▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – PLUVICTO® (LUTETIUM (^{177}LU) VIPIVOTIDE TETRAXETAN) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Lutetium (^{177}Lu) vipivotide tetraxetan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 1,000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.

The total amount of radioactivity per single-dose vial is 7,400 MBq ± 10% at the date and time of administration. Given the fixed volumetric activity of 1,000 MBq/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 the required amount of radioactivity at the date and time of administration.

Excipients of known effect

Each mL of solution contains up to 0.312 mmol (7.1 mg) of sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

PLUVICTO is a clear, colourless to slightly yellow solution with a pH range of 4.5 to 7.0.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PLUVICTO is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Important safety instructions

PLUVICTO is a radiopharmaceutical and should be handled with appropriate safety measures to minimise radiation exposure (see section 4.4 Special warnings and precautions for use). 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 authorised to license the use of radiopharmaceuticals.

Patient identification

Patients should be identified for treatment by PSMA imaging.

Dosage regimen

The recommended PLUVICTO dose is 7,400 MBq intravenously every 6 weeks (± 1 week) for up to a total of 6 doses or until disease progression, or unacceptable toxicity.

Medical castration with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in patients not surgically castrated).

Treatment monitoring

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

- Haematology (haemoglobin, white blood cell count, absolute neutrophil count, platelet count)
- Kidney function (serum creatinine, calculated creatinine clearance [CLcr])
- 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 (to a dose of 5,900 MBq); 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 5,900 MBq).
	Recurrent Grade 3 dry mouth after one dose reduction	Permanently discontinue PLUVICTO.
Gastrointestinal toxicity	Grade ≥3 (not amenable to medical intervention)	Withhold PLUVICTO until improvement to Grade 2 or baseline. Reduce PLUVICTO dose by 20% (to 5,900 MBq).
	Recurrent Grade ≥ 3 gastrointestinal toxicity after one dose reduction	Permanently discontinue PLUVICTO.
Myelosuppression, (anaemia, thrombocytopaenia, leukopaenia, neutropaenia, pancytopaenia)	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 haematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated.
	Grade ≥3	Withhold PLUVICTO until improvement to Grade 1 or baseline. Reduce PLUVICTO dose by 20% (to 5,900 MBq).
	Recurrent Grade ≥3 myelosuppression after one dose reduction	Permanently discontinue PLUVICTO.
Renal toxicity	Defined as: • Confirmed serum creatinine increase (Grade ≥2) • Confirmed CLcr <50 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 CLcr; calculate using Cockcroft-Gault with actual body weight	Withhold PLUVICTO until improvement or return to baseline. Reduce PLUVICTO dose by 20% (to 5,900 MBq).
	Grade ≥3 renal toxicity	Permanently discontinue PLUVICTO.
	Recurrent renal toxicity after one dose reduction	Permanently discontinue PLUVICTO.
Spinal cord compression	Any	Withhold PLUVICTO until the compression has been adequately treated and any neurological sequela have stabilised and ECOG performance status has stabilised.
Fracture in weight-bearing bones	Any	Withhold PLUVICTO until the fracture has been adequately stabilised/treated and ECOG performance status has stabilised.

Adverse reaction	Severity[a]	Dose modification
AST or ALT elevation	AST or ALT >5 times ULN in the absence of liver metastases	Permanently discontinue PLUVICTO.
Fatigue	Grade ≥3	Withhold Pluvicto until improvement to Grade 2 or baseline.
Electrolyte or metabolic abnormalities	Grade ≥2	Withhold Pluvicto until improvement to Grade 1 or baseline
Other non-haematologic toxicity [see Section 4.8, Adverse Effects – Undesirable Effects]	Any unacceptable toxicity	Permanently discontinue PLUVICTO.
	Any serious 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; 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

Renal impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment with baseline CLcr ≥50 mL/min by Cockcroft-Gault. Treatment with PLUVICTO is not recommended in patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end-stage renal disease as the pharmacokinetic profile and safety of Pluvicto have not been studied in these patients.

