▼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 pathway inhibitor (ARPI) therapy, and:

- are considered appropriate to delay taxane-based chemotherapy, or
- have received prior 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 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, dose reduction or permanent discontinuation of treatment with PLUVICTO. If a treatment delay due to an adverse reaction persists for >4 weeks, treatment discontinuation with PLUVICTO may be considered. 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.
Fatigue	Grade ≥3	Withhold Pluvicto until improvement to Grade 2 or baseline.

Adverse reaction	Severity[a]	Dose modification
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][b]	Any unacceptable toxicity	Permanently discontinue PLUVICTO.
	Any serious adverse reaction that requires treatment delay of > 4 weeks	Permanently discontinue PLUVICTO.
	AST or ALT >20 times ULN in the absence of liver metastases	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.

[b]Including elevation of AST or ALT

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 of age 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 the syringe method, as an infusion using the gravity method, or as an infusion using the peristaltic pump method.

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

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

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. Manage cases of extravasation as per institutional guidelines.

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

Preparation instructions

- Use aseptic technique and radiation shielding when handling or administering PLUVICTO, using tongs as needed to minimise radiation exposure.
- Visually inspect the product under a shielded screen for particulate matter and discolouration prior to administration. Discard the vial if particulates and/or discolouration are present.
- PLUVICTO is a ready-to-use solution for single use only. Do not inject the PLUVICTO solution directly into any other intravenous solution.
- Confirm the amount of radioactivity of PLUVICTO delivered to the patient with an appropriately calibrated dose calibrator prior to and after each PLUVICTO administration.
- Dispose of any unused medicinal product or waste material in accordance with national regulations.

Intravenous methods of administration

Instructions for the syringe method

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

intravenous catheter that is primed with 0.9% sterile sodium chloride solution and that is used exclusively for PLUVICTO administration to the patient.

- When the desired PLUVICTO radioactivity has been delivered, stop the syringe pump and then change the position of the 3-way stopcock valve to flush the syringe with 25 mL of 0.9% sodium chloride solution. Restart the syringe pump.
- After the flush of the syringe has been completed, 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

- 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 0.9% sterile 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 0.9% sterile 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 primed 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 0.9% sterile sodium chloride solution via the short needle into the PLUVICTO vial (the 0.9% sterile 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 0.9% sterile sodium chloride solution 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 peristaltic pump method

- Insert a filtered 2.5 cm, 20 gauge needle (short venting needle) into the PLUVICTO vial. Ensure that the short needle does not touch the PLUVICTO solution in the vial and do not connect the short needle directly to the patient or to the peristaltic pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the PLUVICTO vial, ensuring that the long needle touches and is secured to the bottom of the PLUVICTO vial during the entire infusion. Connect the long needle and a 0.9% 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 pump according to the manufacturer's instructions.
- Prime the line by opening the 3-way stopcock valve and pumping the PLUVICTO solution through the tubing until it reaches the exit of the valve.

- Prime the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the primed intravenous catheter to the patient and set the 3-way stopcock valve such that the PLUVICTO solution is in line with the peristaltic pump.
- Infuse an appropriate volume of PLUVICTO solution at approximately 25 mL/h to deliver the desired radioactivity.
- When the desired PLUVICTO radioactivity has been delivered, stop the peristaltic pump and then change the position of the 3-way stopcock valve so that the peristaltic pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic 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[a] for PLUVICTO in the VISION sub-study

	Absorbed dose per unit activity (Gy/GBq) (N = 29)		Calculated absorbed dose for 7.4 GBq administration (Gy)		Calculated absorbed dose for 6 x 7.4 GBq (44.4 GBq cumulative activity) (Gy)	
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
Oesophagus	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
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] Absorbed dose estimates were derived using OLINDA v2.2. 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 others 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.

After each administration of PLUVICTO, the following general recommendations for patients can be considered along with national, local, and institutional procedures and regulations:

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

Myelosuppression

PLUVICTO can cause severe and life-threatening myelosuppression, including anaemia, thrombocytopaenia, leukopaenia, and neutropaenia.

