PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PLUVICTO™

lutetium (^{177}Lu) vipivotide tetraxetan injection

Sterile Solution for Intravenous Injection/Infusion

1000 MBq/mL at calibration

Therapeutic Radiopharmaceutical

ATC Code: V10XX05

Novartis Pharmaceuticals Canada Inc.

700 Saint-Hubert St., Suite 100
Montreal, Quebec
H2Y 0C1

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PLUVICTO™ (lutetium (^{177}Lu) vipivotide tetraxetan injection) is indicated for:

- The treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have received at least one androgen receptor pathway inhibitor (ARPI) and taxane-based chemotherapy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No clinically relevant differences in efficacy were observed between patients ≥ 65 years and those younger than 65 years.

2 CONTRAINDICATIONS

PLUVICTO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.
- Myelosuppression can occur in patients treated with PLUVICTO (see 7 WARNINGS AND PRECAUTIONS). Cases of severe and life-threatening myelosuppression have been reported.
- Renal toxicity can occur in patients treated with PLUVICTO (see 7 WARNINGS AND PRECAUTIONS). Cases of severe renal injury have been reported.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

PLUVICTO is a radiopharmaceutical and should be handled with appropriate safety measures to minimize radiation exposure (see 7 WARNINGS AND PRECAUTIONS). Waterproof gloves and effective radiation shielding should be used 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.

Tumour PSMA expression should be verified before treatment with PLUVICTO. In clinical trials, patients were selected on the basis of PSMA expression detected by PET diagnostic imaging using ^{68}Ga-PSMA-11 (see 14 CLINICAL TRIALS).

4.2 Recommended Dose and Dosage Adjustment

The recommended PLUVICTO dose is 7.4 GBq (7400 MBq) (200 mCi) intravenously every 6 weeks for up to 6 doses, or until disease progression, or unacceptable toxicity.

Monitoring Recommendations

Laboratory tests should be performed before and during treatment with PLUVICTO.

- Hematology (hemoglobin, white blood cell count, absolute neutrophil count, platelet count)
- Kidney function (serum creatinine, calculated creatinine clearance [CrCl])
- Liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood serum albumin, total blood bilirubin)

Dose modifications for adverse reactions

Recommended dose modifications of PLUVICTO for adverse reactions are provided in Table 1. Management of severe or intolerable adverse reactions may require temporary dose interruption (extending the dosing interval by 4 weeks from 6 weeks up to 10 weeks), dose reduction or permanent discontinuation of treatment with PLUVICTO. If a treatment delay due to an adverse reaction persists for >4 weeks, treatment with PLUVICTO must be discontinued. The dose of PLUVICTO may be reduced by 20% once; the dose should not be re-escalated. If a patient has further adverse reactions that would require an additional dose reduction, treatment with PLUVICTO must be discontinued.

Table 1 – Recommended Dose Modifications of PLUVICTO for Adverse Reactions

Adverse reaction	Severity[a]	Dose modification
Dry mouth	Grade 3	Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
Gastrointestinal toxicity	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).
Myelosuppression (Anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia)	Grade 2	Withhold PLUVICTO until improvement to Grade 1 or baseline. Manage as deemed appropriate. The use of growth factors is permitted but should be discontinued once improved to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated.

Adverse reaction	Severity[a]	Dose modification
	Grade ≥3	Withhold PLUVICTO until improvement to Grade 1 or baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
Renal toxicity	Defined as: • Confirmed serum creatinine increase (Grade ≥2) • Confirmed CrCl <30 mL/min; calculate using Cockcroft-Gault with actual body weight	Withhold PLUVICTO until improvement.
	Defined as: • Confirmed ≥40% increase from baseline serum creatinine and • Confirmed >40% decrease from baseline CrCl; 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).
	Recurrent renal toxicity (Grade ≥3)	Permanently discontinue PLUVICTO.
Spinal cord compression	Any	Withhold PLUVICTO until the compression has been adequately treated and any neurological sequela have stabilized and ECOG performance status has stabilized.
Fracture in weight-bearing bones	Any	Withhold PLUVICTO until the fracture has been adequately stabilized/treated and ECOG performance status has stabilized.
AST or ALT elevation	AST or ALT >5 times ULN in the absence of liver metastases	Permanently discontinue PLUVICTO.

Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

Grading according to most current Common Terminology Criteria for Adverse Events (CTCAE).

[a]The same thresholds are also applicable to baseline values at the time of treatment initiation with PLUVICTO.

Special Populations

Pediatric (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No dose adjustment of PLUVICTO is required in patients aged 65 years or older.

Renal impairment: Exposure of lutetium (^{177}Lu) vipivotide tetraxetan injection is expected to increase with the degree of renal impairment (see 10 CLINICAL PHARMACOLOGY). No dose adjustment is recommended for patients with mild (baseline CrCl 60 to 89 mL/min by Cockcroft-Gault) renal impairment and insufficient data are available for drawing a conclusion for patients with moderate (CrCl 30 to 59 mL/min) renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Renal function and adverse reactions should be monitored frequently in patients with mild to moderate renal impairment. The pharmacokinetic profile and safety of PLUVICTO have not been studied in patients with severe (CrCl 15 to 29 mL/min) renal impairment or end-stage renal disease.

Hepatic impairment: There is insufficient data available for drawing a conclusion for patients with mild hepatic impairment. PLUVICTO has not been studied in patients with moderate or severe hepatic impairment.

4.4 Administration

The recommended dose of PLUVICTO may be administered intravenously as an injection using a disposable syringe fitted with a syringe shield (with or without a syringe pump), as an infusion using the gravity method (with or without an infusion pump), or as an infusion using the vial (with a peristaltic infusion pump).

A reduced dose of PLUVICTO should be administered using the syringe method (with or without a syringe pump) or the vial method (with a peristaltic infusion pump). Using the gravity method to administer a reduced dose of PLUVICTO is not recommended since it may result in delivery of the incorrect volume of PLUVICTO if the dose is not adjusted prior to administration.

Prior to administration, flush the intravenous catheter used exclusively for PLUVICTO administration with ≥10 mL of 0.9% sterile sodium chloride solution to ensure patency and to minimize the risk of extravasation. Cases of extravasation should be managed as per institutional guidelines.