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment. PLUVICTO has not been studied in patients with moderate or severe hepatic impairment.

Paediatric patients (below 18 years of age)

The safety and effectiveness of PLUVICTO in pediatric patients have not been established. There is no relevant use of PLUVICTO in the paediatric population in the indication of treatment of PSMA-expressing prostate cancer.

Elderly patients (65 years of age or older)

No dose adjustment is recommended in patients 65 years or older.

Method of administration

PLUVICTO is a ready-to-use solution for injection for single use in one patient only. Discard any unused medicinal product.

Administration instructions

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 minimise the risk of extravasation. Cases of extravasation should be managed as per institutional guidelines.

Patients should be advised to remain well hydrated and to urinate frequently before and after administration of PLUVICTO.

Preparation instructions

- Aseptic technique and radiation shielding should be used when handling or administering PLUVICTO, using tongs as needed to minimise radiation exposure.
- The vial should be visually inspected under a shielded screen for particulate matter and discolouration prior to administration. The vial should be discarded if particulates or discolouration 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.

Intravenous methods of administration

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.

Radiation dosimetry

Dosimetry of lutetium (^{177}Lu) vipivotide tetraxetan was collected in 29 patients in the Phase III 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, 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 for PLUVICTO in the VISION sub-study

	Absorbed dose per unit activity (mGy/MBq)[a] (N = 29)		Calculated absorbed dose for 7,400 MBq administration (mGy)[a]		Calculated absorbed dose for 6 x 7,400 MBq (44,400 GBq cumulative activity) (mGy)[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
Osophagus	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
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

	Absorbed dose per unit activity (mGy/MBq)[a] (N = 29)		Calculated absorbed dose for 7,400 MBq administration (mGy)[a]		Calculated absorbed dose for 6 x 7,400 MBq (44,400 GBq cumulative activity) (mGy)[a]	
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.*

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Radiation exposure to patients, medical personnel, and household contacts should be minimised 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.

Patient preparation

Patients should be encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation, especially after high activities, e.g., radionuclide therapy.

After the procedure

Before the patient is released, the nuclear medicine physician or healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimise radiation exposure to others. This includes special instructions with regards to toilet use, showering, laundry, waste disposal, emergency medical assistance, unplanned

hospital visits or traveling.

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.

Myelosuppression

PLUVICTO can cause severe and life-threatening myelosuppression, including anaemia, thrombocytopaenia, leukopaenia, and neutropaenia. In the VISION study, myelosuppression including fatal cases occurred more frequently in patients who received PLUVICTO plus best standard of care (BSoC) compared to patients who received BSoC alone, including anaemia, thrombocytopaenia, leukopaenia, and neutropaenia (see section 4.8 Adverse effects (Undesirable effects)). Two deaths (0.4%) due to intracranial haemorrhage and subdural haematoma in association with thrombocytopaenia were observed in patients who received PLUVICTO. One death due to sepsis and concurrent neutropaenia was observed in patients who received PLUVICTO.
Haematology laboratory tests, including haemoglobin, white blood cell count, absolute neutrophil count, and platelet count, 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 section 4.2 Dose and method of administration).

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 section 4.8 Adverse effects (Undesirable effects)).

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 CLcr, 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 section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties – special populations).

Renal impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Exposure (AUC) of lutetium (^{177}Lu) vipivotide tetraxetan is expected to increase with the degree of renal impairment (see section 5.2 - Pharmacokinetic properties). Patients with mild or moderate renal impairment may be at greater risk of toxicity. Renal function and

adverse reactions should be frequently monitored in patients with mild to moderate renal impairment (see section 4.2 – Dose and method of administration). Treatment with PLUVICTO is not recommended in patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end-stage renal disease.