In the PSMAfore study, myelosuppression occurred more frequently in patients who received PLUVICTO compared to patients who switched to another ARPI therapy (see section 4.8 Adverse effects (undesirable effects)).

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

PLUVICTO can cause severe renal toxicity.

In the PSMAfore study, renal toxicity was comparable in patients who received PLUVICTO compared to patients who switched to another ARPI therapy (see section 4.8 Adverse effects (undesirable effects)).

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. 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). No animal studies using lutetium (^{177}Lu) vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-foetal development; however, radioactive emissions, including those from PLUVICTO can cause foetal harm.

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)

PSMAfore

Summary of the safety profile

The safety of PLUVICTO was evaluated in the Phase III PSMAfore study in patients with progressive, PSMA-positive mCRPC previously treated with ARPI therapy. Of the 468 patients randomised, 459 patients received at least one dose of randomised treatment. Patients received either PLUVICTO 7,400 MBq administered every 6 weeks (N = 227) or a change in ARPI (N = 232).

Among patients who received PLUVICTO, the median number of doses of PLUVICTO received was 6 (range: 1 to 6), with 63.4% of patients who received all 6 doses of PLUVICTO. The median cumulative dose of PLUVICTO was (42,400 MBq) (range: 7,000 to 45,400). The median duration of exposure to randomised treatment was 8.4 months (range: 0.4 to 11.6) for patients who received PLUVICTO and 6.5 months (range: 0.03 to 29.2) for patients who received a change in ARPI. The data analyses presented below do not include patients who crossed over to receive PLUVICTO after receiving treatment in the change in ARPI arm.

Table 3 summarises the incidence of adverse drug reactions. The most common adverse drug reactions (≥20%) in patients who received PLUVICTO include: dry mouth (60.8%), fatigue (52.9%), nausea (31.7%), anaemia (27.3%), constipation (22.0%) and decreased appetite (21.6%). The most common Grade 3 to 4 adverse drug reactions (≥5%) in patients who received PLUVICTO include: anaemia (6.2%).

Tabulated summary of adverse drug 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 drug reactions in patients who received PLUVICTO compared to a change in ARPI in PSMAfore[a]

