swissmedic

Date: 3 March 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Pluvicto

International non-proprietary name: lutetium(^{177}Lu) vipivotide tetraxetan

Lutetium-177 is produced from ytterbium-176 and is non-carrier added.

Pharmaceutical form: solution for injection/infusion

Dosage strength(s): 1000 MBq/ml

Route(s) of administration: intravenous

Marketing authorisation holder: Advanced Accelerator Applications International SA

Marketing authorisation no.: 68684

Decision and decision date: approved on 24 February 2023

Note:

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

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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
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body mass index
BRCA	Breast cancer
BSC	Best Supportive Care
BSoC	Best Standard of Care
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CRPC	Castration-resistant prostate cancer
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interaction
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
ESI-MS	Electrospray ionisation
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration (USA)
GC	Gas chromatography
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MCBS	Magnitude of Clinical Benefit Scale
mCRPC	Metastatic castration-resistant prostate cancer
mHNPC	Metastatic hormone-naïve prostate cancer
Min	Minimum
MRHD	Maximum recommended human dose
MS	Mass spectrometry
MTD	Maximum tolerated dose
N/A	Not applicable
NAAD	Novel Androgen Axis Drug
NCCN	National Comprehensive Cancer Network

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NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PC	Prostate cancer
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Pharmacodynamics
PFS	Progression-free survival
PFS-FAS	Progression-free survival - full analysis set
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PSP	Pediatric study plan (US FDA)
rPFS	Radiographic progression-free survival
RMP	Risk management plan
SAE	Serious adverse event
SSE	Symptomatic skeletal 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)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for lutetium(^{177}Lu) vipivotide tetraxetan in the above-mentioned medicinal product.
Lutetium-177 is produced from ytterbium-176 and is non-carrier added.

2.2 Indication and dosage

2.2.1 Requested indication

Therapeutic radiopharmaceutical

^{177}Lu-PSMA-617 {Tradename} 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 (AR)-inhibition and taxane-based chemotherapy or are medically ineligible for taxanes.

2.2.2 Approved indication

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 taxane-based chemotherapy (see "Properties/Actions").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The standard dosage for adults is 7400 MBq every 6 weeks.
No dose adjustment is necessary for elderly persons (> 65 years).
Depending on the type and severity of the side effects, the dose may be reduced by 20% or the interval of intake may be prolonged. In the worst case, the therapy must be discontinued.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	4 July 2022
Formal control completed	15 July 2022
Preliminary decision	30 September 2022
Response to preliminary decision	23 November 2022
Final decision	24 February 2023
Decision	approval

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3 Medical context

Prostate cancer (PC) is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020 accounting for 15% of all cancers diagnosed.

In Switzerland, in 2020, PC was by far the most commonly diagnosed cancer in men, accounting for about 21% of all new cases, and almost 1,300 men died from PC, which corresponds to about 7% of all cancer deaths, ranking PC as the second most frequent cause of cancer deaths in Switzerland. For patients diagnosed with metastatic disease, the overall 5-year survival rate is about 30 to 35%. However, the 5-year survival is substantially lower in patients with mCRPC, 11% in asymptomatic/minimally symptomatic cases, 5% in symptomatic cases but not treated/progressed on chemotherapy, and 2% in mCRPC that has progressed on/after first-line chemotherapy.

Androgen deprivation therapy (ADT) is the gold standard for the treatment of metastatic prostate cancer (mPC)." The goal is to lower testosterone to a castrate level (<1.7 nmol/L; <50 ng/dL). In patients with hormone-naïve mPC (mHNPC), ADT can be combined with the chemotherapeutic agent docetaxel or with Novel Androgen Axis Drugs (NAADs), such as abiraterone acetate (inhibitor of CYP17, a critical enzyme in androgen biosynthesis), apalutamide and enzalutamide (second-generation anti-androgens).

Rising PSA after initial response to ADT generally suggests disease progression and, in the presence of castrate levels of testosterone, indicates castration-resistant PC (CRPC). According to the definition of the European Society for Medical Oncology (ESMO), two out of the three following criteria need to be met for the diagnosis of disease progression: PSA progression, radiographic progression and clinical progression.

