swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Pluvicto and Pluvicto CA

International non-proprietary name: lutetium(177-Lu) vipivotide tetraxetan / lutetium(177-Lu(CA)) vipivotide tetraxetan

Pharmaceutical form:	solution for injection/infusion
Dosage strength(s):	Pluvicto/Pluvicto CA 1000 MBq/ml
Route(s) of administration:	intravenous
Marketing authorisation holder:	Novartis Pharma Schweiz AG
Marketing authorisation no.:	68684 and 69027
Decision and decision date:	extension of therapeutic indication approved on 21.04.2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
AR	Androgen receptor
ARPI	Androgen receptor pathway inhibitor
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BICR	Blinded independent central review
BRCA	Breast Cancer gene
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HRR	Homologous recombination repair
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
mCRPC	Metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone-sensitive prostate cancer
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PARP	Poly (adenosine diphosphate-ribose) polymerase
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival

PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSMA	Prostate-specific membrane antigen
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Diagnostic or therapeutic radiopharmaceutical
This application for a diagnostic radiopharmaceutical / therapeutic radiopharmaceutical has been reviewed by Swissmedic and the Expert Commission for Radiopharmaceuticals.

2.2 Indication and dosage

2.2.1 Requested indication

The applied text is highlighted in violet:

Pluvicto/Pluvicto CA is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibitor (ARPI) therapy ~~and taxane-based chemotherapy~~, and
• are considered appropriate to delay taxane-based chemotherapy, or
• have received prior taxane-based chemotherapy (see "Properties/Actions").

2.2.2 Approved indication

Pluvicto/Pluvicto CA is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and for whom
• a delay of taxane-based chemotherapy is considered appropriate, or
• who have already received taxane-based chemotherapy.
(see "Warnings and precautions" and the study population in "Properties/Actions").

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	25 June 2025
Formal control completed	27 June 2025
List of Questions (LoQ)	23 September 2025
Response to LoQ	20 November 2025
Preliminary decision	23 January 2026
Response to preliminary decision	13 March 2026
Final decision	21 April 2026
Decision	approval

3 Medical context

Prostate cancer is the most frequently diagnosed cancer in men in Europe and the fifth leading cause of death due to cancer in Europe. In the metastatic setting, patients with hormone-sensitive prostate cancer (mHSPC) remain responsive to androgen deprivation therapy (ADT). ADT combined with an androgen receptor pathway inhibitor (ARPI), such as abiraterone, apalutamide, darolutamide, or enzalutamide, constitutes the standard first-line therapy in this setting.
If disease advances, progression to metastatic castration-resistant prostate cancer (mCRPC) is common. CRPC is defined by disease progression despite castrate testosterone levels (<50 ng/dL), demonstrated by biochemical, radiographic, and/or clinical evidence.

ADT is generally continued after progression, as testosterone suppression remains important despite limited direct evidence from randomised trials. Treatment selection depends on prior therapies, disease characteristics, genomic profile, symptoms, and patient fitness.

For patients without prior ARPI or chemotherapy exposure, which are asymptomatic or mildly symptomatic without visceral metastases, ARPIs such as abiraterone or enzalutamide are commonly preferred. Both agents significantly improve radiographic progression-free survival (rPFS) and overall survival (OS), while delaying the need for chemotherapy.

Docetaxel remains the preferred first chemotherapy option for chemotherapy-naïve patients with aggressive disease, as indicated by high tumour burden, visceral metastases, rapid progression, or poor genomics. Cabazitaxel may be considered in selected older or frail patients but is generally reserved for later-line treatment, post-ARPI and post docetaxel.

PARP inhibitors are available for selected patients, particularly those with BRCA or homologous recombination repair (HRR) alterations. Pembrolizumab may be used in patients with MSI-H/MMR-deficient tumours. 177Lu-PSMA-617 (Pluvicto®) is a treatment option in patients with PSMA-positive mCRPC after prior ARPI and taxane therapy. Radium-223 remains an option for symptomatic bone-predominant disease without visceral metastases.

The widespread use of ARPIs in the mHSPC setting has complicated subsequent mCRPC management. Increasing evidence shows cross-resistance between ARPIs, particularly abiraterone and enzalutamide. Consequently, major guidelines (ESMO, ASCO) generally discourage sequential use of different ARPIs after progression on a prior ARPI, especially in patients with rapid progression or short treatment responses. However, ARPI switching remains common in clinical practice.

4 Quality aspects

Not applicable.

5 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology and method of administration.
No environmental risk is expected by the extension of the indication. This was considered acceptable.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

6 Clinical aspects

6.1 Clinical pharmacology

No new pharmacokinetic or pharmacodynamic data were provided within this submission.

6.2 Dose finding and dose recommendation

No new dose finding data were provided. The requested dose corresponds to the approved dose in patients pretreated with an ARPI and docetaxel.

6.3 Efficacy

The Applicant provided results of the pivotal study PSMAfore, which is an open-label, multi-centre, randomised, phase 3 study comparing ^{177}Lu-PSMA-617 (named AAA617 hereafter) vs. a change of androgen receptor pathway inhibitor (ARPI) in taxane-naïve patients with progressive metastatic castration-resistant prostate cancer (mCRPC).
The study was initiated in 2021, and the results were presented with data cut-offs (DCOs) of 02 Oct 2022 (primary radiographic progression-free survival [rPFS] analysis), 27 Feb 2024 (overall survival [OS] interim analysis 3), and 01 Jan 2025 (final OS analysis).
Eligible patients had PSMA-positive disease, prior progression on one second-generation ARPI, and, based on investigator assessment, were considered appropriate candidates for an alternative ARPI and for deferral of taxane-based chemotherapy.
A total of n=469 patients were randomised 1:1 to either AAA617 (7.4 GBq every 6 weeks for up to 6 cycles) or ARPI switch (abiraterone or enzalutamide).
The primary endpoint was rPFS assessed by blinded independent central review (BICR). OS was the key secondary endpoint. Patients in the ARPI arm were permitted to cross over to AAA617 after confirmed radiographic progression.

Baseline characteristics were well balanced between treatment arms. Median age was approximately 71–72 years, and most patients were White (91%) and had ECOG performance status 0–1. Prior abiraterone was applied in 51-56% of patients and prior enzalutamide in 36-40%. Approximately 81% had received prior ARPI treatment in the CRPC setting.