	Pluvicto* (N = 227)			Change in ARPI (N = 232)		
Adverse drug reactions	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**
Infections and infestations						
Urinary tract infection[c]	13 (5.7%)	Common	3 (1.3%)	18 (7.8%)	Common	7 (3.0%)
Oral fungal infection[d]	7 (3.1%)	Common	0	2 (0.9%)	Uncommon	0
Blood and lymphatic system disorders						
Anaemia	62 (27.3%)	Very common	14 (6.2%)	45 (19.4%)	Very common	16 (6.9%)
Leukopaenia[e]	25 (11.0%)	Very common	5 (2.2%)	6 (2.6%)	Common	2 (0.9%)
Thrombocytopenia	23 (10.1%)	Very common	7 (3.1%)	9 (3.9%)	Common	2 (0.9%)
Lymphopaenia	15 (6.6%)	Common	10 (4.4%)	3 (1.3%)	Common	1 (0.4%)
Pancytopenia	1 (0.4%)	Uncommon	0	1 (0.4%)	Uncommon	0
Metabolism and nutrition disorders						
Decreased appetite	49 (21.6%)	Very common	0	43 (18.5%)	Very common	1 (0.4%)
Nervous system disorders						
Dysgeusia[f]	20 (8.8%)	Common	0	7 (3.0%)	Common	0
Headache	19 (8.4%)	Common	0	11 (4.7%)	Common	0
Dizziness	10 (4.4%)	Common	0	13 (5.6%)	Common	0
Eye disorders						
Dry eye[g]	14 (6.2%)	Common	0	2 (0.9%)	Uncommon	0
Ear and labyrinth disorders						
Vertigo	4 (1.8%)	Common	0	3 (1.3%)	Common	0
Gastrointestinal disorders						
Dry mouth[h]	138 (60.8%)	Very common	2 (0.9%)	6 (2.6%)	Common	0
Nausea	72 (31.7%)	Very common	0	27 (11.6%)	Very common	1 (0.4%)
Constipation	50 (22.0%)	Very common	1 (0.4%)	33 (14.2%)	Very common	0
Diarrhoea	38 (16.7%)	Very common	0	21 (9.1%)	Common	1 (0.4%)
Vomiting	26 (11.5%)	Very common	0	11 (4.7%)	Common	0
Abdominal pain[i]	21 (9.3%)	Common	2 (0.9%)	19 (8.2%)	Common	1 (0.4%)
Oesophageal disorder[j]	9 (4.0%)	Common	1 (0.4%)	2 (0.9%)	Uncommon	0
Stomatitis	3 (1.3%)	Common	1 (0.4%)	2 (0.9%)	Uncommon	0
Skin and subcutaneous tissue disorders						
Dry skin[k]	9 (4.0%)	Common	0	5 (2.2%)	Common	0
Renal and urinary disorders						
Acute kidney injury[l]	15 (6.6%)	Common	3 (1.3%)	18 (7.8%)	Common	7 (3.0%)
General disorders and administration site conditions						
Fatigue[m]	120 (52.9%)	Very common	3 (1.3%)	124 (53.4%)	Very common	12 (5.2%)
Oedema peripheral	19 (8.4%)	Common	0	28 (12.1%)	Very common	0
Pyrexia	6 (2.6%)	Common	1 (0.4%)	10 (4.3%)	Common	0
Investigations						
Weight decreased	15 (6.6%)	Common	1 (0.4%)	32 (13.8)	Very common	3 (1.3%)

Abbreviation: ARPI, androgen receptor pathway inhibitor.

**Patients in the PLUVICTO arm do not include patients who crossed over to receive PLUVICTO after receiving treatment in the change in ARPI arm.*

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

	Pluvicto* (N = 227)			Change in ARPI (N = 232)		
Adverse drug reactions	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**

[b]Only includes Grades 3 to 4 adverse drug reactions, no grade 5 adverse drug reactions recorded during treatment phase.

[c]Urinary tract infection includes urinary tract infection, cystitis, and urinary tract infection enterococcal.

[d]Oral fungal infection includes candida infection, oral candidiasis, oral fungal infection, and oropharyngeal candidiasis.

[e]Leukopaenia includes neutropenia and leukopenia.

[f]Dysgeusia includes dysgeusia and taste disorder.

[g]Dry eye includes dry eye and xerophthalmia.

[h]Dry mouth includes dry mouth, mucosal dryness, salivary hyposecretion, dry throat, and lip dry.

[i]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and epigastric discomfort.

[j]Oesophageal disorder includes gastrooesophageal reflux disease, dysphagia, oesophagitis, and burn oesophageal.

[k]Dry skin includes xerosis and dry skin.

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

[m]Fatigue includes asthenia and fatigue.

Description of selected adverse drug reactions

Myelosuppression

In the PSMAfore study, myelosuppression occurred more frequently in patients who received PLUVICTO compared to patients who received a change in ARPI (all Grades/Grade ≥3): anaemia (26.9%/6.2%) versus (19.0%/6.9%); thrombocytopaenia (7.5%/2.2%) versus (3.0%/0.9%); neutropaenia (5.7%/1.3%) versus (0.9%/0.4%); leukopaenia (2.2%/0.9%) versus (0%/0%); lymphopaenia (1.8%/0.4%) versus (0%/0%); and pancytopaenia (0.4%/0%) versus (0.4%/0%). One fatal case of bone marrow failure occurred during the long term follow-up period in a patient treated with PLUVICTO.

