimate.

^cHazard ratio based on the stratified Cox PH model.

^dStratified log-rank test one-sided p-value.

Figure 1. Kaplan-Meier Plot of Radiographic Progression-Free Survival in PSMAddition



14.2 Metastatic Androgen Pathway Modulation-Resistant Prostate Cancer

PSMAfore for Patients Previously Treated With ARPI Therapy

The efficacy of PLUVICTO was evaluated in PSMAfore (NCT04689828), a randomized (1:1), multicenter, open-label trial that evaluated PLUVICTO (N = 234) versus a change in ARPI (N = 234) in patients with progressive, PSMA-positive mAPMR prostate cancer. Randomization was stratified by setting of prior ARPI use [androgen pathway

modulation-resistant (APMR) prostate cancer vs. androgen pathway modulation-naïve or -sensitive (APMN/S) prostate cancer] and by symptomatology [asymptomatic or mildly symptomatic vs. symptomatic]. Patients were required to have a castrate level of serum/plasma testosterone by either medical castration or prior orchiectomy at study entry. Patients were required to have progressed only once on an ARPI (abiraterone acetate, enzalutamide, darolutamide, or apalutamide). Prior taxane-based chemotherapy was only allowed in the adjuvant or neoadjuvant setting greater than 12 months before enrollment. Patients were considered appropriate for delay of taxane-based chemotherapy by the investigator. Patients were required to have PSMA-positive mAPMR prostate cancer defined as having at least one tumor lesion (soft tissue or bone) with gallium Ga 68 gozetotide uptake greater than in normal liver. Patients were considered ineligible if any intraprostatic lesion or any one lesion larger than size criteria [organs ≥ 1 cm in longest diameter, lymph nodes ≥ 2.5 cm in short axis, bones (soft tissue component) ≥ 1 cm in longest diameter] had gallium Ga 68 gozetotide uptake less than or equal to uptake in normal liver.

Patients received PLUVICTO 7.4 GBq (200 mCi) every 6 weeks for 6 doses or a change in ARPI. Supportive care administered at the investigator's discretion included bone-targeted agents; ADT; or palliative radiotherapy.

The major efficacy outcome measure was rPFS as determined by BICR per PCWG3-modified RECIST v1.1 criteria. Additional efficacy outcome measures were OS and ORR.

The median age was 72 years (range, 43 to 94 years); 91% were White; 2.6% Black or African American; 0.6% Asian; 6% were Hispanic or Latino; 77% not Hispanic or Latino; 17% ethnicity not reported/unknown; 99% had ECOG PS0-1.

PSMAfore demonstrated a statistically significant improvement in rPFS for PLUVICTO compared to a change in ARPI.

Of patients that were randomized to receive a change in ARPI, 141 patients (60%) crossed over to receive PLUVICTO after confirmation of radiographic disease progression by BICR.

Efficacy results for PSMAfore are presented in Table 12 and Figure 2.

Table 12: Efficacy Results in PSMAfore

	PLUVICTO	ARPI
Radiographic Progression-free Survival (rPFS)^a	N = 233^b	N = 234
Number of events (progression or death), n (%)	60 (26)	106 (45)
Median, months (95% CI) ^c	9.3 (7, NE)	5.6 (4, 6)
Hazard ratio (95% CI) ^d	0.41 (0.29, 0.56)	
P-value ^e	< 0.0001	
Overall Survival (OS)	N = 234	N = 234
Deaths, n (%)	142 (61)	157 (67)
Median, months (95% CI) ^c	24.5 (19.5, 28.9)	23.1 (19.6, 25.5)
Hazard ratio (95% CI) ^d	0.91 (0.72, 1.14)	
P-value ^e	NS	
Overall Response Rate (ORR)^{a,f}		
Patients with measurable disease at baseline	N = 72	N = 72
ORR (CR + PR), n (%)	35 (49)	10 (14)
(95% CI)	(37, 61)	(7, 24)
Complete response (CR), n (%)	15 (21)	2 (2.8)
Partial response (PR), n (%)	20 (28)	8 (11)

Abbreviations: ARPI, androgen receptor pathway inhibitor; NE, Not estimable; NS, Not statistically significant.