The trial met its primary endpoint at the primary analysis (DCO 02 Oct 2022) with an estimated 59% reduction in the risk of radiographic progression or death in favour of the AAA617 arm (HR = 0.41 with 95% CI: 0.29, 0.56). Median rPFS was 9.3 months (95% CI: 6.77, NE) in the AAA617 arm and 5.6 months (95% CI: 4.04, 5.95) in the ARPI arm. Updated analysis (DCO 27 Feb 2024) confirmed the effect (HR 0.49, 95% CI: 0.39, 0.61, median rPFS 11.6 months vs. 5.6 months).
Benefits were consistent across major subgroups, including patients previously treated with either abiraterone or enzalutamide.

The final OS data (DCO 01 Jan 2025) with 60.7% OS events in the AAA617 arm and 67.1% in the ARPI arm showed a median OS of 24.5 months (95% CI 19.55, 28.94) in the AAA617 arm and of 23.1 months (95% CI 19.61, 25.53) in the ARPI arm (HR 0.91, 95%CI 0.72, 1.14; one-sided p-value 0.20). Interpretation of OS was complicated by a high crossover rate, with 60% of patients in the ARPI arm later receiving AAA617.

Compared with ARPI switching, AAA617 showed a higher objective response rate (48.6% vs 13.9%),

delayed deterioration in quality of life (FACT-P HR 0.61), and longer treatment-free intervals after therapy completion. No meaningful difference was observed in time to chemotherapy (HR 1.07).

6.4 Safety

The safety analysis included n=227 patients treated with AAA617 and n=232 patients with ARPI switching. Results were presented with the DCO of 27 Feb 2024. Median treatment exposure at that time was longer with AAA617 (8.4 months) than with ARPI (6.5 months), and most AAA617 patients completed all six planned treatment cycles.

Treatment-emergent adverse events (TEAEs) were common in both arms (98.7% AAA617 vs 97.4% ARPI). However, Grade ≥3 TEAEs were less frequent with AAA617 (35.7%) than with ARPI (48.3%). Similarly, serious adverse events (SAEs) occurred less often with AAA617 (20.3%) compared with ARPI (32.3%).

The most common TEAEs with AAA617 were dry mouth, asthenia, nausea, anaemia, fatigue, constipation, and decreased appetite.
Compared with ARPI, AAA617 was associated more frequently with dry mouth, nausea, anaemia, constipation, diarrhoea, vomiting, and dysgeusia. In contrast, hypertension, hypokalaemia, weight loss and haematuria were reported more frequently in the ARPI arm.

Four patients (1.8%) in the AAA617 arm and 5 patients (2.2%) in the ARPI arm had an SAE with a fatal outcome. Reasons for death were COVID-19 pneumonia, cardiac arrest, intestinal ischaemia, and sepsis in the AAA617 arm, and cardiac arrest, cerebrovascular accident, coma, dyspnoea, and multiple organ dysfunction syndrome in the ARPI arm.

TEAEs leading to treatment discontinuation were reported in 5.7% of patients in the AAA617 arm and in 5.2% of patients in the ARPI arm.

Dry mouth was the most characteristic toxicity of AAA617, defined as a safety topic of interest. It was reported in 60.8% vs. 2.6% in the AAA617 arm vs. the ARPI arm, respectively. The events were mostly low grade (Grade 3 in 0.9%).

The safety update provided with the DCO of 01 Jan 2025 did not identify any new safety signals. One treatment-related fatal event of bone marrow failure was reported during long-term follow-up.

6.5 Final clinical benefit risk assessment

Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease with limited treatment options after progression on androgen receptor pathway inhibitors (ARPIs). Current guidelines generally recommend docetaxel following ARPI failure; however, ARPI switching is common in clinical practice.

The pivotal phase 3 PSMAfore study demonstrated a statistically significant improvement in radiographic progression-free survival (rPFS) with 177Lu-PSMA-617 (AAA617) compared with switching to an alternative ARPI in taxane-naïve, PSMA-positive mCRPC patients previously treated with one ARPI. Benefit was consistent across major subgroups, including prior abiraterone and enzalutamide exposure.
The trial did not demonstrate a statistically significant overall survival (OS) benefit (HR 0.91, 95% CI 0.72-1.14; median OS: 24.5 vs 23.1 months). Interpretation of OS was complicated by a substantial

crossover rate, with approximately 60% of patients randomised to the control arm receiving AAA617 after progression.

The main limitation of study PSMAfore relates to the choice of comparator. At the time of study initiation, ARPI-to-ARPI sequencing was already increasingly discouraged by guidelines due to cross-resistance, while docetaxel would have been considered the preferred next-line treatment. Consequently, the control arm may not fully represent current standard of care for many patients. However, as the study population was specifically limited to patients for whom delaying taxane-based chemotherapy was considered clinically appropriate, the choice of the comparator arm is considered acceptable overall. Patients with an indication for immediate taxane-based chemotherapy were not eligible for inclusion in the study.
However, it remains a limitation of the study that suitability for delaying chemotherapy was based on investigator judgment only without the definition of any objective criteria.

The safety profile of AAA617 was consistent with previous experience and generally manageable. Compared with ARPI switching, fewer Grade ≥3 adverse events and fewer serious adverse events were reported. The most characteristic toxicities were dry mouth and myelosuppression.

The overall benefit-risk balance of AAA617 is considered favourable in the context of the medical need in mCRPC, based on the statistically significant improvement in rPFS, the fixed maximum duration of the treatment, and its acceptable and distinct safety profile.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Pluvicto/Pluvicto CA was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo-pro.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

Pluvicto®/-CA

Composition

Active substances

Pluvicto: Lutetium (^{177}Lu) vipivotide tetraxetan: 1,000 MBq/ml at the date and time of calibration.
Lutetium-177 is produced from ytterbium-176 and is non-carrier added.
Pluvicto CA: Lutetium (^{177}Lu) vipivotide tetraxetan: 1,000 MBq/ml at the date and time of calibration.
Lutetium-177 is produced from lutetium-176 and is carrier-added. The medicinal product contains the impurity lutetium-177m.

Excipients

Acetic acid, sodium acetate (0.41 mg/ml), gentisic acid, sodium ascorbate (50.0 mg/ml), pentetic acid, water for injections.
Each ml of solution contains up to 7.1 mg (0.312 mmol) of sodium.