Fertility

Radiations of lutetium (^{177}Lu) vipivotide tetraxetan may potentially have toxic effects on male gonads and spermatogenesis. The recommended cumulative dose of 44 400 MBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause infertility.

Contraception in males

Male patients are advised not to father a child and to use a condom for intercourse during treatment with PLUVICTO and for 14 weeks after the last dose (see section 4.6 – Fertility, pregnancy and lactation).

Use in hepatic impairment

See section 4.2, Dose and method of administration and section 5.2 Pharmacokinetic properties, metabolism.

Use in the elderly

See section 4.2, Dose and method of administration and section 5.2 Pharmacokinetic properties, special populations.

Paediatric use

The safety and efficacy of PLUVICTO in paediatric patients have not been established.

Effects on laboratory tests

See section 4.2, Dose and method of administration – treatment monitoring.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical drug interaction studies have been performed.

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*.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies were conducted to determine the effects of lutetium (^{177}Lu) vipivotide tetraxetan on fertility. Radiations of lutetium (^{177}Lu) vipivotide tetraxetan may potentially have toxic effects on male gonads and spermatogenesis. The recommended cumulative dose of 44,400 MBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause infertility. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm can be discussed as an option for male patients before treatment.

Use in pregnancy – Pregnancy Category X

Risk summary

The safety and efficacy of PLUVICTO have not been established in females as PLUVICTO is not indicated for use in females. No animal studies using lutetium (^{177}Lu) vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-foetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Based on its mechanism of action, PLUVICTO can cause foetal harm when administered to a pregnant woman (see section 5.1 Pharmacodynamic properties, Clinical trials).

Contraception

Males

Based on its mechanism of action, male patients should be advised not to father a child and to use condoms for intercourse during treatment with PLUVICTO and for 14 weeks after the last dose (see section 5.1 Pharmacodynamic properties, Clinical trials).

Use in lactation.

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 in human milk or its effects on the breastfed child or on milk production.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines have not been assessed. PLUVICTO may have a minor influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of PLUVICTO was evaluated in the Phase III VISION study in patients with progressive, PSMA-positive mCRPC. Of the 831 patients randomised, 734 patients received at least one dose of randomised treatment. Patients received at least one dose of either PLUVICTO 7,400 MBq 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 37,500 MBq (range: 7,000 to 48,300). The median duration of exposure to randomised treatment was 7.8 months (range: 0.3 to 24.9) for patients who received PLUVICTO plus BSoC and 2.1 months (range: 0.0 to 26.0) for patients who received BSoC alone. The median duration of follow-up was 14.8 months for patients receiving PLUVICTO plus BSoC.

Table 3 summarises the incidence of adverse reactions. The most common adverse reactions (≥20%) occurring at a higher incidence in patients who received PLUVICTO plus BSoC compared to BSoC alone include fatigue: (43.1%), dry mouth (39.3%), nausea (35.3%), anaemia (31.8%), decreased appetite (21.2%), and constipation (20.2%). 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: anaemia (12.9%), thrombocytopaenia (7.9%), lymphopaenia (7.8%), and fatigue (5.9%).

Tabulated summary of adverse reactions

Adverse drug reactions (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 3 Adverse reactions 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	**Frequency category**	**All grades %**	**Grades 3 to 4[b] %**	**Frequency category**	**All grades %**	**Grades 3 to 4[b] %**
Blood and lymphatic system disorders						
Anaemia	Very common	31.8%	12.9%	Very common	13.2%	4.9%
Thrombocytopaenia	Very common	17.2%	7.9%	Common	4.4%	1.0%
Leukopaenia[c]	Very common	15.7%	4.2%	Common	2.0%	0.5%
Lymphopaenia	Very common	14.2%	7.8%	Common	3.9%	0.5%
Pancytopaenia[d]	Common	1.7%	1.3%[b]	-	0	0
Nervous system disorders						
Dizziness	Common	8.3%	0.9%	Common	4.4%	0