ADT is generally continued in most men with CRPC in conjunction with secondary therapies after progression on the initial ADT regimen. Treatment modalities for mCRPC patients include chemotherapy agents, such as docetaxel and cabazitaxel, NAADs, radiotherapy with radium-223 (for patients with bone metastases only), and immunotherapeutic approaches using sipuleucel-T (not licensed in Switzerland). For BRCA-mutated mCRPC, rucaparib (not licensed in Switzerland) and olaparib are treatment options after failure of NAADs.

No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e. hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist. However, clinical parameters of aggressive disease like a short response to mHNPC therapy, high tumour burden, rapid pace of progression, visceral metastases, poor genomics (p53, RB, MYC) should rather prompt the use of chemotherapy or clinical trials than e.g. NAADs. Generally, patients with mCRPC who are candidates for cytotoxic therapy should be offered docetaxel.

For most men who have progressed while receiving a docetaxel-based regimen for CRPC and who can tolerate it, cabazitaxel is suggested. Abiraterone or enzalutamide [ESMO-MCBS v1.1 scores: 4] are recommended for asymptomatic / mildly symptomatic men with chemotherapy-naïve mCRPC.

In patients with prior docetaxel and prior antiandrogen therapy, cabazitaxel or docetaxel rechallenge are the preferred treatment options.

^{177}Lu-PSMA-617 is a radionuclide therapy consisting of the radioactive nuclide ^{177}Lu and the ligand vipivotide tetraxetan (INN of PSMA-617), which consists of the vipivotide (binding site for the prostate-specific membrane antigen [PSMA]) and the tetraxetan, which is the binding site for the radioactive nuclide. ^{177}Lu-PSMA-617 delivers therapeutic radiation to prostate cancer cells via its binding to PSMA.

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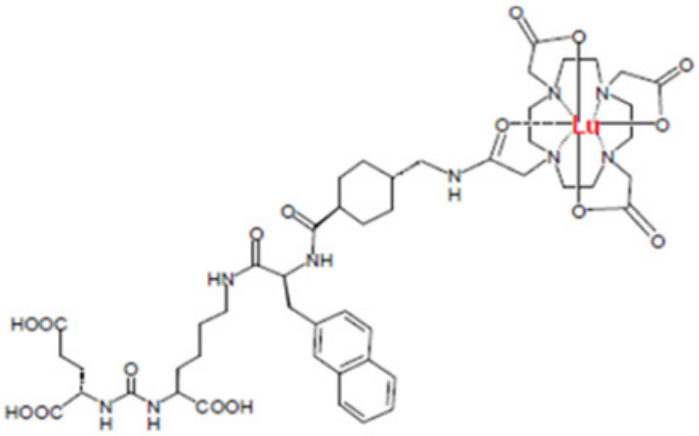
4 Quality aspects

4.1 Drug substance

Lutetium (^{177}Lu) vipivotide tetraxetan is a new therapeutic radiopharmaceutical drug substance. ^{177}Lu-PSMA-617 is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC).

Molecular structure of the Drug Substance:



INN: lutetium (^{177}Lu) vipivotide tetraxetan

Drug Substance Ligand

INN: vipivotide tetraxetan

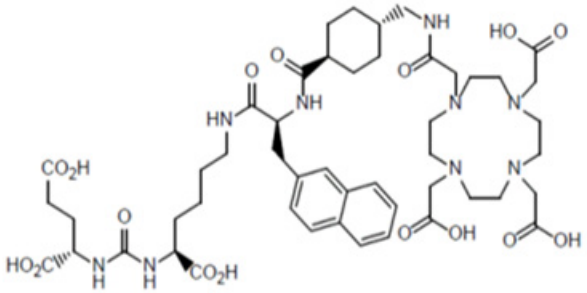
Chemical name (IUPAC): (3*S*,10*S*,14*S*)-3-[(Naphthalen-2-yl)methyl]-1,4,12-trioxo-1-[(1*r*,4*S*)-4-({2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetamido}methyl)cyclohexyl]-2,5,11,13-tetraazahexadecane-10,14,16-tricarboxylic acid

Chemical name (CAS): L-Lysine, N^2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N^6-[3-(2-naphthalenyl)-*N*-[[*trans*-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl] cyclohexyl]carbonyl]-L-alanyl]-

Molecular formula: $C_{49}H_{71}N_9O_{16}$

Relative molecular mass: 1042.14

Molecular structure of ligand:



The ligand vipivotide tetraxetan is a white to off-white solid. It is slightly soluble in water.