Specifications

Radiochemical purity: Lutetium (^{177}Lu) vipivotide tetraxetan and (^{177}Lu) vipivotide tetraxetan isomer: ≥95.00%
Radiochemical purity: Free ^{177}Lu + ^{177}Lu-DTPA: ≤5.0%
Radiochemical purity: ^{177}Lu-PSMA-617 fragments: ≤5.0%
Radionuclide purity: Lutetium (^{177}Lu) vipivotide tetraxetan: ≥99.9%

Pharmaceutical form and quantity of active substance per unit

Ready-to-use radiotherapeutic agent for direct administration; 1 ml of solution contains 1,000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.
Sterile, clear, colourless to slightly yellow solution for intravenous injection/infusion with a pH of 4.5-7.0.
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.

Indications/Potential uses

Radiopharmaceutical
Pluvicto/Pluvicto CA is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and for whom

- a delay of taxane-based chemotherapy is considered appropriate,
  or
- who have already received taxane-based chemotherapy.

(see “Warnings and precautions” and the study population in “Properties/Actions”).

Dosage/Administration

The medicinal product is intended exclusively for use in appropriately controlled areas within a hospital or clinic.
Pluvicto/Pluvicto CA must be administered only after diagnosis and in the presence of a Swiss Medical Association (FMH) nuclear medicine physician (or a federally recognised equivalent).

Patient selection

PSMA imaging is required to select PSMA-positive mCRPC patients.

Usual dosage

The recommended Pluvicto/Pluvicto CA dose is 7,400 MBq intravenously every 6 weeks (±1 week) for a maximum of 6 doses or until disease progression or unacceptable toxicity.

Treatment monitoring

Laboratory tests should be performed before and during treatment with Pluvicto/Pluvicto CA.

- 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)

It is recommended to perform these tests at least once within 7 days before administration. It is also recommended to perform these tests 4-6 weeks after the last administration of Pluvicto/Pluvicto CA and then every 2 to 4 months in order to determine any possible delayed-onset adverse effects (see “Adverse effects”). The dosing may have to be modified based on the test results (see *Table 1*).

Dose modification due to adverse effects/interactions

Recommended dose modifications of Pluvicto/Pluvicto CA for adverse drug reactions are provided in *Table 1*. Management of severe or intolerable adverse drug reactions may require temporary dose interruption, dose reduction or permanent discontinuation of treatment with Pluvicto/Pluvicto CA.

If treatment interruption due to an adverse drug reaction persists for longer than 4 weeks, discontinuation of treatment with Pluvicto/Pluvicto CA may be considered. The dose of Pluvicto/Pluvicto CA may be reduced by 20% to 5,900 MBq once; the dose should not be re-escalated. If a patient has further adverse drug reactions that would require an additional dose reduction, treatment with Pluvicto/Pluvicto CA must be discontinued.

Table 1: Recommended dose modifications of Pluvicto/Pluvicto CA for adverse drug reactions

Adverse drug reaction	*Severity*[a]	*Dose modification*
Dry mouth	Grade 3	Reduce Pluvicto/Pluvicto CA dose by 20% to 5,900 MBq.
Gastrointestinal toxicity	Grade ≥3 (not amenable to medical intervention)	Withhold Pluvicto/Pluvicto CA until improvement to grade 2 or baseline. Reduce Pluvicto/Pluvicto CA dose by 20% to 5,900 MBq.
Myelosuppression (anaemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia)	Grade 2	Withhold Pluvicto/Pluvicto CA until improvement to grade 1 or baseline.
	Grade ≥3	Withhold Pluvicto/Pluvicto CA until improvement to grade 1 or baseline. Reduce Pluvicto/Pluvicto CA dose by 20% to 5,900 MBq.
Renal toxicity	Defined as: • Confirmed serum creatinine increase (grade ≥2) • Confirmed CLcr <30 ml/min; calculate using Cockcroft-Gault with current body weight	Withhold Pluvicto/Pluvicto CA until improvement.
	Defined as: • Confirmed ≥40% increase in serum creatinine from baseline *and* • Confirmed >40% decrease from baseline CLcr; calculate using Cockcroft-Gault with current body weight	Withhold Pluvicto/Pluvicto CA until improvement or return to baseline. Reduce Pluvicto/Pluvicto CA dose by 20% to 5,900 MBq.
	Recurrent renal toxicity (grade ≥3)	Permanently discontinue Pluvicto/Pluvicto CA.
Spinal cord compression	Any	Withhold Pluvicto/Pluvicto CA until the compression has been adequately treated and any neurological sequelae have stabilised and ECOG performance status has stabilised.
Fracture in weight-bearing bones	Any	Withhold Pluvicto/Pluvicto CA until the fracture has been adequately stabilised/treated and ECOG performance status has stabilised.

Adverse drug reaction	*Severity*[a]	*Dose modification*
AST or ALT elevation	AST or ALT >20 times ULN in the absence of liver metastases	Permanently discontinue Pluvicto/Pluvicto CA.
Other non-haematological toxicity	Any unacceptable toxicity	Permanently discontinue Pluvicto/Pluvicto CA.
	Any severe adverse drug reaction requiring a treatment delay of >4 weeks.	Permanently discontinue Pluvicto/Pluvicto CA.
	Any grade 3 or 4 recurrent adverse drug reaction or grade 2 persistent and intolerable adverse drug reaction after a dose reduction	Permanently discontinue Pluvicto/Pluvicto CA.
List of 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/Pluvicto CA.*		

Special dosage instructions

Patients with hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment.

Patients with renal impairment

No dose adjustment is recommended for patients with mild (baseline CLcr 60 to 89 ml/min by Cockcroft-Gault) to moderate (CLcr 30 to 59 ml/min) renal impairment. Treatment with Pluvicto/Pluvicto CA is not recommended in patients with severe (CLcr 15 to 29 ml/min) renal impairment or end-stage renal disease as the pharmacokinetic profile and safety of Pluvicto/Pluvicto CA have not been studied in these patients.

Elderly patients

No dose adjustment is recommended in patients aged 65 years and over.

Children and adolescents

The safety and efficacy of Pluvicto/Pluvicto CA in paediatric patients have not been established.

Method of administration

Instructions for administration:
The recommended dose of Pluvicto/Pluvicto CA 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/Pluvicto CA directly from the original container.
Use the syringe method or peristaltic pump method when administering a reduced dose of Pluvicto/Pluvicto CA following a dose modification due to an adverse drug reaction. When using the gravity method to administer a reduced dose, adjust the Pluvicto/Pluvicto CA dose before administration to avoid delivery of an incorrect volume of Pluvicto/Pluvicto CA.
Prior to administration, the intravenous catheter used exclusively for Pluvicto/Pluvicto CA administration must be flushed 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.