^aBy BICR per PCWG3-modified RECIST v1.1 criteria.

^bExcludes one patient in the PLUVICTO arm who was randomized after the data cut-off for the rPFS primary analysis.

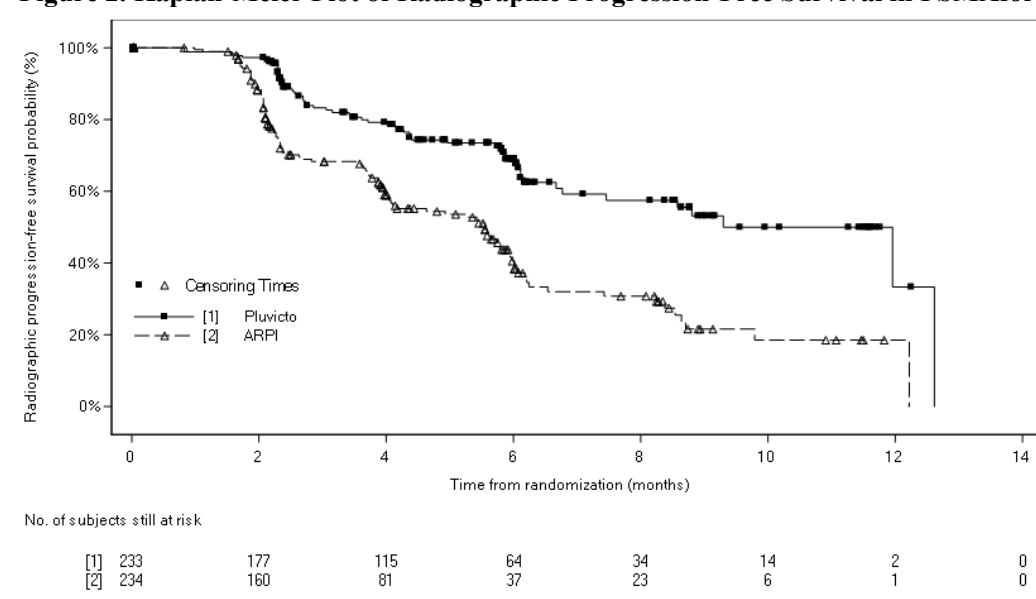
^cBased on Kaplan-Meier estimate.

^dHazard ratio based on the stratified Cox PH model.

^eStratified log-rank test one-sided p-value.

^fResponses are based on soft tissue and bone lesion assessment.

Figure 2. Kaplan-Meier Plot of Radiographic Progression-Free Survival in PSMAfore



VISION for Patients Previously Treated With ARPI Therapy and Taxane-Based Chemotherapy

The efficacy of PLUVICTO was evaluated in VISION (NCT03511664), a randomized (2:1), multicenter, open-label trial of PLUVICTO plus BSoC (N = 551) versus BSoC alone (N = 280) in patients with progressive, PSMA-positive mAPMR prostate cancer. Randomization was stratified by baseline lactate dehydrogenase (LDH ≤ 260 IU/L vs. > 260 IU/L), presence of liver metastases (yes vs. no), ECOG PS score (0 or 1 vs. 2), and inclusion of an ARPI as part of BSoC (yes vs. no) at the time of randomization. Patients were required to have a castrate level of serum/plasma testosterone by either medical castration or prior orchiectomy at study entry. Patients were required to have received at least one ARPI, and 1 or 2 prior taxane-based chemotherapy regimens. Eligible patients were required to have PSMA-positive mAPMR prostate cancer defined as having at least one tumor lesion (soft tissue or bone) with gallium Ga 68 gozetotide uptake greater than in normal liver. Patients were considered ineligible if any one lesion larger than size criteria [organs ≥ 1 cm in short axis, lymph nodes ≥ 2.5 cm in short axis, bones (soft tissue component) ≥ 1 cm in short axis] had gallium Ga 68 gozetotide uptake less than or equal to uptake in normal liver.