	PLUVICTO plus BSoC (N = 529)			BSoC (N = 205)		
Adverse reactions	**Frequency category**	**All grades %**	**Grades 3 to 4[b] %**	**Frequency category**	**All grades %**	**Grades 3 to 4[b] %**
Headache	Common	7.0%	0.8%	Common	2.0%	0
Dysgeusia[e]	Common	7.0%	0	Common	1.5%	0
Eye disorders						
Dry eye	Common	3.0%	0	Uncommon	1.0%	0
Ear and labyrinth disorders						
Vertigo	Common	(2.1%)	0	-	0	0
Gastrointestinal disorders						
Dry mouth[f]	Very common	39.3%	0	Uncommon	0.5%	0
Nausea	Very common	35.3%	1.3%	Very common	16.6%	0.5%
Constipation	Very common	20.2%	1.1%	Very common	11.2%	0.5%
Vomiting[g]	Very common	19.1%	0.9%	Common	6.3%	0.5%
Diarrhoea	Very common	18.9%	0.8%	Common	2.9%	0.5%
Abdominal pain[h]	Very common	11.2%	1.1%	Common	6.3%	0.5%
Renal and urinary disorders						
Urinary tract infection[i]	Very common	11.5%	3.8%	Uncommon	1.0%	0.5%
Acute kidney injury[j]	Common	8.5%	3.2%	Common	5.9%	2.9%
General disorders and administration site conditions						
Fatigue	Very common	43.1%	5.9%	Very common	22.9%	1.5%
Decreased appetite	Very common	21.2%	1.9%	Very common	14.6%	0.5%
Weight decreased	Very common	10.8%	0.4%	Common	8.8%	0
Oedema peripheral[k]	Common	9.8%	0.4%	Common	6.8%	0.5%
Pyrexia	Common	6.8%	0.4%	Common	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 pancytopaenia. Grade 5 (fatal) pancytopaenia was reported in 2 patients who received PLUVICTO plus BSoC.

[c]Leukopaenia includes leukopaenia and neutropaenia.

[d]Pancytopaenia includes pancytopaenia and bicytopaenia.

[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]Oedema peripheral includes oedema peripheral, fluid retention, and fluid overload.

Description of selected adverse reactions

Myelosuppression

In the VISION study, myelosuppression occurred more frequently in patients who received PLUVICTO plus BSoC compared to patients who received BSoC alone (all Grades/Grade ≥3): anaemia (31.8%/12.9%) versus (13.2%/4.9%); thrombocytopaenia (17.2%/7.9%) versus (4.4%/1.0%); leukopaenia (12.5%/2.5%) versus (2.0%/0.5%); lymphopaenia (14.2%/7.8%) versus (3.9%/0.5%); neutropaenia (8.5%/3.4%) versus (1.5%/0.5%); pancytopaenia (1.5%/1.1%) versus (0%/0%) including two fatal events of pancytopaenia in patients who received PLUVICTO plus BSoC; and bicytopaenia (0.2%/0.2%) versus (0%/0%).

Myelosuppression adverse reactions that led to permanent discontinuation in ≥0.5% of patients who received PLUVICTO plus BSoC included: anaemia (2.8%), thrombocytopaenia (2.8%), leukopaenia (1.3%), neutropaenia (0.8%), and pancytopaenia (0.6%). Myelosuppression adverse reactions that led to dose interruptions/dose reductions in ≥0.5% of patients who received PLUVICTO plus BSoC included: anaemia (5.1%/1.3%), thrombocytopaenia (3.6%/1.9%), leukopaenia (1.5%/0.6%), and neutropaenia (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%).