Myelosuppression adverse drug reactions that led to permanent discontinuation in ≥0.5% of patients who received PLUVICTO included: thrombocytopaenia (1.3%). Myelosuppression adverse drug reactions that led to dose interruptions/dose reductions in ≥0.5% of patients who received PLUVICTO included: anaemia (1.8%/0.4%) and neutropaenia (0.9%/0.4%).

Renal toxicity

In the PSMAfore study, renal toxicity was comparable in patients who received PLUVICTO compared to patients who received a change in ARPI (all Grades/Grade 3 to 4): blood creatinine increased (4.4%/0%) versus (3.0%/0%); acute kidney injury (2.2%/1.3%) versus (3.9%/2.2%); renal failure (0.9%/0.4%) versus (1.3%/0.9%); and blood urea increased (0.4%/0%) versus (0%/0%).

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

VISION

Summary of the safety profile

The safety of PLUVICTO was evaluated in the Phase III VISION study in patients with progressive, PSMA-positive mCRPC previously treated with ARPI therapy and taxane-based chemotherapy. 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 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 36.5) for patients who received PLUVICTO plus BSoC and 2.1 months (range: 0.0 to 34.0) for patients who received BSoC alone. The median duration of follow-up was 15.3 months for patients receiving PLUVICTO plus BSoC.

Table 4 summarises the incidence of adverse reactions. The most common adverse reactions (≥20%) in patients who received PLUVICTO include fatigue: (48.0%), dry mouth (39.3%), nausea (35.7%), anaemia (31.9%), decreased appetite (21.4%), and constipation (20.2%). The most common Grade 3 to 4 adverse reactions (≥5%) in patients who received PLUVICTO include: anaemia (12.9%), thrombocytopaenia (7.9%), lymphopaenia (7.8%), and fatigue (6.6%).

Tabulated summary of adverse reactions

Adverse drug reactions (Table 4) 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 4 Adverse reactions 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] %**
Infections and infestations						
Oral fungal infection[c]	Common	2.5%	0	Uncommon	1.0%	0.5%
Blood and lymphatic system disorders						
Anaemia	Very common	31.9%	12.9%	Very common	13.2%	4.9%
Thrombocytopaenia	Very common	17.2%	7.9%	Common	4.4%	1.0%
Leukopaenia[d]	Very common	15.7%	4.2%	Common	2.0%	0.5%
Lymphopaenia	Very common	14.2%	7.8%	Common	3.9%	0.5%
Pancytopaenia[e]	Common	1.7%	1.3%[b]	-	0	0
Bone marrow failure	Uncommon	0.2%	0.2%[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[f]	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[g]	Very common	39.3%	0	Uncommon	1.0%	0
Nausea	Very common	35.7%	1.3%	Very common	16.6%	0.5%
Constipation	Very common	20.2%	1.1%	Very common	11.2%	0.5%
Vomiting[h]	Very common	19.1%	0.9%	Common	6.3%	0.5%
Diarrhoea	Very common	19.1%	0.8%	Common	2.9%	0.5%
Abdominal pain[i]	Very common	11.5%	1.3%	Common	6.3%	0.5%
Oesophageal disorder[j]	Common	3.4%	0.2%	Common	1.5%	0
Stomatitis	Common	1.7%	0.2%	-	0	0
Skin and subcutaneous tissue disorders						
Dry skin[k]	Common	1.5%	0	Uncommon	1.0%	0
Renal and urinary disorders						
Urinary tract infection[l]	Very common	11.9%	3.8%	Uncommon	1.0%	0.5%
Acute kidney injury[m]	Common	9.1%	3.4%	Common	5.9%	2.9%
General disorders and administration site conditions						
Fatigue[n]	Very common	48.0%	6.6%	Very common	29.3%	2.4%
Decreased appetite	Very common	21.4%	1.9%	Very common	14.6%	0.5%
Weight decreased	Very common	11.0%	0.4%	Common	9.8%	0.5%
Oedema peripheral[o]	Very Common	10.0%	0.4%	Common	6.8%	1.0%
Pyrexia	Common	7.0%	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 and bone marrow failure. Grade 5 (fatal) pancytopaenia was reported in 2 patients who received PLUVICTO plus BSoC. Grade 5 (fatal) bone marrow failure was reported in 1 patient who received Pluvicto plus BSoC.