Intravenous methods of administration

Instructions for the syringe method

1. Draw off the appropriate volume of Pluvicto/Pluvicto CA solution to deliver the desired radioactivity. Use a disposable syringe with a syringe guard and a sterile, 9 cm long, 18-gauge disposable needle (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/Pluvicto CA solution in the vial.
2. If using a syringe pump, fit the syringe into the shielded pump and connect a 3-way stopcock valve between the syringe and an intravenous catheter primed with 0.9% sterile sodium chloride solution and used for Pluvicto/Pluvicto CA administration to the patient.
3. Administer Pluvicto/Pluvicto CA 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/Pluvicto CA administration to the patient.
4. When the desired Pluvicto/Pluvicto CA 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% sterile sodium chloride solution. Restart the syringe pump.
5. 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

1. Insert a 2.5 cm, 20 gauge needle (short needle) into the Pluvicto/Pluvicto CA vial and connect via a catheter to 500 ml of 0.9% sterile sodium chloride solution (used to transport the Pluvicto/Pluvicto CA solution during the infusion). Ensure that the short needle does not touch the Pluvicto/Pluvicto CA 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/Pluvicto CA vial prior to the initiation of the Pluvicto/Pluvicto CA infusion and do not inject the Pluvicto/Pluvicto CA solution directly into the 0.9% sterile sodium chloride solution.

2. Insert a second, 9 cm, 18 gauge needle (long needle) into the Pluvicto/Pluvicto CA vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto/Pluvicto CA 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/Pluvicto CA infusion into the patient.
3. Use a clamp or infusion pump to regulate the flow of sterile 0.9% sodium chloride solution through the short needle into the Pluvicto/Pluvicto CA vial (the sterile 0.9% sodium chloride solution entering the vial through the short needle will transfer the Pluvicto/Pluvicto CA solution from the vial to the patient via the intravenous catheter connected to the long needle over a total duration of approximately 30 to 40 minutes).
4. During the infusion ensure that the level of solution in the Pluvicto/Pluvicto CA vial remains constant.
5. Disconnect the vial from the long needle and clamp the sterile 0.9% sodium chloride solution once the level of radioactivity is stable for at least five minutes.
6. Follow the infusion with an intravenous flush of ≥10 ml of 0.9% sterile sodium chloride solution through the venous catheter to the patient.

Instructions for the peristaltic pump method

1. Insert a filtered, 2.5 cm, 20 gauge needle (short venting needle) into the Pluvicto/Pluvicto CA vial. Ensure that the short needle does not touch the Pluvicto/Pluvicto CA solution in the vial and do not connect the short needle directly to the patient or to the peristaltic pump.
2. Insert a second, 9 cm, 18 gauge needle (long needle) into the Pluvicto/Pluvicto CA vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto/Pluvicto CA 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.
3. Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic pump following the manufacturer’s instructions.
4. Pre-fill the line by opening the 3-way stopcock valve and pumping the Pluvicto-/Pluvicto CA solution through the tubing until it reaches the exit of the valve.
5. 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.

6. Connect the pre-filled venous catheter to the patient and set the 3-way stopcock valve such that the Pluvicto/Pluvicto CA solution is in line with the peristaltic pump.
7. Infuse an appropriate volume of Pluvicto/Pluvicto CA solution at approximately 25 ml/h to deliver the desired radioactivity.
8. When the desired Pluvicto/Pluvicto CA 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 infusion pump and infuse an intravenous flush of ≥10 ml of 0.9% sterile sodium chloride solution through the venous catheter to the patient.

Radiation exposure

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/Pluvicto CA are shown in *Table 2*. The organs with the highest radiation absorbed doses are the lacrimal glands and salivary glands.
The maximum penetration depth of lutetium-177 in tissue is approximately 2 mm and the mean penetration depth 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 ×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

	Absorbed dose per unit activity (Gy/GBq) (N=29)		*Calculated absorbed dose for 7.4 GBq administration (Gy)*		*Calculated absorbed dose for 6 ×7.4 GBq (44.4 GBq cumulative activity) (Gy)*	
Organ	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
[a] Absorbed dose estimates were calculated using OLINDA v2.2. Values have been calculated based on dosimetry estimates at full precision and rounded to relevant digits.						

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under “Composition”.

Warnings and precautions

Risks from radiation exposure

Pluvicto/Pluvicto CA contributes to the patient’s long-term cumulative radiation exposure. Long-term cumulative radiation exposure can be associated with an increased risk of cancer.
Radiation exposure to patients, medical personnel and other persons should be minimised during and after treatment with Pluvicto/Pluvicto CA consistent with institutional good radioprotection practices, patient management procedures and instructions to the patient for follow-up radiation protection at home.
Patients should be encouraged to drink as much as possible and to void the bladder as often as possible to reduce bladder radiation, especially after high activities, e.g. radionuclide therapy with Pluvicto/Pluvicto CA.
Before the patient is released, the nuclear medicine physician should explain the radioprotection measures to be taken by the patient to minimise radiation exposure to others in line with national, local and institutional procedures and regulations.

Myelosuppression

Pluvicto/Pluvicto CA can cause severe and life-threatening myelosuppression, including anaemia, thrombocytopenia, leukopenia and neutropenia (see section “Adverse effects”).
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 CA.
Treatment with Pluvicto/Pluvicto CA should be temporarily interrupted, the dose reduced or permanently discontinued, and patients should be clinically managed based on the severity of myelosuppression (see “Dosage/Administration”).

Renal toxicity

Pluvicto/Pluvicto CA can cause severe renal toxicity (see section “Adverse effects”).

Patients should be informed that they should remain well hydrated and urinate frequently before and after administration of Pluvicto/Pluvicto CA. Kidney function tests, including serum creatinine and calculated CLcr, should be performed before and during treatment with Pluvicto/Pluvicto CA. Treatment with Pluvicto/Pluvicto CA should be temporarily interrupted, the dose reduced or permanently discontinued based on the severity of renal toxicity (see “Dosage/Administration”). Exposure (AUC) to Pluvicto is expected to increase with the degree of renal impairment (see “Kinetics in specific patient groups”). Patients with mild to moderate renal impairment may be at greater risk of toxicity. Renal function and adverse drug reactions should be frequently monitored in patients with mild to moderate renal impairment (see “Dosage/Administration”).