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Synthesis:

The synthesis of the ligand vipivotide tetraxetan has been adequately described and the process is controlled with appropriate in-process controls and tests for isolated intermediates. The quality of starting materials, reagents, solvents and auxiliary materials used in the manufacturing process of vipivotide tetraxetan is adequately controlled.
The development of the commercial manufacturing process for drug substance followed a systematic approach which has been addressed in suitable detail. A clear overview of batches used in development, toxicological, preclinical and clinical studies, validation and stability has been presented. Full batch analytical data are provided. Changes introduced have been presented in sufficient detail and have been justified. Based on the outcome of development studies, critical process parameters, in-process controls and specifications for raw materials, intermediates and drug substance ligand have been defined.

Structure elucidation:

The structure of vipivotide tetraxetan is supported by the synthetic route and has been fully elucidated using adequate analytical techniques. Enantiomeric purity and isomerisations are sufficiently controlled. Potential impurities have been adequately discussed. Based on a detailed evaluation, the presence of nitrosamines can be excluded.

Specification:

The active substance specification is determined and set based on the intended therapeutic use of the compound, the microdose amount of vipivotide tetraxetan in the maximum daily dose and the synthetic process. In addition, the justifications are based on the applicable regulatory guidelines including the principles of the Ph. Eur. General Monograph 2902, Chemical Precursors for Radiopharmaceutical Preparations and Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

The specification includes tests for appearance, identity by monoisotopic mass, IR, residual solvents (GC), impurities (HPLC), assay (HPLC), enantiomeric Purity (GC-MS), residual solvents (GC), elemental impurities (ICP-MS), water content, amount of filling (HPLC), bacterial endotoxins (LAL) and bioburden (membrane filtration).The reporting threshold and limits for individual and total impurities in vipivotide tetraxetan are as presented in the European Pharmacopoeia General Monograph 2902, Chemical Precursors for Radiopharmaceutical Preparations and considered appropriate.

Analytical Methods:

The analytical methods used have been adequately described in the corresponding Ph. Eur. General Monographs, and non-compendial methods have been appropriately validated in accordance with ICH guidelines. The tests identity (monoisotopic mass by ESI-MS), assay and impurities by HPLC, amount of filling [net peptide] by HPLC, residual solvents by GC, enantiomeric impurities by GC-MS, and water content by GC have been validated in compliance with ICH Q2 and shown to fulfil the respective requirements.
Batch analysis data are provided for a number of batches used in toxicological studies, clinical trials, stability studies and the validation of the intended commercial process. The analytical results are in full compliance with the specified limits and show only little variability with respect to the individual parameters tested, thus demonstrating reliable and reproducible manufacturing with consistent results from batch to batch.

Container-closure system:

The container-closure system for the lyophilised drug substance ligand vipivotide tetraxetan (clear plastic vials with gray stoppers and sealed with aluminium seal and aluminium tear-off cap) is adequately described, and its suitability is assured.

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Stability:

Appropriate stability data have been generated, resulting in a suitable retest period when packaged in the packaging type as described above.

4.2 Drug product

Description and composition:

Clear colourless to slightly yellow solution, free from visible particles, packed in a sterile 30 mL glass vial. The filling volume required for 7.4 GBq ± 10% at the time of administration is calculated for each single dose and can range from 7.5 mL to 12.5 mL.

Pharmaceutical development:

The development of the product has been described, the choice of excipients is justified and their functions explained.

Manufacture:

Two manufacturers of starting material Lu-177 (carrier-added and non-carrier-added) are described.

Specification:

The drug product specifications include tests for appearance, identification by HPLC and UV, pH, chemical purity, bacterial endotoxins, sterility, radiochemical purity, specific activity and radionuclidic purity by gamma-spectrometry. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on an appropriate number of batches. The batch analysis results show that the finished products meet the specifications proposed.

Container closure system:

Sterile 30 mL glass vial with bromobutyl rubber stopper and aluminium cap.

Stability:

Stability studies were carried out for several batches and timepoints after production. All results were within the specifications. The storage condition and expiry date in the information for healthcare professionals are acceptable.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

5.1 Introduction

The investigators prepared a surrogate formulation with the non-radioactive isotope Lu-175 using the same procedure relied upon for the production of ^{177}Lu-PSMA-617. The non-radioactive formulation was used in various nonclinical studies and contained ^{175}Lu-PSMA-617 as well as unlabelled PSMA-617.