Instructions for the syringe method (with or without a syringe pump)

- After disinfecting the vial stopper, 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.
- 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 pre-filled with 0.9% sterile sodium chloride solution and that is used exclusively for PLUVICTO administration to the patient.
- Once the desired PLUVICTO radioactivity has been administered, perform an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the gravity method (with or without an infusion pump)

- Insert a 2.5 cm, 20 gauge needle (short needle) into the PLUVICTO vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (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 sodium chloride solution to flow into the PLUVICTO vial prior to the initiation of the PLUVICTO infusion and do not inject the PLUVICTO solution directly into the sodium chloride solution.
- 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 pre-filled with 0.9% sterile sodium chloride solution 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 sodium chloride solution via the short needle into the PLUVICTO vial (the sodium chloride solution 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 saline 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% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the vial method (with a peristaltic infusion pump)

- Insert a 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 infusion 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% sterile sodium chloride solution 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 infusion pump following the pump manufacturer's instructions.
- Pre-fill 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.
- Pre-fill the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the pre-filled intravenous catheter to the patient and set the 3-way stopcock valve such that the PLUVICTO solution is in line with the peristaltic infusion 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 infusion pump and then change the position of the 3-way stopcock valve so that the peristaltic infusion pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic infusion pump and infuse an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

4.7 Instructions for Preparation and Use

- Aseptic technique and radiation shielding should be used when handling or administering PLUVICTO, using tongs as needed to minimize radiation exposure.
- The vial should be visually inspected under a shielded screen for particulate matter and discoloration prior to administration. The vial should be discarded if particulates or discoloration are present.
- PLUVICTO is a ready-to-use solution for single use only. The PLUVICTO solution should not be injected directly into any other intravenous solution.
- The amount of radioactivity delivered to the patient should be confirmed with an appropriately calibrated dose calibrator prior to and after PLUVICTO administration.
- Any unused medicinal product or waste material should be disposed of in accordance with national regulations.

4.8 Radiation Dosimetry

Dosimetry of lutetium (^{177}Lu) vipivotide tetraxetan injection 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 adult patients receiving PLUVICTO are shown in Table 2. The organs with the highest radiation absorbed doses are lacrimal glands, salivary glands, colon (left and right), rectum, 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 for PLUVICTO in the VISION sub-study

	Absorbed dose per unit activity (Gy/GBq)[a] (N = 29)		Calculated absorbed dose for 7.4 GBq administration (Gy)[a]		Calculated absorbed dose for 6 x 7.4 GBq (44.4 GBq cumulative activity) (Gy)[a]	
Organ	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.033	0.025	0.24	0.19	1.5	1.1
Brain	0.007	0.005	0.049	0.035	0.30	0.22
Esophagus	0.025	0.026	0.18	0.19	1.1	1.1
Eyes	0.022	0.024	0.16	0.18	0.99	1.1

	Absorbed dose per unit activity (Gy/GBq)[a] (N = 29)		Calculated absorbed dose for 7.4 GBq administration (Gy)[a]		Calculated absorbed dose for 6 x 7.4 GBq (44.4 GBq cumulative activity) (Gy)[a]	
Gallbladder wall	0.028	0.026	0.20	0.19	1.2	1.1
Heart wall	0.17	0.12	1.2	0.83	7.8	5.2
Kidneys	0.43	0.16	3.1	1.2	19	7.3
Lacrimal glands	2.1	0.47	15	3.4	92	21
Left colon	0.58	0.14	4.1	1.0	26	6.0
Liver	0.090	0.044	0.64	0.32	4.0	2.0
Lungs	0.11	0.11	0.76	0.81	4.7	4.9
Osteogenic cells	0.036	0.028	0.26	0.21	1.6	1.3
Pancreas	0.027	0.026	0.19	0.19	1.2	1.1
Prostate	0.027	0.026	0.19	0.19	1.2	1.1
Red marrow	0.035	0.020	0.25	0.15	1.5	0.90
Rectum	0.56	0.14	4.0	1.1	25	6.2
Right colon	0.32	0.078	2.3	0.58	14	3.4
Salivary glands	0.63	0.36	4.5	2.6	28	16
Small intestine	0.071	0.031	0.50	0.23	3.1	1.4
Spleen	0.067	0.027	0.48	0.20	3.0	1.2
Stomach wall	0.025	0.026	0.18	0.19	1.1	1.1
Testes	0.023	0.025	0.16	0.18	1.0	1.1
Thymus	0.025	0.026	0.18	0.19	1.1	1.1
Thyroid	0.26	0.37	1.8	2.7	11	16
Total body	0.037	0.027	0.27	0.20	1.6	1.2
Urinary bladder wall	0.32	0.025	2.3	0.19	14	1.1

[a]Values have been calculated based on dosimetry estimates at full precision and rounded to relevant digits.

5 OVERDOSAGE

In the event of administration of a radiation overdose with PLUVICTO, the radiation absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. It is helpful to estimate the effective radiation dose that was applied and appropriate supportive care measures should be given as clinically indicated.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Sterile solution for injection/infusion 1000 MBq/mL at calibration	Acetic acid (0.30 mg/mL) Gentisic acid (0.39 mg/mL) Pentetic acid (0.10 mg/mL) Sodium acetate (0.41 mg/mL) Sodium ascorbate (50.0 mg/mL) Water for injections (q.s. to 1 mL)

One mL of solution contains 1000 MBq (27 mCi) of lutetium (^{177}Lu) vipivotide tetraxetan injection at the date and time of calibration.

The total amount of radioactivity per single-dose vial is 7.4 GBq (7400 MBq) (200 mCi) ± 10% at the date and time of administration. Given the fixed volumetric activity of 1000 MBq/mL (27 mCi/mL) at the date and time of calibration, the volume of the solution in the vial can range from 7.5 mL to 12.5 mL in order to provide a total of 7.4 GBq (7400 MBq) (200 mCi) of radioactivity at the date and time of administration.

The mass of vipivotide tetraxetan can range from 112.5 mcg to 187.5 mcg. The target concentration of vipivotide tetraxetan is 15 mcg/mL.

6.1 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 4.

Table 4 – Lutetium-177 Main Radiations

Radiation	Energy (keV)	Iβ$^-$%	Iγ%
β$^-$	176.5	12.2	
β$^-$	248.1	0.05	

Radiation	Energy (keV)	Iβ⁻%	Iγ%
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

6.2 External Radiation

Table 5 summarizes the radioactive decay properties of lutetium-177.

Table 5 – 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

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Contamination

The following measures should be taken for 2 days after receiving the radiopharmaceutical product: Toilet should be used instead of urinal. Toilet should be flushed several times after use.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

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.

Radiation exposure to patients, medical personnel, and household contacts should be minimized during and after treatment with PLUVICTO consistent with institutional good radiation safety practices, patient management procedures, and instructions to the patient for follow-up radiation protection at home.

Patients should be encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation.

Before the patient is released, the nuclear medicine physician or healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimize radiation exposure to others.

Following administration of PLUVICTO, patients should be advised to:

- limit close contact (less than 1 meter) with household contacts for 2 days or with children and pregnant women for 7 days.
- refrain from sexual activity for 7 days.
- sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

Hematologic

PLUVICTO can cause severe and life-threatening myelosuppression, including anemia, thrombocytopenia, leukopenia, and neutropenia. In the VISION study, myelosuppression occurred more frequently in patients who received PLUVICTO plus best standard of care (BSoC) compared to patients who received BSoC alone (see 8 ADVERSE REACTIONS, Adverse Reactions of Special Interest).