[c]Oral fungal infection includes oral candidiasis, candida infection, oral fungal infection, oropharyngitis fungal, and tongue fungal infection.

[d]Leukopaenia includes leukopaenia and neutropaenia.

[e]Pancytopaenia includes pancytopaenia and bicytopaenia.

[f]Dysgeusia includes dysgeusia and taste disorder.

[g]Dry mouth includes dry mouth, lip dry, salivary hyposecretion, and dry throat.

[h]Vomiting includes vomiting and retching.

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

[j]Oesophageal disorder includes gastrooesophageal reflux disease, dysphagia, and oesophagitis.

[k]Dry skin includes dry skin and xeroderma.

	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] %**

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

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

[n]Fatigue includes fatigue and asthenia.

[o]Oedema peripheral includes oedema peripheral, fluid retention, and hypervolaemia.

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 (31.9%/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; bicytopaenia (0.2%/0.2%) versus (0%/0%); and bone marrow failure (0.2%/0.2%) versus (0%/0%) including one fatal event of bone marrow failure in patients who received PLUVICTO plus BSoC.

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 (5.7%/0.2%) versus (2.4%/0.5%); acute kidney injury (3.8%/3.2%) 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.

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

PSMAfore: PSMA-positive mCRPC previously treated with ARPI therapy

The efficacy of PLUVICTO in patients with progressive, PSMA-positive mCRPC previously treated with ARPI therapy was established in PSMAfore, a randomised, multicenter, open-label Phase III study. Four hundred and sixty-eight (N = 468) patients were randomised (1:1) to receive either PLUVICTO 7,400 MBq every 6 weeks for a total of 6 doses (N = 234) or a change in ARPI (N = 234).

Patients maintained castrate levels of serum/plasma testosterone by either medical castration or prior orchiectomy. Eligible patients were required to be candidates for ARPI switch, have PSMA-positive mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1, at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic and hematological function.

Eligible patients were also required to have progressed only once on an ARPI (abiraterone acetate, enzalutamide, darolutamide, or apalutamide). Prior taxane-based chemotherapy was only allowed in the adjuvant or neoadjuvant setting greater than 12 months before enrollment. Patients 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 PSMA-positive mCRPC defined as having at least one tumor lesion with gallium (^{68}Ga) gozetotide uptake greater than in normal liver. Patients were considered ineligible if any intraprostatic lesion or any one lesion larger than size criteria [organs ≥ 1 cm in longest diameter, lymph nodes ≥ 2.5 cm in short axis, bones (soft tissue component) ≥ 1 cm in longest diameter] had gallium (^{68}Ga) gozetotide uptake less than or equal to uptake in normal liver.

Supportive care administered at the physician's discretion included: bone-targeted agents including zoledronic acid, denosumab, or other bisphosphonates; androgen deprivation therapy (ADT); palliative radiotherapy. Patients randomised to the change in ARPI arm were allowed to cross over to receive PLUVICTO upon radiographic disease progression confirmed by blinded independent central review (BICR) or continue to receive any other therapy at the physician's discretion.

The primary efficacy endpoint was radiographic progression-free survival (rPFS) as determined by BICR per Prostate Cancer Working Group 3 (PCWG3) criteria. The key secondary efficacy endpoint was overall survival (OS).

Demographic and baseline disease characteristics were balanced between the treatment arms. The median age was 72 years (range: 43 to 94 years); 91% White; 2.6% Black or African American; 0.6% Asian; 99% had ECOG PS0-1. Randomisation was stratified by setting of prior ARPI use (castration-resistant prostate cancer (CRPC) vs. hormone-sensitive prostate cancer (HSPC)) and by symptomatology (asymptomatic or mildly symptomatic vs.

symptomatic (score >3 on item 3 of the Brief Pain Inventory-Short Form (BPI-SF) questionnaire)).