Patients received PLUVICTO 7.4 GBq (200 mCi) every 6 weeks for a maximum of 6 doses plus BSoC or BSoC alone. BSoC administered at the investigator's discretion included ketoconazole; radiation therapy to localized prostate cancer targets; bone-targeted agents; ADT; ARPIs. Patients continued treatment for up to 4-6 doses, or until disease progression or unacceptable toxicity. Patients with stable disease or partial response after 4 doses of PLUVICTO plus BSoC received up to 2 additional doses per investigator's discretion.

The major efficacy outcome measures were OS and rPFS as determined by BICR per PCWG3-modified RECIST v1.1 criteria. An additional efficacy outcome measure was ORR.

The median age was 71 years (range, 40 to 94 years); 87% were White; 7% Black or African American; 2.4% Asian; 1.7% were Hispanic or Latino; 86% not Hispanic or Latino; 13% ethnicity not reported; 92% had ECOG PS0-1; 8% had ECOG PS2. All patients had received at least one prior taxane-based chemotherapy regimen and 41% of patients received two. One prior ARPI had been administered to 51% of patients, 41% of patients had received 2, and 8% of patients had received 3 or more. During the treatment period, 53% of patients in the PLUVICTO plus BSoC arm and 68% of patients in the BSoC alone arm received at least one ARPI.

VISION demonstrated a statistically significant improvement in both major efficacy outcome measures of OS and rPFS by BICR with PLUVICTO plus BSoC compared to treatment with BSoC alone. Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early drop out in the control arm.

Efficacy results for VISION are presented in Table 13 and Figure 3.

Table 13: Efficacy Results in VISION

	PLUVICTO plus BSoC	BSoC
Overall Survival (OS)	N = 551	N = 280
Deaths, n (%)	343 (62)	187 (67)
Median, months (95% CI) ^a	15.3 (14.2, 16.9)	11.3 (9.8, 13.5)
Hazard ratio (95% CI) ^b	0.62 (0.52, 0.74)	
P-value ^c	< 0.001	
Overall Response Rate (ORR)^{d,e}		
Patients with measurable disease at baseline	N = 184	N = 64
ORR (CR + PR), n (%)	91 (49)	1 (1.6)
(95% CI)	(42, 57)	(0, 8)
Complete response (CR), n (%)	17 (9)	0 (0)
Partial response (PR), n (%)	74 (40)	1 (1.6)
P-value ^f	< 0.001	

Abbreviations: BSoC, best standard of care.

^aBased on Kaplan-Meier estimate.

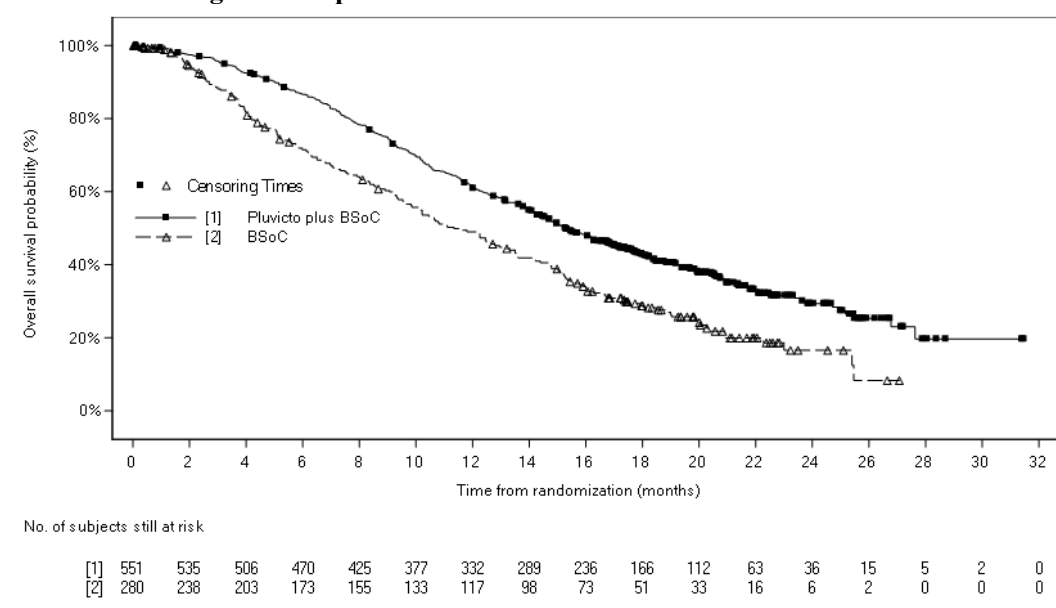
^bHazard ratio based on the stratified Cox PH model.