Hematology laboratory tests should be performed before and during treatment with PLUVICTO. PLUVICTO should be withheld, dose reduced, or permanently discontinued and patients should be clinically managed as deemed appropriate based on the severity of myelosuppression (see 4 DOSAGE AND ADMINISTRATION).

Renal

PLUVICTO can cause severe renal toxicity. In the VISION study, renal toxicity occurred more frequently in patients who received PLUVICTO plus BSoC compared to patients who received BSoC alone (see 8 ADVERSE REACTIONS, Adverse Reactions of Special Interest).

Patients should be advised to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Kidney function laboratory tests, including serum creatinine and calculated CrCl, should be performed before and during treatment with PLUVICTO. PLUVICTO should be withheld, dose reduced, or permanently discontinued based on the severity of renal toxicity (see 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

Contraception

Males

Based on its mechanism of action, 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 10 CLINICAL PHARMACOLOGY and 16 NON-CLINICAL TOXICOLOGY).

- **Fertility**

  No studies were conducted to determine the effects of lutetium (^{177}Lu) vipivotide tetraxetan injection on fertility. The recommended cumulative dose of 44.4 GBq (44400 MBq) of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

7.1 Special Populations

7.1.1 Pregnant Women

The safety and efficacy of PLUVICTO have not been established in females/pregnant women as PLUVICTO is not indicated for use in females. No animal studies using lutetium (^{177}Lu) vipivotide tetraxetan injection have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Based on its mechanism of action, PLUVICTO can cause fetal harm when administered to a pregnant woman (see 10 CLINICAL PHARMACOLOGY).

7.1.2 Breast-feeding

The safety and efficacy of PLUVICTO have not been established in females as PLUVICTO is not indicated for use in females. There are no data on the presence of lutetium (^{177}Lu) vipivotide tetraxetan injection in human milk or its effects on the breastfed child or on milk production.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of the 529 patients who received at least one dose of PLUVICTO plus best standard of care (BSoC) in the VISION study, 387 patients (73%) were 65 years or older and 143 patients (27%) were 75 years or older. No overall difference in efficacy was observed based on age. Grade ≥3 adverse events occurred in 53.5% of patients aged 65 years or older as compared to 50.7% in younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of PLUVICTO was evaluated in the VISION study in patients with progressive, PSMA-positive mCRPC who have been treated with at least one androgen receptor pathway inhibitor (ARPI) and taxane-based chemotherapy.

The most common adverse reactions (≥10%) occurring at a higher incidence in patients who received PLUVICTO plus BSoC compared to BSoC alone include: fatigue (43.1% vs 22.9%), dry mouth (39.3% vs 0.5%), nausea (35.3% vs 16.6%), anemia (31.8% vs 13.2%), decreased appetite (21.2% vs 14.6%), constipation (20.2% vs 11.2%), vomiting (19.1% vs 6.3%), diarrhea (18.9% vs 2.9%), thrombocytopenia (17.2% vs 4.4%), leukopenia (15.7% vs 2.0%), lymphopenia (14.2% vs 3.9%), urinary tract infection (11.5% vs 1.0%), and weight decreased (10.8% vs 8.8%). The most common Grade 3 to 4 adverse reactions (≥5%) occurring at a higher incidence in patients who received PLUVICTO plus BSoC compared to BSoC alone include: anemia (12.9% vs 4.9%), thrombocytopenia (7.9% vs 1.0%), lymphopenia (7.8% vs 0.5%), and fatigue (5.9% vs 1.5%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of PLUVICTO was evaluated in the VISION study. Of the 831 patients randomized, 734 patients received at least one dose of randomized treatment. Patients received at least one dose of either PLUVICTO 7.4 GBq (7400 MBq) (200 mCi) administered every 6 to 10 weeks plus BSoC (N = 529) or BSoC alone (N = 205). Among patients who received PLUVICTO plus BSoC, the median number of doses of PLUVICTO received was 5 (range: 1 to 6), with 67.7% of patients who received at least 4 doses of PLUVICTO and 46.5% of patients who received a total of 6 doses of PLUVICTO. The median cumulative dose of PLUVICTO was 37.5 GBq (range: 7.0 to 48.3 GBq). The median duration of exposure to randomized treatment was 7.8 months (range: 0.3 to 24.9 months) for patients who received PLUVICTO plus BSoC and 2.1 months (range: 0.0 to 26.0 months) for patients who received BSoC alone. The median duration of follow-up was 14.8 months for patients who received PLUVICTO plus BSoC and 10.6 months for patients who received BSoC alone.

Serious adverse events occurred in 36.3% of patients who received PLUVICTO plus BSoC. Serious adverse events in >1% of patients who received PLUVICTO plus BSoC included: anemia (2.8%), urinary tract infection (2.5%), hematuria (2.1%), sepsis (1.9%), acute kidney injury (1.7%), back pain (1.7%), pneumonia (1.3%), pyrexia (1.3%), bone pain (1.1%), pancytopenia (1.1%), pulmonary embolism (1.1%), and spinal cord compression (1.1%).

Fatal serious adverse events occurred in 3.6% of patients who received PLUVICTO plus BSoC included: sepsis (0.8%), pancytopenia (0.4%), acute hepatic failure, bone marrow failure, COVID-19, disease progression, escherichia sepsis, euthanasia, intracranial hemorrhage, hepatic failure, ischemic stroke, metastases to central nervous system, multiple organ dysfunction syndrome, aspiration pneumonia, and subdural hematoma (0.2% each).

PLUVICTO was permanently discontinued due to adverse events in 11.9% of patients. Adverse events leading to permanent discontinuation of PLUVICTO in ≥0.5% of patients who received PLUVICTO plus BSoC included: anemia (2.8%), thrombocytopenia (2.8%), leukopenia (1.3%), neutropenia (0.8%), and pancytopenia (0.6%).

Adverse events leading to a dose interruption/reduction of PLUVICTO occurred in 16.1%/5.7% of patients. Adverse events leading to dose interruption/dose reduction of PLUVICTO in ≥0.5% of patients who received PLUVICTO plus BSoC included: anemia (5.1%/1.3%), thrombocytopenia (3.6%/1.9%), leukopenia (1.5%/0.6%), and neutropenia (0.8%/0.6%), aspartate aminotransferase increased (0.6%/0%), hematuria (0.6%/0%), and dry mouth (0%/0.6%).

Table 6 summarizes the incidence of adverse reactions.