Efficacy results for PSMAfore are presented in Table 5 and Figure 1. At the primary analysis (data cut-off (DCO) date: 02-Oct-2022), treatment with PLUVICTO demonstrated a statistically significant improvement in rPFS by BICR compared to a change in ARPI therapy. There was an estimated 59% risk reduction of radiographic disease progression or death. An updated analysis of rPFS was conducted at the time of the third interim OS analysis (DCO date: 27-Feb-2024) and the results were consistent with the primary analysis. The final analysis of OS (DCO date 01-Jan-2025) was conducted after the occurrence of 299 deaths without accounting for crossover, following the intent-to-treat (ITT) principle.

Table 5 Efficacy results in PSMAfore

Efficacy parameters	**Pluvicto**	**Change in ARPI**
Primary efficacy endpoints		
Radiographic progression-free survival (rPFS)[a]	N = 233	N = 234
Events (progression or death), n (%)	60 (25.8%)	106 (45.3%)
Radiographic progressions, n (%)	53 (22.7%)	99 (42.3%)
Deaths, n (%)	7 (3.0%)	7 (3.0%)
Hazard ratio (95% CI)[b]	0.41 (0.29, 0.56)	
P-value[c]	<0.001	
Median, months (95% CI)[d]	9.3 (6.8, NE)	5.6 (4.0, 6.0)
Updated median, months (95% CI)[e]	11.6 (9.3, 14.2)	5.6 (4.2, 6.0)
Key secondary efficacy endpoints		
Overall survival (OS)[f]	N = 234	N = 234
Deaths, n (%)	142 (60.7%)	157 (67.1%)
Median, months (95% CI)[d]	24.5 (19.5, 28.9)	23.1 (19.6, 25.5)
Hazard ratio (95% CI)[b]	0.91 (0.72, 1.14)	
P-value[c]	0.20	

Abbreviations: CI, confidence interval; NE, not estimable; BICR, blinded independent central review; PCWG3, prostate cancer working group 3; RECIST, response evaluation criteria in solid tumors.

[a]By BICR per PCWG3 criteria. Based on data cut-off (DCO) date 02-Oct-2022.

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

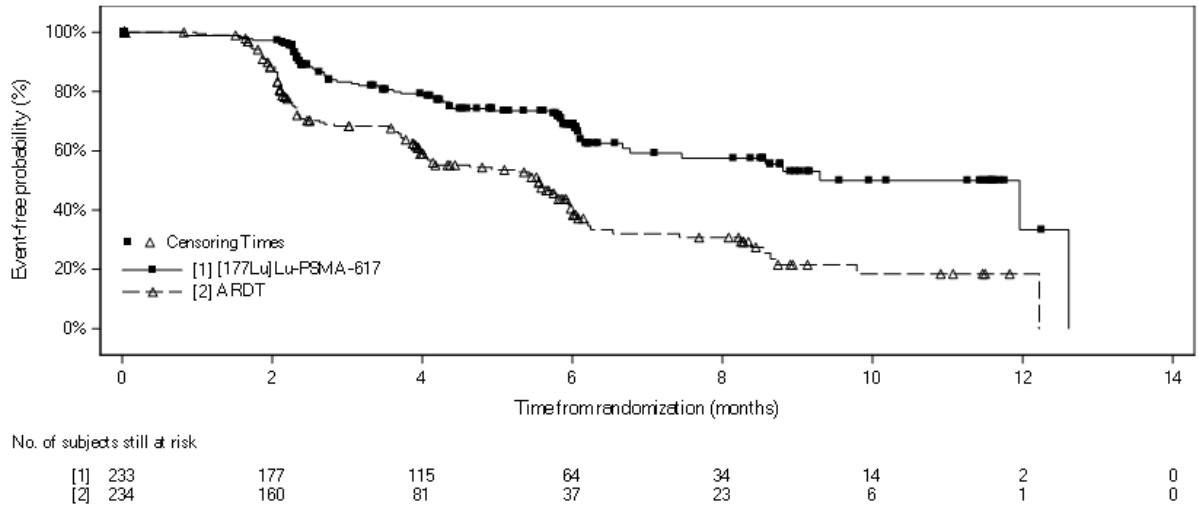
[c]Stratified log-rank test one-sided p-value.