5.2 Pharmacology

Experimental *in vitro* data showed that PSMA-617 binds to the prostate cancer cell line LNCaP with an average K_D of 4.7± 0.1 nM. This is comparable to published data. The compound also demonstrated a highly efficient internalisation into PSMA-positive cells. Published *in vivo* studies describe anti-tumour activity of ^{177}Lu-PSMA-617 in murine tumour models for prostate cancer.

The investigations on secondary pharmacology showed no cytotoxicity of ^{175}Lu-PSMA-617 as well as unlabelled PSMA-617 in PSMA-positive as well as PSMA-negative cell lines. The highest concentration tested in this assay was 10 µM, which is approximately 132-fold the theoretical clinical C_{max} of the total PSMA-617 peptide following administration of ^{177}Lu-PSMA-617. At a concentration of 10 µM, ^{175}Lu-PSMA-617 did not interact in binding, enzyme, or uptake assays.

The applicant conducted stand-alone safety pharmacology studies with ^{175}Lu-PSMA-617 for the cardiovascular, central nervous and respiratory systems. No significant effects occurred in the central nervous or respiratory system in rats at the high dose of 1.8 mg/kg. This dose corresponds to a human equivalent dose of 10.8 mg/m^2 and results in a safety margin of 67. In the hERG assay, the formulation analysis revealed that the cells were not exposed at the targeted concentrations lowering the safety margin to 15. The ECG investigations in minipigs did not identify any safety concern. The investigations performed in the toxicity study also confirmed the lack of a signal.

5.3 Pharmacokinetics

The applicant provided adequate validation studies to determine ^{175}Lu-PSMA-617 in rat and minipig plasma. Biodistribution studies showed that ^{177}Lu-PSMA-617 was non-specifically distributed in healthy rats after single intravenous injection, with the exception of the kidneys, where accumulation was observed. However, the radioactivity was eliminated fast without significant retention in this organ. Furthermore, ^{177}Lu-PSMA-617 did not accumulate in the submandibular glands, and there was no uptake in the brain. Non-radioactive ^{175}Lu-PSMA-617 as well as unlabelled PSMA-617 bound to plasma proteins in humans, rats and minipigs in the range of 50-70%. Neither substance preferentially distributed into the erythrocytes of rats, dogs, minipigs, mice and humans.

In vitro metabolic studies revealed that ^{175}Lu-PSMA-617 and PSMA-617 were stable in liver or kidney S9 fraction as well as in plasma from humans, rats, and minipigs for up to 2 hours. *In vivo* studies were not conducted.

5.4 Toxicology

The toxicology programme consisted of two single-dose studies with ^{175}Lu-PSMA-617, one repeated-dose study with PSMA-617, and a mutagenicity study with PSMA-617. Considering the intended indication and patient population, the radioactive component of the therapy as well as the treatment schedule, this is acceptable.

The investigators performed *in vivo* studies in rats and Göttingen minipigs. The applicant justified this selection with the fact that PSMA is highly conserved in these species.

The single- and repeated-dose studies did not identify any relevant safety concern and resulted in estimated exposure margins for PSMA-617 between 15 and 400 (based on body surface area). PSMA-617 was not mutagenic under the tested conditions.

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Carcinogenicity studies as well as reproductive and developmental toxicity studies have not been conducted with ^{177}Lu-PSMA-617, the unlabelled precursor molecule PSMA-617, or non-radioactive ^{175}Lu-PSMA-617, as they are not required according to the relevant guidelines.

Based on the ERA for ^{177}Lu-PSMA-617, the risk for the environment is considered low and further studies are not required.

The nonclinical safety specifications in the RMP adequately reflect the nonclinical findings. The waiver granted by the EMA regarding paediatric development is accepted.

5.5 Nonclinical conclusions

Overall, the submitted nonclinical documentation is sufficient to support the approval of Pluvicto/Pluvicto CA with the new active substance ^{177}Lu PSMA-617 in the proposed indication. The applicant adequately characterised pharmacological properties as well as the pharmacokinetic and toxicity profiles. The relevant information has been included in the information for healthcare professionals.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

The pharmacokinetics of ^{177}Lu-PSMA-617 in blood (measured based on radioactive decay) following a single administration of the intended therapeutic radioactive dose of 7400 MBq, has been characterised in a sub-study of the pivotal Phase 3 study in 30 patients with prostate cancer.