Table 6 – Adverse reactions (≥ 1%) occurring at a higher incidence in patients who received PLUVICTO plus BSoC compared to BSoC alone in VISION[a]

	PLUVICTO plus BSoC (N = 529)		BSoC (N = 205)	
Adverse reactions	**All grades n (%)**	**Grades 3 to 4[b] n (%)**	**All grades n (%)**	**Grades 3 to 4[b] n (%)**
Blood and lymphatic system disorders				
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Leukopenia[c]	83 (15.7)	22 (4.2)	4 (2.0)	1 (0.5)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Pancytopenia[d]	9 (1.7)	7 (1.3)[b]	0	0
Nervous system disorders				
Dizziness	44 (8.3)	5 (0.9)	9 (4.4)	0
Headache	37 (7.0)	4 (0.8)	4 (2.0)	0
Dysgeusia[e]	37 (7.0)	0	3 (1.5)	0
Eye disorders				
Dry eye	16 (3.0)	0	2 (1.0)	0
Ear and labyrinth disorders				
Vertigo	11 (2.1)	0	0	0
Gastrointestinal disorders				
Dry mouth[f]	208 (39.3)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)

	PLUVICTO plus BSoC (N = 529)		BSoC (N = 205)	
Adverse reactions	**All grades n (%)**	**Grades 3 to 4[b] n (%)**	**All grades n (%)**	**Grades 3 to 4[b] n (%)**
Vomiting[g]	101 (19.1)	5 (0.9)	13 (6.3)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Abdominal pain[h]	59 (11.2)	6 (1.1)	13 (6.3)	1 (0.5)
Renal and urinary disorders				
Urinary tract infection[i]	61 (11.5)	20 (3.8)	2 (1.0)	1 (0.5)
Acute kidney injury[j]	45 (8.5)	17 (3.2)	12 (5.9)	6 (2.9)
General disorders and administration site conditions				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Weight decreased	57 (10.8)	2 (0.4)	18 (8.8)	0
Peripheral edema[k]	52 (9.8)	2 (0.4)	14 (6.8)	1 (0.5)
Pyrexia	36 (6.8)	2 (0.4)	7 (3.4)	0

Abbreviation: BSoC, best standard of care.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

[b]Only includes Grades 3 to 4 adverse reactions, with the exception of pancytopenia. Grade 5 (fatal) pancytopenia was reported in 2 patients who received PLUVICTO plus BSoC.

[c]Leukopenia includes leukopenia and neutropenia.

[d]Pancytopenia includes pancytopenia and bicytopenia.

[e]Dysgeusia includes dysgeusia and taste disorder.

[f]Dry mouth includes dry mouth, aptyalism, and dry throat.

[g]Vomiting includes vomiting and retching.

[h]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

[i]Urinary tract infection includes urinary tract infection, cystitis, and cystitis bacterial.

[j]Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.

[k]Peripheral edema includes peripheral edema, fluid retention, and fluid overload.

Adverse Reactions of Special Interest

Myelosuppression

In the VISION study, myelosuppression occurred more frequently in patients who received PLUVICTO plus BSoC compared to patients who received BSoC alone (Grade ≥3): decreased hemoglobin (15% vs 7%), anemia (12.9% vs 4.9%) ; decreased platelets (9% vs 2.5%), thrombocytopenia (7.9% vs 1.0%); decreased leukocytes (7% vs 2%), leukopenia (2.5% vs 0.5%); decreased lymphocytes (47% vs 18%), lymphopenia (7.8% vs 0.5%); decreased neutrophils (4.5% vs 0.5%), neutropenia (3.4% vs 0.5%); pancytopenia (1.1% vs 0%) including two fatal events of pancytopenia in patients who received PLUVICTO plus BSoC; and bicytopenia (0.2% vs 0%). Two deaths (0.4%) due to intracranial hemorrhage

and subdural hematoma in association with thrombocytopenia were observed in patients who received PLUVICTO. One death due to sepsis and concurrent neutropenia was observed in patients who received PLUVICTO.

Myelosuppression adverse reactions that led to permanent discontinuation in ≥0.5% of patients who received PLUVICTO plus BSoC included: anemia (2.8%), thrombocytopenia (2.8%), leukopenia (1.3%), neutropenia (0.8%), and pancytopenia (0.6%). Myelosuppression adverse reactions that led to dose interruptions/dose reductions in ≥0.5% of patients who received PLUVICTO plus BSoC included: anemia (5.1%/1.3%), thrombocytopenia (3.6%/1.9%), leukopenia (1.5%/0.6%), and neutropenia (0.8%/0.6%).

Renal toxicity

In the VISION study, renal toxicity occurred more frequently in patients who received PLUVICTO plus BSoC compared to patients who received BSoC alone (all Grades/Grades 3 to 4): blood creatinine increased (5.3%/0.2%) versus (2.4%/0.5%); acute kidney injury (3.6%/3.0%) versus (3.9%/2.4%); renal failure (0.2%/0%) versus (0%/0%); and blood urea increased (0.2%/0%) versus (0%/0%).

Renal adverse reactions that led to permanent discontinuation in ≥0.2% of patients who received PLUVICTO plus BSoC included: blood creatinine increased (0.2%). Renal adverse reactions that led to dose interruptions/dose reductions in ≥0.2% of patients who received PLUVICTO plus BSoC included: blood creatinine increased (0.2%/0.4%) and acute kidney injury (0.2%/0%).

8.3 Less Common Clinical Trial Adverse Reactions

Uncommon treatment-emergent adverse events (<1%), irrespective of causality, occurring in patients who received PLUVICTO plus BSoC in VISION included:

Blood and lymphatic system disorders: bone marrow failure, febrile neutropenia, normocytic anemia

Cardiac disorders: ventricular tachycardia

Congenital, familial and genetic disorders: vascular malformation

Eye disorders: conjunctival oedema, eye swelling, periorbital oedema, swelling of eyelid

Gastrointestinal disorders: lip dry, swollen tongue

General disorders and administrative site disorders: decreased activity, generalised oedema, localised oedema, swelling face

Hepatobiliary disorders: acute hepatic failure, cholestasis, hepatic failure, hepatic lesion, hepatitis, hepatocellular injury, jaundice

Infections and infestations: conjunctivitis

Injury, poisoning and procedural complications: cystitis radiation, infusion related reaction, overdose, subdural haematoma

Investigations: gamma-glutamyltransferase increased, international normalised ratio increased, urine output decreased

Metabolism and nutrition disorders: cachexia

Neoplasms benign, malignant and unspecified (including cysts and polyps): basal cell carcinoma, malignant melanoma, metastases to central nervous system, metastases to meninges, squamous cell carcinoma, squamous cell carcinoma of skin

Nervous system: cerebral haemorrhage, haemorrhage intracranial, hepatic encephalopathy, lethargy, loss of consciousness

Renal and urinary disorders: proteinuria

Reproductive system and breast disorders: scrotal oedema

Respiratory, thoracic and mediastinal disorders: acute respiratory failure, pneumonitis, respiratory distress, sneezing

Skin and subcutaneous tissue disorders: blister, dermatitis, dermatitis acneiform, dermatitis bullous, eczema, erythema, pruritis, rash erythematous, rash maculo-papular