Repeated administration of Pluvicto in patients after initial therapy

Only limited and primarily retrospective data are available on the re-administration of Pluvicto in patients after initial treatment. Based on these data, no conclusions can be drawn regarding efficacy and safety.

Fertility

Radiation from lutetium (^{177}Lu) vipivotide tetraxetan may potentially have toxic effects on male gonads and spermatogenesis. The recommended cumulative Pluvicto/Pluvicto CA dose of 44,400 MBq results in a radiation absorbed dose to the testes within a range in which infertility may be induced. A genetic consultation is recommended if patients wish to have children after treatment. The possibility of sperm cryopreservation can be discussed as an option with male patients before treatment (see “Pregnancy/Breast-feeding”).

Contraception in males

Male patients are advised not to father a child and to use a condom for sexual intercourse during treatment with Pluvicto/Pluvicto CA and for 14 weeks after the last dose (see “Pregnancy/Breast-feeding”).

Sodium content

This medicinal product contains up to 88.75 mg (3.9 mmol) sodium per vial, equivalent to 4.4% of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

Interactions

Lutetium (^{177}Lu) vipivotide tetraxetan is not expected to have any clinically significant interactions with other medicinal products. No clinical drug interaction studies were 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 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 is not an inhibitor of BCRP, P-gp, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 *in vitro*.

Pregnancy/Breast-feeding

Pluvicto/Pluvicto CA is not intended for use in females.

Women of childbearing potential and men of reproductive potential

Based on its mechanism of action, male patients are advised not to father a child and to use a condom for sexual intercourse during treatment with Pluvicto/Pluvicto CA and for 14 weeks after the last dose.

Pregnancy

No animal studies have been conducted with lutetium (^{177}Lu) vipivotide tetraxetan. However, all radiopharmaceuticals, including Pluvicto/Pluvicto CA, have the potential to cause fetal harm.

Breast-feeding

There are no data on the presence of lutetium (^{177}Lu) vipivotide tetraxetan in human milk or its effects on the breast-fed infant or milk production.

Fertility

No studies were conducted to determine the effects of lutetium (^{177}Lu) vipivotide tetraxetan on fertility. Radiation from 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/Pluvicto CA results in a radiation absorbed dose to the testes within a range in which Pluvicto/Pluvicto CA may cause infertility. A genetic consultation is recommended if patients wish to have children after treatment. The possibility of sperm cryopreservation can be discussed as an option with male patients before treatment (see “Warnings and precautions”).

Effects on ability to drive and use machines

There have been no studies on the effects of this product on the ability to drive or to use machines.

Adverse effects

Unless otherwise stated, the frequency of the listed adverse effects is based on data from the PSMAfore (pre-taxane) and VISION (post-taxane) studies, in which 756 patients received at least one dose of 7,400 MBq Pluvicto as randomised study treatment (the median number of doses was six). The most common side effects are: Fatigue (49.5%), dry mouth (45.8%), nausea (34.8%), anaemia (30.7%), decreased appetite (21.4%) and constipation (20.8%). The most common Grade 3 to 4 side effects are: Anaemia (10.8%), lymphopenia (6.7%), thrombocytopenia (6.5%) and fatigue (5.0%).

Tabulated summary of adverse effects

The adverse effects (*Table 3*) are listed by MedDRA system organ class. Within each system organ class, adverse effects are ranked by frequency, with the most frequent first. In addition, the frequency category for each adverse effect 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[a]

System organ class **Adverse reactions**	**Frequency category**	**All grades** **n (%)**	**Grades 3 to 4[b]** **n (%)**
Infections and infestations			
Oral fungal infection[c]	Common	20 (2.6)	0 (0.0)
Blood and lymphatic system disorders			
Anaemia	Very common	232 (30.7)	82 (10.8)
Thrombocytopenia	Very common	115 (15.2)	49 (6.5)
Leukopenia[d]	Very common	108 (14.3)	27 (3.6)
Lymphopenia	Very common	91 (12.0)	51 (6.7)
Pancytopenia[e]	Common	10 (1.3)	7 (0.9)
Bone marrow failure	Uncommon	1 (0.1)	1 (0.1)
Nervous system disorders			
Dysgeusia[f]	Common	57 (7.5)	0 (0.0)
Headache	Common	56 (7.4)	4 (0.5)
Dizziness	Common	55 (7.3)	5 (0.7)
Eye disorders			
Dry eye	Common	31 (4.1)	0 (0.0)
Ear and labyrinth disorders			
Vertigo	Common	15 (2.0)	0 (0.0)
Gastrointestinal disorders			
Dry mouth[g]	Very common	346 (45.8)	2 (0.3)
Nausea	Very common	263 (34.8)	7 (0.9)

Constipation	Very common	157 (20.8)	7 (0.9)
Diarrhoea	Very common	139 (18.4)	4 (0.5)
Vomiting[h]	Very common	127 (16.8)	5 (0.7)
Abdominal pain[i]	Very common	84 (11.1)	9 (1.2)
Oesophageal disorder[j]	Common	27 (3.6)	2 (0.3)
Stomatitis	Common	12 (1.6)	2 (0.3)

Skin and subcutaneous tissue disorders			
Dry skin[k]	Common	14 (1.9)	0 (0.0)
Renal and urinary disorders			
Urinary tract infection[l]	Very common	76 (10.1)	23 (3.0)
Acute kidney injury[m]	Common	62 (8.2)	20 (2.6)
General disorders and administration site conditions			
Fatigue[n]	Very common	374 (49.5)	38 (5.0)
Decreased appetite	Very common	162 (21.4)	10 (1.3)
Decreased weight	Common	73 (9.7)	3 (0.4)
Peripheral oedema[o]	Common	72 (9.5)	2 (0.3)
Pyrexia	Common	43 (5.7)	3 (0.4)

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

[b] Includes only Grade 3 to 4 adverse effects, with the exception of pancytopenia and bone marrow failure. Grade 5 (fatal) pancytopenia was reported in 2 patients who received Pluvicto. Grade 5 (fatal) bone marrow failure was reported in 1 patient who received Pluvicto.

[c] Oral fungal infection includes oral candidiasis, Candida infection, oral fungal infection, oropharyngeal fungal infection, oropharyngeal candidiasis and tongue fungal infection.

[d] Leukopenia includes leukopenia and neutropenia.

[e] Pancytopenia includes pancytopenia and bicytopenia.

[f] Dysgeusia includes dysgeusia and taste disorder.

[g] Dry mouth includes dry mouth, mucosal dryness, salivary hyposecretion, dry lips and dry throat.