ADME

^{177}Lu-PSMA-617 is administered by i.v. bolus injection or infusion. Maximal whole blood concentrations were usually attained at the end of infusion.

Distribution

Plasma protein binding and blood/plasma partitioning was studied *in vitro* for the stable isotope-containing form ^{175}Lu-PSMA-617, which showed a protein-bound fraction of 60-70%. ^{175}Lu-PSMA-617 was not distributed to human erythrocytes. Protein binding and blood plasma partitioning of ^{177}Lu-PSMA-617 are considered to be similar.

The mean apparent volume of distribution of ^{177}Lu-PSMA-617 was 123 L.

Distribution of radioactivity was assessed by whole body dosimetry. The organs receiving the highest absorbed radiation dose were salivary glands and lacrimal glands.

Metabolism and excretion

In vitro assays for metabolic stability were conducted using unlabelled PSMA-617 and non-radioactive ^{175}Lu-PSMA-617. However, the results are considered to be valid for ^{177}Lu-PSMA-617 as well. Both unlabelled PSMA-617 and non-radioactive ^{175}Lu-PSMA-617 showed only minimal degradation in human liver and kidney S9 fractions and in human plasma.

No dedicated mass balance and metabolite profiling study was conducted. However, urine samples were collected as part of the PK sub-study. The relative abundance of ^{177}Lu-PSMA-617 and other radioactive species was assessed in these samples, but no absolute quantification or structural identification of metabolites was conducted. Parent ^{177}Lu-PSMA-617 was detected in all samples at a relative concentration ranging from 49% to 100% of total radioactivity. Apart from the parent compound, nine potential metabolites were detected, which mostly emerged at later time points.

Based on these data, renal elimination of unchanged parent compound seems to be the dominating elimination pathway for ^{177}Lu-PSMA-617.

The mean total systemic clearance of ^{177}Lu-PSMA-617 was 2.04 L/hr, and the mean terminal half-life was 41.6 hours. The effective half-live, accounting for the decay of ^{177}Lu-PSMA-617, was approximately 33 hours.

Dose-linearity and time-dependency

As only one dose level has been studied, a potential dose-dependency in the PK of ^{177}Lu-PSMA-617 cannot be assessed.

Accumulation and potential time-dependent effects on the PK after administration of multiple doses have not been studied. However, considering the half-life, the dosing interval and the low potential for (time-dependent) interactions, such effects are considered unlikely to occur.

Special Populations

No dedicated PK study in subjects with hepatic impairment was submitted. As the liver is not considered to be the primary organ responsible for the elimination of ^{177}Lu-PSMA-617, no dose adjustment is recommended for any degree of hepatic impairment.

The effect of renal impairment was investigated as part of the PopPK analysis of the PK data from the VISION sub-study in 30 PSMA patients. This dataset included 10 patients with mild renal impairment

(60 mL/min ≤ CrCl < 90 mL/min) and one patient with a CrCl value of 54.0 mL/min. The dataset did not include any subjects with severe (CrCl < 30 mL/min) renal impairment. CrCl was found to have a significant effect on ^{177}Lu-PSMA-617 clearance, which resulted in predicted increases in AUC_{inf}, of ~ 1.2-fold and 1.4-fold in patients with mild or moderate renal impairment, respectively. Renal impairment had only a limited effect on Cmax.

Considering that ^{177}Lu-PSMA-617 is predominantly cleared renally, an effect of CrCl on Cl is in line with theoretical expectations. The PK data in subjects with moderate and severe renal impairment is too limited to allow conclusions to be drawn with respect to dose recommendations. However, ^{177}Lu-PSMA-617 has been used in patients with moderate renal impairment in the VISION study. Post-hoc analysis of safety data in patients with different baseline eGFR showed no clear additional acute toxicity attributable to ^{177}Lu-PSMA-617. Nevertheless, further investigations to establish an appropriate dose in patients with moderate and severe renal impairment will be conducted.

In addition, no dose adjustments based on baseline body weight, BMI or age are required. A potential effect of race / ethnic background on the PK of ^{177}Lu-PSMA-617 was not investigated, as all subjects in the PK sub-study were white.