Vascular disorders: flushing

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 7 – Select laboratory abnormalities (≥ 10%) that worsened from baseline in patients with PSMA-positive mCRPC who received PLUVICTO plus BSoC compared to BSoC alone (between arm difference of ≥5% Grades 1 to 4) in VISION[a]

Laboratory abnormalities	PLUVICTO plus BSoC[b]			BSoC[c]		
	Number of patients (N)	Grades 1 to 4 n (%)	Grades 3 to 4 n (%)	Number of patients (N)	Grades 1 to 4 n (%)	Grades 3 to 4 n (%)
Chemistry						
Decreased calcium	525	204 (39)	13 (2.5)	198	55 (28)	6 (3)
Decreased sodium	529	177 (33)	3 (0.6)[d]	198	45 (23)	2 (1)
Increased aspartate aminotransferase	526	148 (28)	6 (1.1)	197	35 (18)	2 (1)[d]
Increased creatinine	529	125 (24)	5 (0.9)[d]	198	28 (14)	1 (0.5)[d]
Increased potassium	529	128 (24)	3 (0.6)	197	35 (18)	1 (0.5)[d]
Increased sodium	529	58 (11)	0[d]	198	10 (5)	0[d]
Hematology						
Decreased lymphocytes	506	428 (85)	237 (47)	194	98 (51)	34 (18)
Decreased hemoglobin	529	335 (63)	79 (15)[d]	198	68 (34)	13 (7)[d]
Decreased leukocytes	529	294 (56)	36 (7)	198	44 (22)	4 (2)
Decreased platelets	529	236 (45)	49 (9)	198	40 (20)	5 (2.5)
Decreased neutrophils	508	140 (28)	23 (4.5)	196	17 (9)	1 (0.5)

Abbreviation: BSoC, best standard of care.

Laboratory abnormalities	PLUVICTO plus BSoC[b]			BSoC[c]		
	Number of patients (N)	Grades 1 to 4 n (%)	Grades 3 to 4 n (%)	Number of patients (N)	Grades 1 to 4 n (%)	Grades 3 to 4 n (%)

[a]*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.*

[b]*The 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.*

[c]*The 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.*

[d]*No Grade 4 laboratory abnormalities worsening from baseline were reported.*

8.5 Post-Market Adverse Reactions

No post-marketing adverse reactions have been identified to date.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

***In vitro* evaluation of drug interaction potential**

CYP450 enzymes: Vipivotide tetraxetan is not a substrate of cytochrome P450 (CYP450) enzymes. It does not induce cytochrome P450 (CYP) 1A2, 2B6 or 3A4, and it does not inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 *in vitro*.

Transporters: Vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2, and it is not an inhibitor of BCRP, P-gp, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 *in vitro*.

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with lutetium (^{177}Lu) vipivotide tetraxetan injection.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

PLUVICTO (lutetium (^{177}Lu) vipivotide tetraxetan injection) is a prostate-specific membrane antigen (PSMA) targeted radioligand therapy composed of 2 components: 1) vipivotide tetraxetan that is the targeting component recognizing PSMA, and 2) the anti-tumour radionuclide lutetium-177.

The active moiety of PLUVICTO is the radionuclide lutetium-177 which is linked to a targeting moiety that binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of PLUVICTO to PSMA-expressing cancer cells and its internalization, the beta-minus emission from lutetium-177 delivers therapeutic radiation to the targeted cell, as well as to surrounding cells, and induces DNA damage which can lead to cell death.

10.2 Pharmacodynamics

There are no data regarding lutetium (^{177}Lu) vipivotide tetraxetan injection exposure-efficacy relationships and there are limited data redarding exposure-safety relationships and the time course of pharmacodynamic response.

Cardiac electrophysiology

In VISION, an open-label, single-arm uncontrolled sub-study of PLUVICTO adminstered to patients with mCRPC (n=30), no large mean increase from baseline in observed QTc interval (i.e., 10 ms) was detected following single dose administration of PLUVICTO at the recommended therapeutic dose (7.4 GBq) when assessed 24 hours postdose.

10.3 Pharmacokinetics

The pharmacokinetics of lutetium (^{177}Lu) vipivotide tetraxetan injection have been characterized in 30 patients in the Phase III VISION sub-study.

Table 8 – Summary of PLUVICTO Pharmacokinetic Parameters in mCRPC patients

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_{inf} (ng·h/mL)	CL (L/h)	V_d (L)
Single dose geometric mean	6.58	0.266	41.6	52.3	2.04	123

C_{max}: maximum concentration
T_{max}: time of maximum concentration
$t_{½}$: terminal elimination half-life
AUC_{inf}: area under the blood concentration versus time curve from the time of dosing to infinity
CL: total clearance
V_d: volume of distribution based on the terminal elimination phase

Absorption

PLUVICTO is administered intravenously and is immediately and completely bioavailable.

Distribution

Vipivotide tetraxetan and non-radioactive lutetium (^{175}Lu) vipivotide tetraxetan are each 60% to 70% bound to human plasma proteins.

The biodistribution of lutetium (^{177}Lu) vipivotide tetraxetan injection shows primary uptake in lacrimal glands, salivary glands, kidneys, urinary bladder wall, liver, small intestine, and large intestine (left and right colon).

Elimination

Lutetium (^{177}Lu) vipivotide tetraxetan injection is primarily eliminated renally.

Metabolism

Lutetium (^{177}Lu) vipivotide tetraxetan injection does not undergo hepatic or renal metabolism. Results from *in vitro* metabolism studies showed that both vipivotide tetraxetan and non-radioactive lutetium (^{175}Lu) vipivotide tetraxetan were metabolically stable in human liver and kidney S9 fractions for up to 1 hour at 37°C, and in human plasma at 37°C for up to 2 hours.

Special Populations and Conditions

- **Geriatrics:** Of the 529 patients who received at least one dose of PLUVICTO plus best standard of care (BSoC) in the VISION study, 387 patients (73%) were 65 years or older and 143 patients (27%) were 75 years or older.

- **Age/Body weight:** No clinically significant effects on the pharmacokinetic parameters of lutetium (^{177}Lu) vipivotide tetraxetan injection were identified for the following covariates assessed in 30 patients in the Phase III VISION sub-study: age (median: 67 years; range: 52 to 80 years) and body weight (median: 88.8 kg; range: 63.8 to 143.0 kg).

- **Renal impairment:** Based on population pharmacokinetic analysis, exposure of lutetium (^{177}Lu) vipivotide tetraxetan injection is expected to increase with the degree of renal impairment. No dose adjustment is recommended for patients with mild (baseline CrCl 60 to 89 mL/min by Cockcroft-Gault) renal impairment, and insufficient data are available for drawing a conclusion on patients with moderate (CrCl 30 to 59 mL/min) renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Renal function and adverse reactions should be monitored frequently in patients with mild to moderate renal impairment. The pharmacokinetic profile and safety of PLUVICTO have not been studied in patients with severe (CrCl 15 to 29 mL/min) renal impairment or end-stage renal disease.