Second primary malignancies

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself. As PLUVICTO contributes to a patient's overall long-term radiation exposure, which is associated with an increased risk for cancer (see section 4.4 – Special warnings and precautions for use), a potential risk of second primary malignancies cannot be ruled out for radiopharmaceuticals such as PLUVICTO. At the time of the VISION primary analysis (cut-off date 27-Jan-2021), cases of squamous cell carcinoma (4 patients; 0.8%) and basal cell carcinoma, malignant melanoma and squamous cell carcinoma of the skin (1 patient each; 0.2% each) were reported in patients who received PLIVICTO plus BSoC.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at

www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 might be helpful to estimate the effective radiation dose that was applied.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10XX05

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacodynamics

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

There are limited data regarding lutetium (^{177}Lu) vipivotide tetraxetan exposure-safety relationships and the time course of pharmacodynamic response.

Unlabelled vipivotide tetraxetan does not have any pharmacodynamic activity.

Cardiac electrophysiology

The ability of PLUVICTO to prolong the QTc interval at the recommended dose was assessed in 30 patients in the Phase III VISION sub-study. At the recommended dosage, PLUVICTO does not cause large mean increases (>20 ms) in the QTc interval.

Mechanism of action

The active moiety of PLUVICTO is the radionuclide lutetium-177 which is linked to a targeting moiety that binds to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of PLUVICTO to PSMA-expressing cancer cells, 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.

Clinical trials

Clinical safety and efficacy

VISION

The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC was established in VISION, a randomised, multicenter, open-label Phase III study. Eight hundred and thirty-one (N = 831) patients were randomised (2:1) to receive either PLUVICTO 7,400 MBq every 6 weeks for up to a total of 6 doses plus BSoC (N = 551) or BSoC alone (N = 280).

To maintain castration status, all patients continued to receive a GnRH analogue or had prior bilateral orchiectomy. Eligible patients were required to have PSMA-positive mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic, and haematological function. Eligible patients were also 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 (with a regimen defined as a minimum exposure of 2 cycles of a taxane). Patients with unstable symptomatic central nervous system metastases or symptomatic or clinically/radiologically impending spinal cord compression were not eligible for the study. Patients underwent a gallium (^{68}Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have at least one PSMA-positive lesion identified by this scan with gallium (^{68}Ga) gozetotide uptake greater than in normal liver Patients with PSMA-negative lesions (no CT/MRI measurable lesions) were excluded if the PET scan showed poor or no gallium (^{68}Ga) gozetotide uptake, less than or equal to uptake in normal liver.

BSoC administered at the physician's discretion included: supportive measures including pain medications, hydration, blood transfusions, etc.; ketoconazole; radiation therapy (including seeded form or any external beam radiotherapy [including stereotactic body radiotherapy and palliative external beam]) to localised prostate cancer targets; bone-targeted agents including zoledronic acid, denosumab, and any bisphosphonates; androgen-reducing agents including GnRH analogues, any corticosteroid and 5-alpha reductases; AR pathway inhibitors. BSoC excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy treatment.

Patients continued randomised treatment until evidence of tumour progression (based on investigator assessment per Prostate Cancer Working Group 3 [PCWG3] criteria), unacceptable toxicity, use of prohibited treatment, non-compliance or withdrawal, or lack of clinical benefit.

The primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per PCWG3 criteria. An additional secondary efficacy endpoint was overall response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.. Radiographic imaging for tumour assessment (CT with contrast/MRI imaging and bone scan) was done every 8 weeks (±4 days) after the first dose for the first 24 weeks (independent of dose delays), then every 12 weeks (±4 days).

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. Randomisation was stratified by baseline lactase dehydrogenase (LDH), presence of liver metastases, ECOG PS score and inclusion of an AR pathway inhibitor as part of BSoC at the time of randomisation. At randomisation, all patients (100.0%) had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two. At randomisation, 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 randomised 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.

Efficacy results for VISION are presented in Table 4 and Figures 1 and 2. The final analyses of OS and rPFS were event-driven and conducted after the occurrence of 530 deaths and 347 events, respectively. Treatment with PLUVICTO plus BSoC demonstrated a statistically significant improvement in OS and rPFS by BICR compared to treatment with BSoC alone.