Interactions

Effects of other drugs on ^{177}Lu-PSMA-617

^{177}Lu-PSMA-617 was only minimally metabolised *in vitro* in human plasma and liver and kidney S9 fractions. Urinary excretion is considered to be the major elimination pathway, but the contribution of metabolism to the elimination cannot be fully assessed. Therefore, the interaction potential with inhibitors of drug-metabolising enzymes is considered to be rather low, but associated with uncertainty.

Based on in vitro assays, ^{177}Lu-PSMA-617 is no substrate for renal transporters.

Effects of ^{177}Lu-PSMA-617 on other drugs

The interaction potential of ^{175}Lu-PSMA-617 with CYPs and drug transporters was assessed *in vitro,* and the results indicated that ^{175}Lu-PSMA-617

- did not induce CYP1A2, 2B6 or 3A4;
- did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A
- was not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2.
- did not inhibit BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2.

Pharmacodynamics

Secondary Pharmacology (Safety)

Potential effects of ^{177}Lu-PSMA-617 on the QT interval were assessed in a sub-study of the VISION study. Based on ECG assessments at 1, 4 and 24h after a single dose of ^{177}Lu-PSMA-617, the mean change-from-baseline (and the two-sided 90% upper confidence bound) for QTcF was < 10 ms at all timepoints. The categorical analysis indicated no new QTcF > 450 msec and no QTcF changes from baseline >30 msec.

However, maximal concentrations of ^{177}Lu-PSMA-617 were reached within 20 min after the start of the infusion, and concentrations quickly dropped thereafter. Thus, the ECG measuring time points do not cover t_{max}.

Based on a concentration-QTc model, a mean QTcF increase of 8.7 ms (90% UCI 13.6 ms) is predicted at the therapeutic Cmax value. However, this estimate is for an exposure beyond the highest plasma concentration for which ECG data are available and is therefore associated with uncertainty.

Overall, the available limited data do not indicate a major risk for a ^{177}Lu-PSMA-617 to cause prolongation of the QT interval. However, a potentially relevant prolongation soon after infusion

(around t_{max}) cannot be excluded. In addition, the potential to cause QT prolongations has not been studied at supra-therapeutic doses.

6.2 Dose finding and dose recommendation

No dose-finding studies were performed. The proposed dose is based on published literature and clinical experience. Across these publications, doses ranged from 2.0-9.3 GBq/cycle, and schedules typically followed an administration schedule of once every 4 to 12 weeks for 1-8 cycles. In a prospective phase 2 study by Hofmann et al (2018)[1], the dose of 4.4 to 8.7 GBq (mean: 7.5) every 6 weeks for 4 cycles was well tolerated and efficacious.

In addition, a dose of Lutathera (^{177}Lu oxodotreotide) provided class-based information, and external beam radiation dose thresholds in organs at risk provided some general guidance regarding radiation exposures of normal tissue. Based on these considerations, in the VISION study, a dose of 7.4 GBq ^{177}Lu-PSMA-617 was administered intravenously once every 6 weeks for a maximum of 6 cycles (maximum cumulative dose of 44.4 GBq).

6.3 Efficacy

The evaluation of efficacy is based primarily on the pivotal VISION study (PSMA-617-01), which is an ongoing, prospective, open-label, randomised phase 3 study comparing ^{177}Lu-PSMA-617 + Best Supportive Care (BSC)/Best Standard of Care (BSoC) to BSC/BSoC in patients with progressive PSMA-positive mCRPC after prior therapy with a novel antiandrogen axis drug (NAAD) and a taxane-based chemotherapy.

The study was initiated in May 2018 and conducted at n=82 study centres in n=8 countries across Europe and North America. Data cut-off (DCO) for the primary analysis was 27 Jan 2021. During the study, a high, early dropout rate among those patients randomised to BSC/BSoC became evident, with the majority of these dropouts withdrawing consent for follow-up. To curtail this phenomenon, enhanced study site educational measures were implemented on 05 Mar 2019, and the primary rPFS (radiographic progression-free survival) analysis was altered. The progression-free survival (PFS) full analysis set (PFS-FAS) included only patients randomised on, or after, 05 Mar 2019. The sample size was increased accordingly. The overall survival (OS) analysis included all patients (FAS).

Co-primary endpoints of the study were rPFS as assessed by blinded independent central review (BICR) and OS. Key secondary endpoints, subject to type I error control, were overall response rate as measured by RECIST v1.1 (ORR), disease control rate as measured by RECIST v1.1 (DCR), and time to first symptomatic skeletal event (SSE).