^cStratified log-rank test two-sided p-value.

^dResponses are based on soft tissue and bone lesion assessment.

^eBy BICR per PCWG3-modified RECIST v1.1 criteria.

^fStratified Wald's Chi-square test two-sided p-value.

Figure 3. Kaplan-Meier Plot of Overall Survival in VISION

16 HOW SUPPLIED/STORAGE AND HANDLING

PLUVICTO Injection containing 1,000 MBq/mL (27 mCi/mL) of lutetium Lu 177 vipivotide tetraxetan at calibration time is a sterile, preservative-free and clear, colorless to slightly yellow solution for intravenous use supplied in a clear, colorless Type I glass 30 mL single-dose vial containing 7.4 GBq (200 mCi) $\pm$ 10% of lutetium Lu 177 vipivotide tetraxetan at administration time (NDC# 0078-1217-61). The solution volume in the vial can range from 7.5 mL to 12.5 mL in order to provide a total of 7.4 GBq (200 mCi) of radioactivity at administration time.

The product vial is enclosed within a lead shielded container (NDC# 0078-1217-61) for protective shielding and placed in a plastic sealed container. The product is shipped in a type A package.

The shelf life is 120 hours (5 days) from the date and time of calibration.

Store below 30°C (86°F). Do not freeze. Store in the original package to protect from ionizing radiation (lead shielding).

Store PLUVICTO in accordance with local and federal laws on radioactive materials.

Do not use PLUVICTO after the expiration date and time which are stated on the label.

Dispose of any unused medicinal product or waste material in accordance with local and federal laws.

Lutetium-177 for PLUVICTO may be prepared using two different sources of stable nuclides (either lutetium-176 or ytterbium-176) that require different waste management. Lutetium-177 for PLUVICTO is prepared using ytterbium-176 (“non-carrier added”) unless otherwise communicated on the product batch release certificate.

17 PATIENT COUNSELING INFORMATION

Risk From Radiation Exposure

Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.

Before the patient is released, inform patients about the necessary radioprotection precautions to follow to minimize radiation exposure to others.

After each administration of PLUVICTO, advise patients to:

- Limit close contact (less than 3 feet) with others for 2 days or with children and pregnant women for 7 days.
- Refrain from sexual activity for 7 days.
- Sleep in a separate room from others for 3 days, from children for 7 days, or from pregnant women for 15 days [see *Warnings and Precautions (5.1)*].

Myelosuppression

Advise patients to contact their healthcare provider for any signs or symptoms of myelosuppression, such as tiredness, weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or difficulty to stop bleeding, or frequent infections with signs, such as fever, chills, sore throat or mouth ulcers [see *Warnings and Precautions (5.2)*].

Renal Toxicity

Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Advise patients to contact their healthcare provider for any signs or symptoms of renal toxicity, such as passing urine less often than usual or passing much smaller amounts of urine than usual [see *Warnings and Precautions (5.3)*].

Embryo-Fetal Toxicity

Advise males that PLUVICTO can cause fetal harm [see *Warnings and Precautions (5.4), Use in Specific Populations (8.1)*].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see *Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)*].

Infertility

Advise males of reproductive potential that PLUVICTO may cause temporary or permanent infertility [see *Warnings and Precautions (5.5), Use in Specific Populations (8.3)*].

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

©2026 Novartis
PLUVICTO® is a registered trademark of Novartis AG and/or its affiliates.
U.S. Patents 10398791; 10406240; 11318121; 11951190; 12208102