Table 4 Efficacy results in VISION

Efficacy parameters	PLUVICTO plus BSoC	BSoC
Primary efficacy endpoints		
Overall survival (OS)	N = 551	N = 280
Deaths, n (%)	343 (62.3%)	187 (66.8%)
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	
Radiographic progression-free survival (rPFS)[d]	N = 385	N = 196
Events (progression or death), n (%)	254 (66.0%)	93 (47.4%)
Radiographic progressions, n (%)	171 (44.4%)	59 (30.1%)
Deaths, n (%)	83 (21.6%)	34 (17.3%)
Median, months (95% CI)[a]	8.7 (8.3, 10.5)	3.4 (2.4, 4.0)
Hazard ratio (95% CI)[b]	0.40 (0.31, 0.52)	
P-value[c]	<0.001	
Secondary efficacy endpoints		
Best overall response (BOR)		
Patients with evaluable disease at baseline	N = 319	N = 120
Complete response (CR), n (%)	18 (5.6%)	0 (0%)
Partial response (PR), n (%)	77 (24.1%)	2 (1.7%)
Overall response rate (ORR)[e,f]	95 (29.8%)	2 (1.7%)
P-value[g]	<0.001	
Duration of response (DOR)[e]		
Median, months (95% CI)[a]	9.8 (9.1, 11.7)	10.6 (NE, NE)[h]

Abbreviations: BSoC, best standard of care; CI: confidence interval; NE, not evaluable; BICR, blinded independent central review; PCWG3, prostate cancer working group 3; RECIST, response evaluation criteria in solid tumours.

[a]Based on Kaplan-Meier estimate.

[b]Hazard ratio based on the stratified Cox PH model. Hazard ratio <1 favours PLUVICTO plus BSoC.

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

[d]By BICR per PCWG3 criteria.

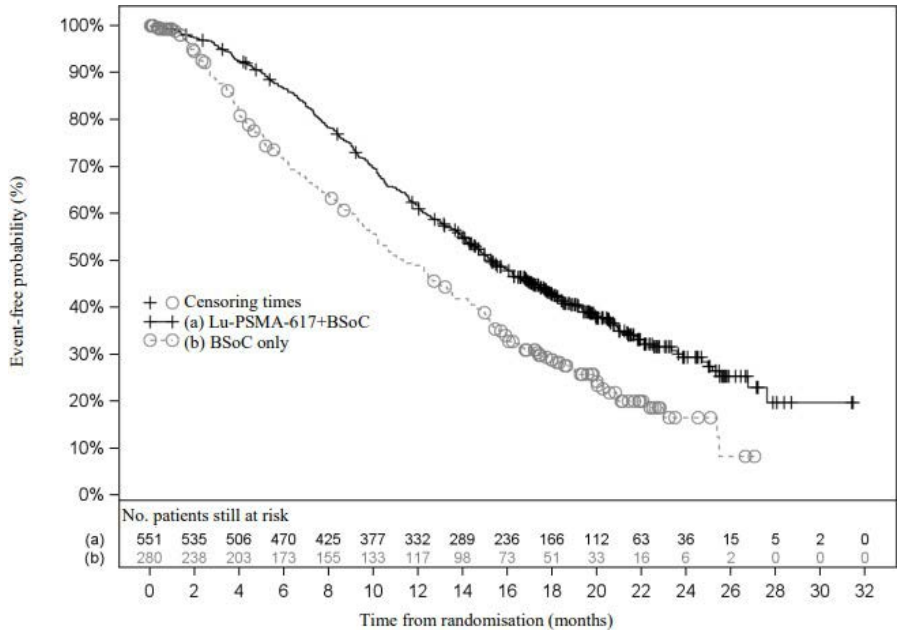
[e]By BICR per RECIST v1.1.

[f]ORR: CR+PR. Confirmed response for CR and PR.