[d]Based on Kaplan-Meier estimate.

[e]Median from third interim OS analysis based on 468 patients (234 Pluvicto arm, 234 control arm). Compared to the primary analysis, the median study duration from randomisation to DCO increased from 7.3 months to 24.1 months.

[f]DCO date: 01-Jan-2025.

Figure 1 Kaplan-Meier plot of BICR-assessed radiographic progression-free survival (rPFS) in PSMAfore



Stratified log-rank test and stratified Cox model using strata per Interactive Response Technology (IRT) defined by setting of prior ARPI use and by symptomatology.
n/N: Number of events/number of patients in treatment arm.

VISION: PSMA-positive mCRPC previously treated with ARPI therapy and taxane-based chemotherapy

The efficacy of PLUVICTO in patients with progressive, PSMA-positive mCRPC previously treated with ARPI therapy and taxane-based chemotherapy 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).

Eligible patients were required to maintain castrate levels of serum/plasma testosterone by either medical castration or prior orchiectomy. Eligible patients were also 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 PSMA-positive mCRPC defined as having at least one tumour lesion with gallium (^{68}Ga) gozetotide uptake greater than in normal liver. Patients were considered ineligible if any one lesion larger than size criteria [organs ≥ 1 cm in short axis, lymph nodes ≥ 2.5 cm in short axis, bones (soft tissue component) ≥ 1 cm in short axis] had gallium (^{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) as determined by blinded independent central review (BICR) per PCWG3 criteria. An additional secondary efficacy endpoint was overall response rate (ORR) as determined 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) ≤ 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 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 6 and Figures 2 and 3. 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 6 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.*