- **Hepatic impairment:** There is insufficient data available for drawing a conclusion for patients with mild hepatic impairment. PLUVICTO has not been studied in patients with moderate or severe hepatic impairment.

11 STORAGE, STABILITY AND DISPOSAL

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

Special precautions for storage

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

Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

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

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with national regulations.

Lutetium-177 for PLUVICTO may be prepared using two different sources of stable isotopes (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.

12 SPECIAL HANDLING INSTRUCTIONS

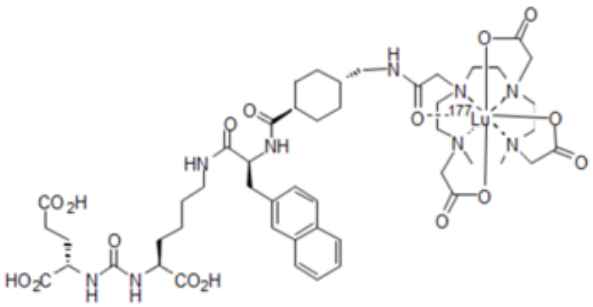
Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in 4 DOSAGE AND ADMINISTRATION.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	lutetium (^{177}Lu) vipivotide tetraxetan injection
Chemical name:	2-[4-[2-[[4-[[(2S)-1-[[(5S)-5-carboxy-5-[[(1S)-1,3-dicarboxy propyl]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+)
Molecular formula and molecular mass:	$C_{49}H_{68}{}^{177}LuN_9O_{16}$, 1216.06 g/mol
Structural formula:	
Physicochemical properties:	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%)

Product Characteristics:

PLUVICTO Injection containing 1000 MBq/mL (27 mCi/mL) of lutetium (^{177}Lu) vipivotide tetraxetan is a sterile, clear, colorless to slightly yellow, and buffered solution with a pH 4.5 to 7.0 supplied in a clear, colorless type I glass vial, closed with a bromobutyl rubber stopper and aluminum seal. Each vial contains a volume of solution that can range from 7.5 mL to 12.5 mL corresponding to a radioactivity of 7.4 GBq (7400 MBq) (200 mCi) ± 10% at the date and time of administration.

The product vial is in a lead shielded container placed in a plastic sealed container. The product is shipped in a type A package.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 9 – Summary of patient demographics for clinical trials in PSMA-positive mCRPC

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
VISION (PSMA-617-01)	Phase III, open-label randomized, open-label, multicenter study	lutetium (^{177}Lu) vipivotide tetraxetan 7.4 GBq q6w for up to a total of 6 doses IV + Best standard of care (BSoC) or BSoC alone	Total: 831 PLUVICTO: 551 BSoC: 280	71 years (40 -94 years)	100% Male

The efficacy of PLUVICTO in patients with progressive, PSMA-positive mCRPC was established in VISION, a randomized (2:1), multicenter, open-label Phase III study that evaluated PLUVICTO 7.4 GBq every 6 weeks for up to a total of 6 doses plus BSoC or BSoC alone. 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 AR pathway inhibitor as part of BSoC (yes vs no) at the time of randomization.

Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumour lesion with ^{68}Ga-PSMA-11 uptake greater than normal liver. Patients were excluded if any lesions exceeding size criteria in short axis [organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm] had uptake less than or equal to uptake in normal liver. Eligible patients were required to have received at least one AR pathway inhibitor, such as abiraterone acetate or enzalutamide, and 1 or 2 prior taxane-based chemotherapy regimens. All patients had received a gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. Patients with unstable symptomatic central nervous system metastases or symptomatic or clinically/radiologically impending spinal cord compression were not eligible for the study.

BSoC administered at the physician's discretion included: supportive measures; ketoconazole; radiation therapy (including seeded form or any external beam radiotherapy) to localized prostate cancer targets; bone-targeted agents including zoledronic acid, denosumab, and any bisphosphonates; androgen-reducing agents including any corticosteroid and 5-alpha reductases; AR pathway inhibitors. Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment were not permitted during the study.

Patients continued treatment for up to 4-6 doses or until evidence of tumour progression, unacceptable toxicity, use of prohibited treatment, non-compliance or withdrawal, or lack of clinical benefit.

The major efficacy outcome measures were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per Prostate Cancer Working Group 3 (PCWG3) criteria.

Demographic and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range: 40 to 94 years); 86.8% White; 6.6% Black or African American; 2.4% Asian; 92.4% had ECOG PS0-1; 7.6% had ECOG PS2. At randomization, all patients had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two. At randomization, 51.3% of patients had received one prior AR pathway inhibitor, 41.0% of patients had received 2, and 7.7% of patients had received 3 or more. During the randomized treatment period, 52.6% of patients in the PLUVICTO plus BSoC arm and 67.8% of patients in the BSoC alone arm received at least one AR pathway inhibitor.

14.2 Study Results

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. There was an estimated 38% reduction in the risk of death based on the hazard ratio in favour of PLUVICTO plus BSoC treatment (HR=0.62; 95% CI: 0.52, 0.74). 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. OS results for VISION are presented in Table 10 and Figure 1.

Table 10 – OS results in VISION

Efficacy parameters	PLUVICTO plus BSoC	BSoC
Primary efficacy endpoint		
Overall survival (OS)[a]	N = 551	N = 280
Deaths, n (%)	343 (62.3%)	187 (66.8%)
Median, months (95% CI)[b]	15.3 (14.2, 16.9)	11.3 (9.8, 13.5)
Hazard ratio (95% CI)[c]	0.62 (0.52, 0.74)	
P-value[d]	<0.001	