[g]Stratified Wald's Chi-square test two-sided p-value.

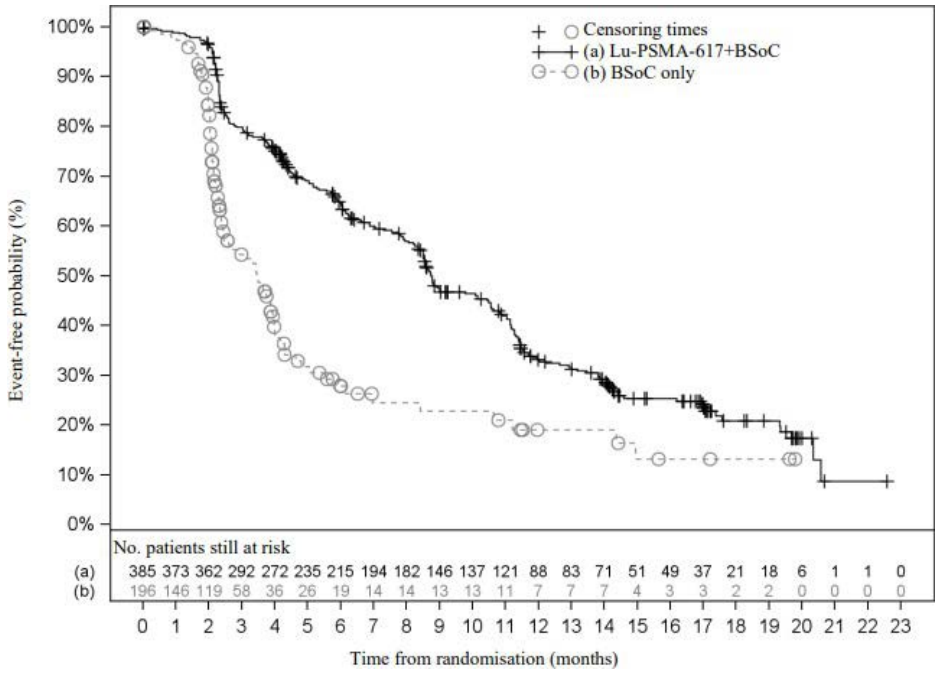
[h]Median DOR in the BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST v1.1 radiographic progression or death.

Figure 1 Kaplan-Meier plot of overall survival in VISION



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of an AR pathway inhibitor in BSoC at time of randomisation. n/N: Number of events/number of patients in treatment arm.

Figure 2 Kaplan-Meier plot of BICR-assessed radiographic progression-free survival (rPFS) in VISION



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of an AR pathway inhibitor in BSoC at time of randomisation.
n/N: Number of events/number of patients in treatment arm.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

PLUVICTO is administered intravenously and is immediately and completely bioavailable.

The geometric mean blood exposure (area under the curve [AUC_{inf}]) for lutetium (^{177}Lu) vipivotide tetraxetan at the recommended dose is 52.3 ng.h/mL (geometric mean coefficient of variation [CV] 31.4%). The geometric mean maximum blood concentration (C_{max}) for lutetium (^{177}Lu) vipivotide tetraxetan is 6.58 ng/mL (CV 43.5%).

Distribution

The geometric mean volume of distribution (V_z) for lutetium (^{177}Lu) vipivotide tetraxetan is 123 L (CV 78.1%).

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

Organ uptake

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

Elimination

The geometric mean clearance (CL) for lutetium (^{177}Lu) vipivotide tetraxetan is 2.04 L/h (CV 31.5%).

Half-life

PLUVICTO shows a bi-exponential elimination with a geometric mean terminal elimination half-life ($T_{½}$) of 41.6 hours (CV 68.8%).

Metabolism

Lutetium (^{177}Lu) vipivotide tetraxetan does not undergo hepatic or renal metabolism.