[h] Vomiting includes vomiting and retching.

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

[j] Oesophageal disorders include gastrooesophageal reflux disease, dysphagia, oesophagitis and oesophageal burn.

[k] Dry skin includes dry skin and xeroderma.

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

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

[n] Fatigue includes fatigue and asthenia.

[o] Peripheral oedema includes peripheral oedema and fluid retention.

Description of specific adverse effects and additional information

Myelosuppression

In the PSMAfore study, myelosuppression occurred more frequently in patients who received Pluvicto (N = 227) than in patients who switched to an alternative ARPI treatment (N = 232) (all grades/Grade ≥3): Anaemia (27.3%/6.2%) versus (19.4%/6.9%); thrombocytopenia (7.9%/2.2%) versus (3.0%/0.9%); neutropenia (5.7%/1.3%) versus (0.9%/0.4%); leukopenia (2.2%/0.9%) versus (0%/0%); lymphopenia (1.8%/0.4%) versus (0%/0%); and pancytopenia (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.
Myelosuppressive adverse effects that led to permanent discontinuation in ≥0.5% of patients treated with Pluvicto were: Thrombocytopenia (1.3%). Myelosuppressive side effects that led to dose interruptions/reductions in ≥0.5% of patients treated with Pluvicto were: Anaemia (1.8%/0.4%) and neutropenia (0.9%/0.4%).

In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus BSoC than in patients who received BSoC alone (all grades/grade ≥3): anaemia (31.9%/12.9%) versus (13.2%/4.9%); thrombocytopenia (17.2%/7.9%) versus (4.4%/1.0%); leukopenia (12.5%/2.5%) versus (2.0%/0.5%); lymphopenia (14.2%/7.8%) versus (3.9%/0.5%); neutropenia (8.5%/3.4%) versus (1.5%/0.5%); pancytopenia (1.5%/1.1%) versus (0%/0%), including two fatal cases of pancytopenia in patients who received Pluvicto plus BSoC; bicytopenia (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 receiving Pluvicto plus BSoC.
Myelosuppression adverse effects that led to permanent discontinuation of treatment in ≥0.5% of patients who received Pluvicto plus BSoC included: anaemia (2.8%), thrombocytopenia (2.8%), leukopenia (1.3%), neutropenia (0.8%) and pancytopenia (0.6%). Myelosuppression adverse drug reactions that led to dose interruptions/dose reductions in ≥0.5% of patients who received Pluvicto plus BSoC included: anaemia (5.1%/1.3%), thrombocytopenia (3.6%/1.9%), leukopenia (1.5%/0.6%) and neutropenia (0.8%/0.6%).

Renal toxicity

In the PSMAfore study, renal toxicity was comparable between patients who received Pluvicto and those who switched to ARPI treatment (all grades/Grade 3 to 4): Increased blood creatinine (4.4%/0%) versus (3.0%/0%); acute renal failure (1.8%/0.9%) versus (4.3%/2.6%); renal impairment (0.9%/0.4%) versus (1.3%/0.9%); and increased blood urea (0.4%/0%) versus (0%/0%).
In patients who received Pluvicto, no renal side effects led to permanent discontinuation of treatment. Renal disorders that led to treatment interruptions or dose reductions in ≥0.4% of patients treated with

Pluvicto were: Increased blood creatinine (0.4%/0%), renal colic (0.4%/0%) and renal impairment (0.4%/0%).

In the VISION study, renal toxicity occurred more frequently in patients who received Pluvicto plus BSoC than in patients who received BSoC alone (all grades/grades 3 to 4): increased blood creatinine (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 increased blood urea (0.2%/0%) versus (0%/0%).
Adverse drug reactions that led to permanent discontinuation in ≥0.2% of patients who received Pluvicto plus BSoC included: increased blood creatinine (0.2%). Adverse drug reactions that led to dose interruptions/dose reductions in ≥0.2% of patients who received Pluvicto plus BSoC included: increased blood creatinine (0.2%/0.4%) and acute kidney injury (0.2%/0%).

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. On average Pluvicto did not cause any major (>20 ms) QT/QTc interval prolongation. Potential effects of supratherapeutic doses were not investigated.

Second primary malignancies

Exposure to ionising radiation is linked with the development of cancer and potential genomic damage. The radiation dose resulting from therapeutic exposure may result in a higher incidence of cancer and mutations. In all cases, it must be ensured that the risks of the radiation exposure are less than those of the disease itself. As Pluvicto/Pluvicto CA contributes to a patient's long-term radiation exposure, which is associated with an increased risk of cancer (see "Warnings and precautions"), a potential risk of second primary malignancies cannot be ruled out for radiopharmaceuticals such as Pluvicto/Pluvicto CA. At the time of the VISION primary analysis (cut-off date 27 January 2021), cases of squamous cell carcinoma (4 patients; 0.8%), basal cell carcinoma, malignant melanoma and squamous cell carcinoma of the skin (1 patient each; 0.2% each) were reported in patients who received Pluvicto and BSoC. In the PSMAfore study, cases of basal cell carcinoma, colon adenocarcinoma, clear cell renal cell carcinoma and renal cell carcinoma (each in 1 patient; each 0.4%) were reported in patients who received Pluvicto.

Reporting suspected adverse effects after marketing authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal ElViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

In the event of administration of a radiation overdose with Pluvicto/Pluvicto CA, the radiation absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide

from the body by forced diuresis and frequent bladder voiding as well as increased hydration. It might be helpful to estimate the effective radiation dose that was applied.

Properties/Actions

ATC code

V10XX05
Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals

Physical characteristics

Lutetium-177 decays to stable hafnium-177 with a half-life of 6,647 days and primarily emits β-radiation with a maximum energy of 498 keV (79%) and photon radiation (γ) of 208 keV (11%) and 113 keV (6.4%).
The main radiations of lutetium-177 are detailed in *Table 4*.

Table 4: Lutetium-177 main radiation types

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

Table 5 provides an overview of the radioactive decay properties of lutetium-177.

Table 5: Physical decay chart: Lutetium-177 physical half-life = 6.647 days

Hours	*Fraction remaining*
0	1.000
1	0.996
2	0.991
5	0.979

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

Mechanism of action

The active moiety of Pluvicto/Pluvicto CA is the radionuclide lutetium-177, which is linked to a targeting moiety that binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of Pluvicto/Pluvicto CA 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.