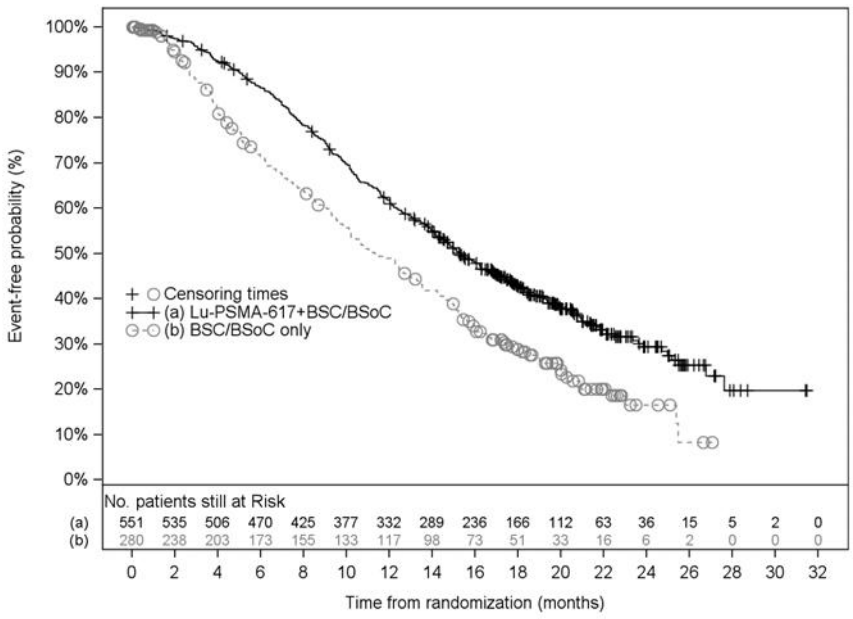
[e]*By BICR per RECIST v1.1.*

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

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

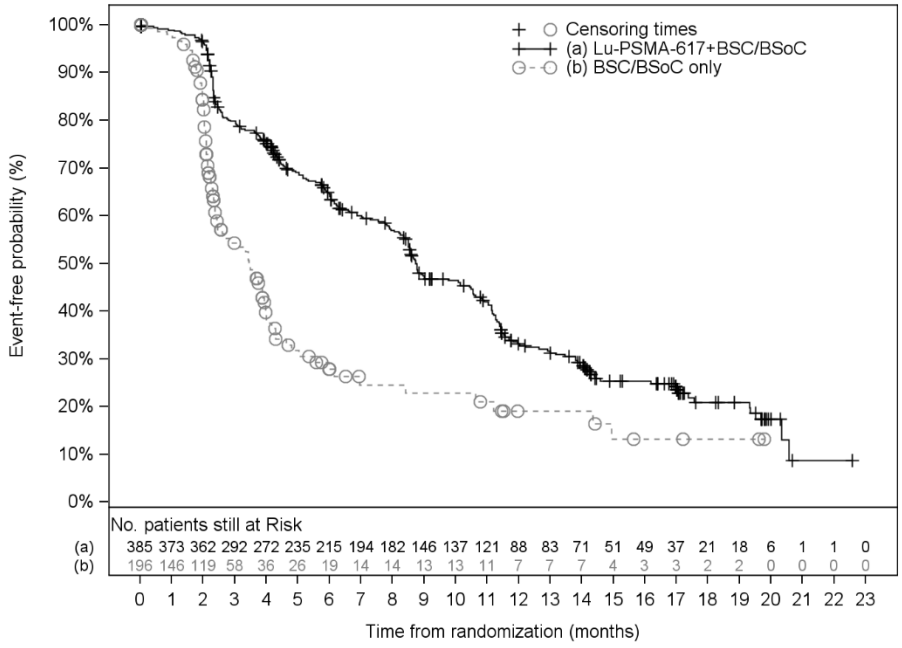
[h]*Median DOR in the BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST v1.1 radiographic progression or death.*

Figure 2 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 3 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 at the recommended dose 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%).

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 227 patients randomised to the PLUVICTO arm who received at least one dose of PLUVICTO in the PSMAfore study, 177 patients (78%) were 65 years or older and 83 patients (37%) were 75 years or older.

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.

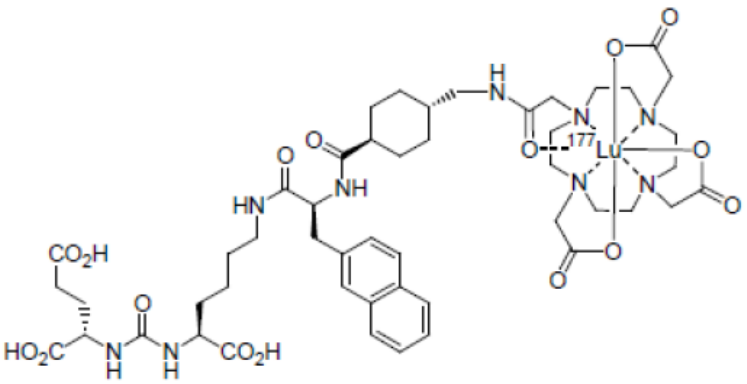
Disposal of any unused product or waste must be in compliance with institutional guidelines developed in accordance with the Federal Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) code of practice and the relevant state or territory regulations.

Lutetium-177 for PLUVICTO is prepared using a stable nuclide 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
ABN 18 004 244 160
Level 25, Victoria Cross Tower
155 Miller Street
North Sydney NSW 2060
Telephone: 1800 671 203
Website: www.novartis.com.au

® = Registered Trademark.

9 DATE OF FIRST APPROVAL

17 July 2024

10 DATE OF REVISION

7 July 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Correction to radiation dosimetry unit of measurement for VISION sub-study in Table 2 (Estimated radiation absorbed dose).
8	Update to Sponsor address

Internal document code:
plu070726i is based on CDS dated 07 April 2025