Excretion

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

Special populations

Use in the elderly

Of the 529 patients who received at least one dose of PLUVICTO plus 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 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

Exposure (AUC) of lutetium (^{177}Lu) vipivotide tetraxetan increased by 20% in patients with mild renal impairment compared to normal renal function. Kidney dosimetry half-life also increased in patients with mild renal impairment compared to normal renal function, 51 hours vs. 37 hours, respectively. Patients with mild or moderate renal impairment may be at greater risk of toxicity (see section 4.4 – Special warnings and precautions for use). No pharmacokinetic data are available for patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end-stage renal disease.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Acetic acid, sodium acetate, gentisic acid, sodium ascorbate, pentetic acid, water for injections.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2 Dose and method of administration.

6.3 SHELF LIFE

120 hours (5 days) from the date and time of calibration.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not freeze.

Store in the original package to protect from ionising 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 after EXP.

6.5 NATURE AND CONTENTS OF CONTAINER

PLUVICTO is supplied in a clear, colourless 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 7,400 MBq ± 10% at the date and time of administration.

The vial is enclosed within a lead container for protective shielding.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

This medicinal product contains radioactive material that must be handled and disposed of responsibly. Refer to section 4.2 Dose and method of administration - Important safety instructions.

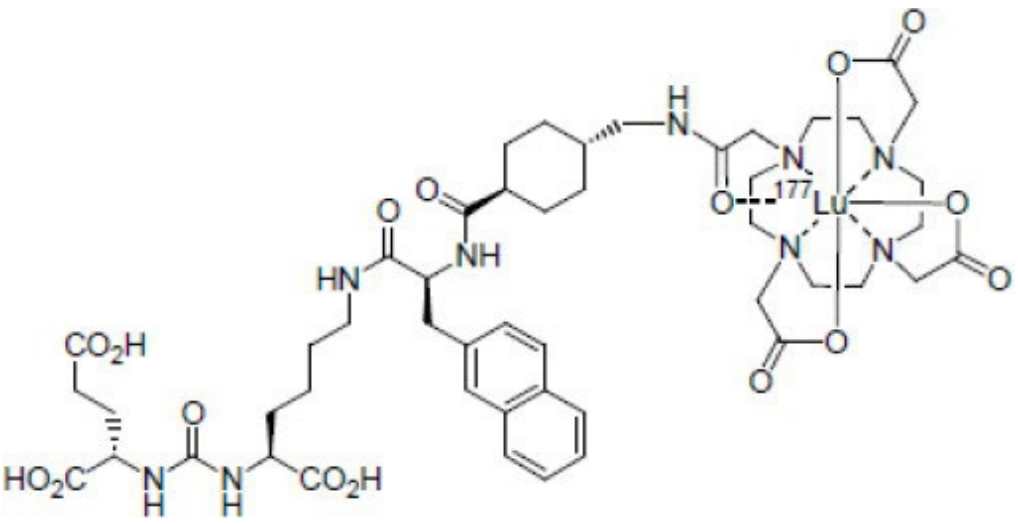
Disposal of any unused product or waste must be in compliance with institutional guidelines developed in accordance with the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) code of practice.

Lutetium-177 is prepared using a stable isotope ytterbium-176 (“non-carrier added”) which should be considered during waste management.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The molecular formula is $C_{49}H_{68}{}^{177}LuN_9O_{16}$. The relative molecular mass is 1216.06 g/mol. The chemical structure is shown below:



CAS number

1703749-62-5

The drug substance ^{177}Lu-PSMA-617 is produced as an aqueous concentrated solution by radiolabelling of the chemical precursor vipivotide tetraxetan (PSMA-617) with ^{177}Lu chloride radioactive starting material. It is clear, colourless to slightly yellow in appearance.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
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Website: www.novartis.com.au

® = Registered Trademark.

9 DATE OF FIRST APPROVAL

TBC

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
-	-

Internal document code:
plu010724i is based on CDS dated 25 April 2022