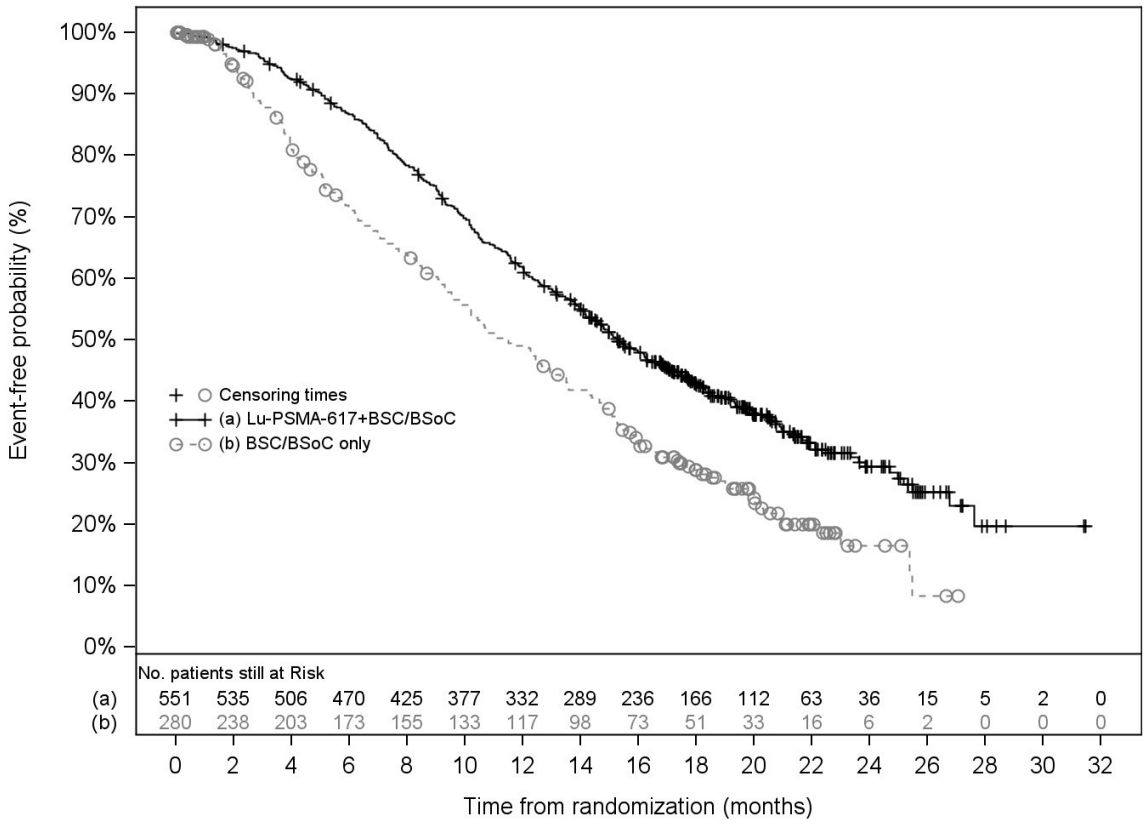
[a] *Analyzed on an intent-to-treat (ITT) basis in all randomized patients.*

[b] *Based on Kaplan-Meier estimate.*

[c] *Hazard ratio based on the stratified Cox PH model.*

[d] *Stratified log-rank test one-sided p-value.*

Figure 1 – Kaplan-Meier plot of overall survival in VISION



15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

No toxicological effects were observed in safety pharmacology studies in rats and minipigs administered a formulation containing a 1:1 mixture of vipivotide tetraxetan and non-radioactive lutetium (^{175}Lu) vipivotide tetraxetan. Single-dose toxicity studies were also conducted using this same non-radioactive formulation at doses of 2 and 4 mg/kg in rats and 0.2, 0.6 and 1.8 mg/kg in minipigs. There were no signs of systemic toxicologic effects and there were no target organs identified in any study. In minipigs, all doses resulted in acute inflammation at the injection site with associated vascular and perivascular necrosis and hemorrhage on Day 2. Following the 14 days observation period, these reactions were still present at the injection site, but with a recovery trend that was more evident in females than males. Safety margins for total vipivotide tetraxetan, relative to a 275 microgram theoretical maximum human dose, were approximately 150-fold and 400-fold in rats and minipigs respectively (based on BSA scaling). No toxicity was noted in the repeat-dose toxicity study in rats where a vipivotide tetraxetan formulation was administered intravenously at 0.04, 0.16 and 0.4 mg/kg on day 1, 8, 15 and 22 for a total of 4 doses. The safety margin relative to the human dose in this

repeat-dose study was 15-fold (based on BSA scaling).

Carcinogenicity

Long-term carcinogenicity studies have not been carried out with lutetium (^{177}Lu) vipivotide tetraxetan injection; however, radiation is a carcinogen, see 7 WARNINGS AND PRECAUTIONS.

Genotoxicity

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

Mutagenicity studies have not been carried out with lutetium (^{177}Lu) vipivotide tetraxetan injection; however, radiation is a mutagen.

Reproductive and Developmental Toxicology

For information on reproductive toxicity, see 7 WARNINGS AND PRECAUTIONS.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PLUVICTO™

lutetium (^{177}Lu) vipivotide tetraxetan injection

Read this carefully before you start taking **PLUVICTO™** and each time you receive a dose. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PLUVICTO**.

Serious Warnings and Precautions

- PLUVICTO should be used by health professionals who are appropriately trained in use of radiopharmaceuticals.
- Bone marrow suppression that may be severe, life-threatening or that may lead to death. Tell your healthcare provider right away if you get any of the following signs and symptoms at anytime during treatment:
  - Tiredness, weakness, and pale skin
  - Shortness of breath
  - Bleeding or bruising more easily than normal or difficulty to stop bleeding
  - Frequent infections with signs such as fever, chills, sore throat or mouth ulcers
- Kidney impairment can occur in patients treated with PLUVICTO. Tell your physician about any kidney condition prior to receiving PLUVICTO.

What is PLUVICTO used for?

This medicine is a radiopharmaceutical product used:

- To treat adults with a certain type of advanced prostate cancer (called prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer [PSMA-positive mCRPC]) that is metastatic (this means it has spread to other parts of the body) and that has already been treated with other anti-cancer treatments.

How does PLUVICTO work?

PLUVICTO binds to a protein called PSMA that is found on the surface of prostate cancer cells. Once bound, the radiation emitted from the lutetium-177 causes the prostate cancer cells to die.

Tests will be performed to see if PSMA is present on the surface of the cancer cells. Your cancer is likely to respond to treatment with PLUVICTO if the test result is positive.

The use of PLUVICTO involves exposure to amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

If you have any questions about how PLUVICTO works or why this medicine has been prescribed for you, ask your nuclear medicine doctor.

What are the ingredients in PLUVICTO?

Medicinal ingredient: lutetium (^{177}Lu) vipivotide tetraxetan.

Non-medicinal ingredients: acetic acid, gentisic acid, pentetic acid, sodium acetate, sodium ascorbate, water for injections (see Other warnings you should know about "PLUVICTO contains sodium").

PLUVICTO comes in the following dosage forms:

Solution for intravenous injection/infusion, 1000 MBq/mL (megabecquerel, the unit used to express radioactivity)

Do not use PLUVICTO if:

- You are allergic to lutetium (^{177}Lu) vipivotide tetraxetan or to any of the other ingredients in this medicine

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PLUVICTO. Talk about any health conditions or problems you may have, including if you:

- Have low level of blood cell counts (hemoglobin, white blood cell count, absolute neutrophil count, platelet count);
- Have or have had 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 (possible signs of myelosuppression);
- Have or have had kidney problems such as passing urine less often than usual or passing much smaller amounts of urine than usual;
- Have or have had any other type of cancer or treatment for cancer, as PLUVICTO contributes to your overall long-term cumulative radiation exposure;
- Are under 18 years of age;
- Are sexually active as all radiopharmaceuticals, including PLUVICTO, have the potential to cause harm to an unborn baby. PLUVICTO may cause temporary or permanent infertility.