Potential patients had to undergo a ^{68}Ga-PSMA-11 PET/CT scan to evaluate PSMA positivity within 4-6 weeks prior to study start. Only PSMA-positive patients meeting all eligibility criteria were randomised in a 2:1 ratio to ^{177}Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC only. Patients in the experimental arm received 7.4 GBq (±10%) ^{177}Lu-PSMA-617 as a slow i.v. injection once every 6 weeks (±1 week) for a maximum of 6 cycles while receiving BSC/BSoC. After cycle 4 treatment and prior to cycle 5 treatment, the investigator had to determine whether the patient showed evidence of response (i.e. radiological, PSA, clinical benefit), had signs of residual disease on CT with contrast/MRI or bone scan, and had good tolerance to the ^{177}Lu-PSMA-617 treatment. BSC/BSoC included supportive measures such as pain medication or transfusions, ketoconazole, androgen-reducing agents, NAADs such as abiraterone, enzalutamide, or apalutamide, radiation therapy, or bone-targeted agents. Cytotoxic chemotherapy, radium-223, or immunotherapy was not allowed as BSC/BSoC in the study.

Tumour assessments with contrast-enhanced CT or MRI and 99Tc bone scan were performed every 8 weeks after C1D1 for the first 24 weeks, then every 12 weeks. In the long-term follow-up (after the

[1] Hofman MS et al. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833

end of study visit), patients were followed for OS status every 3 months for a duration of 24 months or until 508 death events occurred.

Patients were eligible with progressive, ^{68}Ga-PSMA-11 PET/CT scan-positive, histologically, pathologically, and/or cytologically confirmed prostate cancer and a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L). Patients needed to be pre-treated with at least one prior NAAD and with at least one, but no more than two, previous taxane regimens.

Overall, n=831 patients were randomised to either ^{177}Lu-PSMA-617 + BSC/BSoC (n=551, including n=385 on, or after, 05-Mar-2019) or BSC/BSoC only arm (n=280, including n=196 on or after 05-Mar-2019). In the FAS, almost all patients randomised to ^{177}Lu-PSMA-617 + BSC/BSoC were treated with ^{177}Lu-PSMA-617 (96%) and BSC/BSoC (96.7%). In the BSC/BSoC only arm, the rate of patients treated was significantly lower, at 71.8%. The main reason for this was withdrawal of consent.

Demographic and disease baseline characteristics were balanced between treatment arms. Median age was 71 years, with the majority of the patients aged 65 years or older (76.2%). The majority was White (86.1%) with an ECOG PS of 0-1 (92.4%).

The majority had a histological diagnosis of adenocarcinoma (91.2%), with an initial Gleason score of 8-10 (59.8%). Most of the patients had bone metastases (91.5%). Liver and lung metastases were reported in 12.5% and 9.5%, respectively. The baseline and disease characteristics in the PFS FAS were balanced as well.

All patients had received at least one line of prior cancer-related systemic therapy. The median number of prior systemic treatments was five in both treatment arms. The majority of patients had ≥ 3 prior regimens (95.2%). All patients were treated with a prior taxane-containing regimen. One prior taxane-containing regimen was administered in 57.4% and two prior taxane-containing regimens in 41.8% of patients. Approximately half of the patients had n=1 prior NAAD-containing regimen.

The BSC/BSOC arm included more patients who received concomitant NAAD, compared to the experimental arm (67.8% vs. 52.6%). This imbalance is potentially unfavourable to the ^{177}Lu-PSAM-617 + BSC/BSoC arm.

Results of the primary rPFS analysis and the final OS analysis were presented after a median survival follow-up of 20 months. The study met its primary objective, demonstrating a statistically significant improvement in rPFS based on blinded independent central review per PCWG3 criteria for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC, compared to patients receiving BSC/BSoC only (HR=0.40; 99.2% CI: 0.29, 0.57; stratified log-rank test p < 0.001, one-sided). Median rPFS was 8.7 months (95%CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617 + BSC/BSoC arm, and 3.4 months (95%CI: 2.4, 4.0) in the BSC/BSoC only arm. Results are presented for the PFS-FAS. There were more censored patients in the BSC/BSoC only arm compared to the ^{177}Lu-PSMA-617 + BSC/BSoC arm (52.6% vs. 34.0%), due to the higher rate of withdrawals in the BSC/BSoC only arm. Subgroups analysed for rPFS showed consistent results and favoured ^{177}Lu-PSMA-617. The efficacy in terms of rPFS was irrespective of the number of prior NAAD therapies (1 or ≥2) and prior taxane regimen (1 or ≥2).