Pharmacodynamics

There are no data regarding lutetium (^{177}Lu) vipivotide tetraxetan exposure-efficacy relationships and the time course of pharmacodynamic response.
There are only limited data regarding lutetium (^{177}Lu) vipivotide tetraxetan exposure-safety relationships and the time course of pharmacodynamic response.
Vipivotide tetraxetan does not exhibit any pharmacodynamic activity.

Clinical efficacy

PSMAfore study: 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 demonstrated in the PSMAfore study, a randomised, multicentre, 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 to switch to an alternative ARPI (N=234).
Patients maintained castration-equivalent serum/plasma testosterone levels either through medical castration or prior orchiectomy. Eligible patients were those suitable for switching to an alternative ARPI, with PSMA-positive mCRPC, an Eastern Cooperative Oncology Group (ECOG) performance

status (PS) of 0 to 1, at least one metastatic lesion on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic and haematological function. Patients who, in the opinion of the investigator, were considered suitable for taxane-based chemotherapy based on their risk profile were excluded from study participation.
Eligible patients were required to have experienced disease progression on only one prior ARPI therapy (abiraterone acetate, enzalutamide, darolutamide or apalutamide). Prior taxane-based chemotherapy was permitted only if administered as part of adjuvant or neoadjuvant therapy more than 12 months prior to study entry. 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 gallium (^{68}Ga) gozetotide positron emission tomography (PET) to assess PSMA expression in lesions defined by central review criteria. Eligible patients were required to have PSMA-positive mCRPC, defined as at least one tumour lesion with gallium (^{68}Ga) gozetotide uptake greater than that of normal liver tissue. Patients were not eligible for inclusion if an intraprostatic lesion or at least 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] showed gallium (^{68}Ga) gozetotide uptake that was less than or equal to uptake in normal liver tissue. Supportive care administered at the discretion of the investigator included: Medicinal products for the treatment of complications related to bone metastases, including zoledronic acid, denosumab or other bisphosphonates; androgen deprivation therapy (ADT); palliative radiotherapy. Patients randomised to the ARPI comparator arm were permitted, after radiological disease progression confirmed by blinded independent central review (BICR), either to cross over to the Pluvicto arm or to receive another therapy at the discretion of the investigator.
The primary efficacy endpoint was radiographic progression-free survival (rPFS) as assessed by blinded independent central review (BICR) as per Prostate Cancer Working Group 3 (PCWG3) criteria. The key secondary efficacy endpoint was overall survival (OS).

Demographic characteristics and baseline disease characteristics were balanced between the treatment arms. The median age was 72 years (range: 43 to 94 years); 91% were White; 2.6% Black or African American; 0.6% Asian; 99% had an ECOG PS of 0–1. Randomisation was stratified by disease stage at the time of prior ARPI use (castration-resistant prostate cancer (CRPC) versus hormone-sensitive prostate cancer (HSPC)) and by symptom status (asymptomatic or mildly symptomatic versus symptomatic) (score > 3 on item 3 of the Brief Pain Inventory-Short Form (BPI-SF)).

Efficacy results from the PSMAfore study are shown in *Table 6*. Of the patients randomised to receive a change in ARPI therapy, 141 patients (60%) crossed over to Pluvicto following BICR-confirmed radiological disease progression.

Table 6: Efficacy results in PSMAfore

Efficacy parameters	*Pluvicto*	*Switch to ARPI therapy*
Primary efficacy endpoint		
Radiographic progression-free survival (rPFS)[a]	N=233	N=234
Events (progression or death), n (%)	60 (25.8%)	106 (45.3%)
Radiographic progression, 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)
Key secondary efficacy endpoint		
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;
[a]Assessed by means of BICR according to PCWG3 criteria. Based on the data cutoff date of 2 October 2022.
[b]Hazard ratio based on the stratified Cox proportional hazards (Cox-PH) model. A hazard ratio < 1 favours Pluvicto.
[c]One-sided p-value of the stratified log-rank test.
[d]Based on a Kaplan-Meier estimate.
[f]DCO, data cutoff date: 01 January 2025, based on the ITT population.

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

The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC who had previously been treated with ARPI therapy and taxane-based chemotherapy was demonstrated in the VISION study, a randomised, multicentre, open-label phase III study. Eight hundred and thirty-one (N=831) patients were randomised (2:1) to receive either 7,400 MBq of Pluvicto every 6 weeks for 4 to 6 doses plus BSoC (N=551) or BSoC alone (N=280). Patients who had received 4 doses of Pluvicto were

reassessed for evidence of a response, signs of residual disease, and tolerability and could receive up to 2 additional doses at the physician's discretion.

Patients were required to have serum/plasma testosterone levels below the castration threshold due to either through medical castration or prior orchiectomy. Eligible patients were required to have PSMA-positive mCRPC, an ECOG performance status of 0 to 2, at least one metastatic lesion on CT, MRI or bone scan imaging, and adequate renal, hepatic and haematological function.

Progressive disease was determined using either serum PSA or soft-tissue or bone disease progression.

Eligible patients were also required to have received at least one ARPI, such as abiraterone acetate or enzalutamide, and 1 or 2 prior taxane-based chemotherapy regimens (with a regimen defined as minimum 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 gallium (^{68}Ga) gozetotide positron emission tomography (PET) to evaluate PSMA expression in lesions defined by central read criteria.

Eligible patients were required to have PSMA-positive mCRPC, i.e. at least one tumour lesion with gallium (^{68}Ga) gozetotide uptake greater than in normal liver. Patients were considered ineligible if any 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 such as pain medications, hydration, blood transfusions, etc.; ketoconazole; radiotherapy for localised prostate cancer; bone-targeting agents; androgen deprivation therapy (ADT); ARPIs. BSoC excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes and hemi-body radiotherapy.

The alternative primary efficacy endpoints were overall survival (OS) and radiographical progression-free survival (rPFS), as assessed by BICR as per PCWG3 criteria. An additional secondary efficacy endpoint was overall response rate (ORR) by BICR as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

Demographic characteristics and baseline disease state were balanced between the treatment arms. The mean age was 71 years (range: 40 to 94 years); 86.8% were White; 6.6% Black or African American; 2.4% Asian; 92.4% had an ECOG PS of 0–1; 7.6% had an ECOG PS of 2. Randomisation was stratified according to lactate dehydrogenase (LDH ≤260 IU/L vs >260 IU/L), presence of liver metastases (yes vs no), ECOG PS score (0 or 1 vs 2), and intake of an ARPI 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. Based on the available data, no statement can be made on the efficacy of Pluvicto compared to taxane re-exposure in patients who had previously received only one taxane-based chemotherapy and would have been

eligible for chemotherapy as chemotherapy was not a component of the comparator arm. At randomisation, 51.3% of patients had received one prior ARPI, 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 7*. The final analyses of OS and rPFS were event-driven and conducted after the occurrence of 530 deaths and 347 events, respectively. Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring owing to early study discontinuation in the control arm.