Other warnings you should know about:

PLUVICTO contains sodium. This medicine contains up to 88.75 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 4.4% of the recommended maximum daily dietary intake of sodium for an adult.

Before administration of PLUVICTO:

You should drink plenty of water in order to remain hydrated and to urinate as often as possible during the first hours after administration to remove the radiopharmaceutical product from your body.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PLUVICTO:

- There is no information available about the use of PLUVICTO in combination with other medicines.

How to take PLUVICTO:

- PLUVICTO will be administered intravenously (into your vein) under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.
- There are strict laws on the use, handling and disposal of radiopharmaceutical products. PLUVICTO will only be used in special controlled areas. This radiopharmaceutical product will only be handled and given to you by people who are trained and qualified to use it safely.

These persons will take special care for the safe use of this radiopharmaceutical product and will keep you informed of their actions.

Usual dose:

The recommended dose is 7.4 GBq (gigabecquerel, the unit used to express radioactivity).

PLUVICTO is given directly into your vein every 6 weeks for up to a total of 6 doses.

Duration of the procedure

Your nuclear medicine doctor will inform you about the usual duration of the procedure.

If you have questions about how long you will receive PLUVICTO, talk to your nuclear medicine doctor.

Treatment monitoring

Your nuclear medicine doctor will do blood tests before and during treatment to check your condition and to detect any side effects as early as possible. Based on the results, your nuclear medicine doctor may decide to delay, modify or stop your treatment with PLUVICTO if necessary.

After administration of PLUVICTO

For 2 days after the administration of PLUVICTO, drink plenty of water in order to remain hydrated and to urinate as often as possible to eliminate the radiopharmaceutical product from your body.

Because this medicine is radioactive, you will have to follow the instructions described below to minimize radiation exposure to others unless otherwise instructed by your nuclear medicine doctor.

Contact with others in your household, children, and/or pregnant women

- limit close contact (less than 1 meter) with:
    - others in your household for 2 days
    - children and pregnant women for 7 days;
- sleep in a separate bedroom from:
    - others in your household for 3 days
    - children for 7 days
    - pregnant women for 15 days;
- avoid sexual activity for 7 days;
- use effective birth control throughout treatment with PLUVICTO and for 14 weeks after your last dose.

Use of toilets

Take special precautions to avoid contamination during the 2 days after treatment.

- You must always sit when using the toilet.
- It is essential that you use toilet paper every time you use the toilet.
- Always wash your hands well after using the toilet.
- Flush all wipes and/or toilet paper down the toilet immediately after use.
- Flush any tissues or any other items that contain bodily waste, such as blood, urine and feces down the toilet. Items that cannot be flushed down the toilet, such as bandages, must be placed in separate plastic waste disposal bags (according to “Waste disposal recommendations” below).

Showering and laundry

Take a shower every day for at least the first 7 days after treatment. Wash your underwear, pajamas, sheets and any clothes that contain sweat, blood or urine separately from the laundry of others in your household, using a standard washing cycle. You do not need to use bleach and do not need extra rinses.

People with reduced mobility

People who are confined to bed or have reduced mobility will preferably receive assistance from a care provider. It is recommended that when providing assistance in the bathroom, the care provider wears disposable gloves for 2-3 days after administration. Any special medical equipment that could be contaminated by your bodily fluids (e.g. catheters, colostomy bags, bedpans, water nozzles) must be emptied immediately into the toilet and then cleaned. Carers who clean up vomit, blood, urine or feces should wear plastic gloves, which should be disposed of in a separate plastic waste disposal bag (see "Waste disposal recommendations" below).

Waste disposal recommendations

All items to be thrown away should be discarded in a separate plastic waste disposal bag to be used only for this purpose. Keep the plastic waste disposal bags separate from the other household waste and away from children and animals. A member of the hospital staff will tell you how and when to get rid of these waste disposal bags.

Hospitalization and emergency care

If for any reason you require emergency medical assistance or are unexpectedly admitted to the hospital during the first week after your treatment, you should inform the healthcare professionals about the nature, date and dose of your radioactive treatment.

Other precautions

The nuclear medicine doctor will inform you if you need to take any other special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

Overdose:

An overdose is unlikely. However, in the event of an overdose, you will receive the appropriate treatment.

Should you have any further questions on the use of PLUVICTO, please ask the nuclear medicine doctor who supervises the procedure.

Missed Dose:

If you miss an appointment for an administration, contact your nuclear medicine doctor as soon as possible to reschedule.

What are possible side effects from using PLUVICTO?

These are not all the possible side effects you may have when taking PLUVICTO. If you experience any side effects not listed here, tell your healthcare professional.

Very common: *may affect more than 1 in 10 people*

- Tiredness (*fatigue*)
- Dry mouth
- Nausea

- Loss of appetite
- Changes in bowel movements (*constipation* or *diarrhea*)
- Vomiting
- Urinary tract infection
- Abdominal pain
- Weight loss

Common: *may affect up to 1 in every 10 people*

- Swollen hands, ankles or feet (*peripheral edema*)
- Dizziness
- Headache
- Disturbed sense of taste (*dysgeusia*)
- Fever (*pyrexia*)
- Dry eye
- Vertigo

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	
	Only if severe	**In all cases**
VERY COMMON		
Tiredness, weakness, pale skin or shortness of breath (possible signs of low level of red blood cells) *(anemia)*		X
Bleeding or bruising more easily than normal or difficulty to stop bleeding and frequent infections with signs such as fever, chills, sore throat or mouth ulcers (possible signs of low level of white blood cells) *(thrombocytopenia, leukopenia, lymphopenia)*		X
COMMON		
Passing urine less often than usual or passing much smaller amounts of urine than usual (possible sign of kidney problems) *(acute kidney injury)*		X
Tiredness, weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or difficulty to stop bleeding and frequent infections with signs such as fever, chills, sore throat or mouth ulcers (possible signs of low level of blood cells) *(pancytopenia, bone marrow failure, febrile neutropenia)*		X
UNCOMMON		
Fast or irregular heart beat *(ventricular tachycardia)*		X
Bleeding in and/or around the brain that may cause headache, drowsiness, loss of consciousness, confusion, disturbances of speech, movement or sensation *(intracranial hemorrhage, cerebral hemorrhage, subdural hematoma)*		X
General swelling *(generalized edema)*	X	

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	
	Only if severe	**In all cases**
Liver problems that may cause tiredness, yellowing of the skin and/or eyes known as jaundice, stomach pain (*acute hepatic failure, hepatic failure, hepatocellular injury, cholestasis*)		X
Difficulty breathing, low oxygen levels (*acute respiratory failure)*		X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in the appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulations on radioactive materials.

If you want more information about PLUVICTO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.novartis.ca) or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last Revised

PLUVICTO is a trademark.