Table 7: Efficacy results in VISION

Efficacy parameters	*Pluvicto plus BSoC*	*BSoC*
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	
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)[d,e]	95 (29.8%)	2 (1.7%)
p-value[f]	<0.001	

List of abbreviations: BSoC: best standard of care: CI: confidence interval;

[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 RECIST v1.1.

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

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

Pharmacokinetics

The pharmacokinetics of lutetium (^{177}Lu) vipivotide tetraxetan have been characterised in 30 patients in the phase III VISION sub-study. Unless stated otherwise, the pharmacokinetics of lutetium (^{177}Lu) vipivotide tetraxetan are given as the geometric mean (geometric mean coefficient of variation).

Absorption

Pluvicto/Pluvicto CA is administered intravenously and is immediately and completely bioavailable. The blood exposure (area under the curve [AUC_{inf}]) for lutetium (^{177}Lu) vipivotide tetraxetan is 52.3 ng·h/ml (31.4%) and the maximum blood concentration (C_{max}) is 6.58 ng/ml (43.5%) at the recommended dose.

Distribution

The volume of distribution for lutetium (^{177}Lu) vipivotide tetraxetan is 123 l (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 the lacrimal glands, salivary glands, kidneys, urinary bladder wall, liver, small intestine and large intestine (left and right colon).

Metabolism

The metabolism of lutetium (^{177}Lu) vipivotide tetraxetan in humans has not been systematically investigated. Based on available findings, primarily unmetabolised lutetium (^{177}Lu) vipivotide tetraxetan was excreted in the urine and only small amounts of renally excreted metabolites are present in the systemic circulation.

Elimination

The terminal elimination half-life ($T_{½}$) of lutetium (^{177}Lu) vipivotide tetraxetan is 41.6 hours (68.8%) and the clearance (CL) is 2.04 l/h (31.5%).
Lutetium (^{177}Lu) vipivotide tetraxetan is primarily eliminated renally.

Pharmacokinetics in special populations

Renal impairment

Lutetium (^{177}Lu) vipivotide tetraxetan exposure (AUC) increased with decreasing creatinine clearance (CLcr). The pharmacokinetics and safety of Pluvicto/Pluvicto CA have not been studied in patients with severe (CLcr 15 to 29 ml/min) renal impairment or end-stage renal disease.

Hepatic impairment

Pluvicto has not been studied in patients with moderate or severe hepatic impairment.

Elderly patients (65 years of age or over)

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 aged 65 or older and 83 patients (37%) were aged 75 or older.
Of the 529 patients who received at least one dose of Pluvicto plus BSoC in the VISION study, 387 patients (73%) were aged 65 years or older and 143 patients (27%) were aged 75 years or older.
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)

Preclinical data

Safety pharmacology

No toxicological effects were observed in safety pharmacology or single-dose toxicity studies in rats and minipigs administered a non-radioactive formulation containing unlabelled vipivotide tetraxetan and lutetium (^{175}Lu) vipivotide tetraxetan or in repeat-dose toxicity studies in rats administered unlabelled vipivotide tetraxetan.

Carcinogenicity and mutagenicity

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

Reproductive toxicity

No reproductive toxicity studies have been performed with lutetium (^{177}Lu) vipivotide tetraxetan.

Other information

Incompatibilities

This medicinal product may only be mixed with the medicinal products specified under “Dosage/Administration”.

Shelf life

This medicinal product may be stored for a maximum of 120 hours (5 days) from the date and time of calibration.
Do not use Pluvicto/Pluvicto CA after the expiry date and time stated on the label after “EXP”.

Special precautions for storage

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

Storage of radiopharmaceuticals must be in accordance with national regulations on radioactive products.

Instructions for use and handling/radiation protection

The use of radioactive materials in humans is regulated by the Swiss Radiological Protection Ordinance. Prior handling authorisation from the Swiss Federal Office of Public Health is required for the use of radioactive materials.
Radiopharmaceuticals must be received, handled and administered only by authorised persons in specially designated clinical settings. Their receipt, storage, use, transport and disposal are subject to the provisions of relevant radiation protection laws and/or the appropriate licences of the competent regulatory authorities.
Pluvicto/Pluvicto CA is a radiopharmaceutical and should be handled using appropriate safety measures to minimise radiation exposure (see “Warnings and precautions”). Waterproof gloves and effective radiation protection should be used when handling Pluvicto/Pluvicto CA.
Use aseptic technique and radiation shielding when handling or administering Pluvicto/Pluvicto CA, using tongs as needed to minimise radiation exposure.
Visually inspect the product under a shielded screen for particulates and discolouration prior to administration. Discard the vial if particulates and/or discolouration are present. Pluvicto/Pluvicto CA is a ready-to-use solution for single use. The Pluvicto/Pluvicto CA solution must not be injected directly into any other intravenous solution.
Confirm the amount of radioactivity of Pluvicto/Pluvicto CA delivered to the patient with an appropriately calibrated dose calibrator prior to and after each Pluvicto/Pluvicto CA administration.
The administration of Pluvicto/Pluvicto CA may result in significant environmental hazard.
This may be of concern to the immediate family of treated individuals or the general public, depending on the level of radioactivity administered. Suitable precautions in accordance with national regulations must be taken concerning the radioactivity eliminated by patients in order to avoid any contamination.

Waste disposal

Radioactive unused products or waste materials may only be disposed of as per prevailing Swiss radiation protection regulations.

Pluvicto

Lutetium-177 for Pluvicto is produced using the stable nuclide ytterbium-176 (non-carrier added).

Pluvicto CA

Lutetium-177 for Pluvicto CA is produced using the stable isotope lutetium-176 («carrier added») and, due to the presence of metastable lutetium-177 (^{177m}Lu), requires special attention in terms of waste disposal.

Marketing authorisation number

68684, 69027 (Swissmedic)

Pack sizes

Clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal.
Each vial contains a solution volume ranging 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. [A]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch; domicile: 6343 Rotkreuz

Information last revised

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