OS was also statistically significantly improved for patients receiving ^{177}Lu-PSMA-617 + BSC/BSoC compared to patients receiving BSC/BSoC only (HR=0.62; 95% CI: 0.52, 0.74; stratified log-rank test p < 0.001, one-sided). Median OS was 15.3 months (95%CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617 arm and 11.3 months (95%CI: 9.8, 13.5) in the BSC/BSoC arm. The rate of patients censored because they “withdrew consent” was higher in the BSC/BSoC only arm (11.8% vs. 2.7%).

The applicant provided additional sensitivity analyses to account for the potential impact of censoring due to drop-outs. The analyses were appropriate from a statistical point of view and showed robust results. However, less bias is assumed for the OS results than for rPFS, given that a number of death events were not counted as rPFS events due to censoring after two or more assessments were missed.

The key secondary endpoints ORR, DCR and time to first SSE were statistically significantly improved in the ^{177}Lu-PSMA-617 + BSC/BSoC arm.

Further secondary endpoints were not multiplicity-controlled.

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6.4 Safety

The safety population of the VISION study included n=734 patients (n=529 ^{177}Lu-PSMA-617 + BSC/BSoC; n=205 BSC/BSoC only).

The median duration of exposure to randomised treatment was 7.8 months (0.3 - 24.0) in the ^{177}Lu-PSMA-617 + BSC/BSoC arm, compared to 2.1 months (0.0 - 26.0) in the BSC/BSoC only arm. Patients received a median of 5 cycles of ^{177}Lu-PSMA-617.

The median cumulative dose (all cycles) was 37.5 GBq (7.0-48.3), with a median relative dose intensity of 102.6% (90.5-471.3%).

Adverse events (AEs) of any grade were reported in 98.1% of patients in the ^{177}LU-PSMA-617 + BSC/BSoC arm, compared to 82.9% in the BSC/BSoC arm. The following AEs of any grade were reported more frequently (≥10% difference) in the ^{177}Lu-PSMA-617 arm compared to the BSC/BSoC arm: dry mouth (+38.3%), fatigue (+20.2%), nausea (+18.7%), anaemia (+18.6%), diarrhoea (+16%), thrombocytopenia (+12.8%), vomiting (+12.6%), leukopenia (+10.5%), lymphopenia (+10.3%) and urinary tract infection (+10%).

Grade ≥ 3 AEs were observed more frequently in the ^{177}Lu-PSMA-617 arm compared to the BSC/BSoC arm (52.7% vs. 38.0%). The most frequent ≥ G3 AEs (≥ 5%) in the ^{177}Lu-PSMA-617 + BSC/BSoC arm were anaemia (12.9%), thrombocytopenia (7.9%), lymphopenia (7.8%) and fatigue (5.9%).

On-treatment deaths (death occurring during randomised treatment or within 30 days of randomised treatment discontinuation) were observed more frequently in the ^{177}Lu-PSMA-617 + BSC/BSoC arm (12.5% vs. 9.3%). Primary cause of death was disease progression in most of the patients (8.3% and 6.8%, respectively).

Serious adverse events (SAEs) with a fatal outcome were reported more frequently in the ^{177}Lu-PSMA-617 + BSC/BSoC arm compared to the BSC/BSoC arm (3.6% [n=19] vs. 2.9% [n=6]). Overall, n=5 SAEs with fatal outcome were reported as related to ^{177}Lu-PSMA-617. In all of these five events, death was due to, or associated with, myelosuppression. In comparison, none of the patients in the BSC/BSoC only arm died due to a treatment-related AE.

The overall rate of SAEs was higher in the ^{177}Lu-PSMA-617 + BSC/BSoC arm than in the BSC/BSoC only arm (36.3% vs. 27.8%). The following SAEs were reported in the ^{177}Lu-PSMA-617 + BSC/BSoC arm with ≥ 1% higher incidence compared to the BSC/BSoC only arm: anaemia, urinary tract infection, haematuria, pyrexia and pancytopenia.

AEs leading to permanent discontinuation of ^{177}Lu-PSMA-617 were reported in 11.9% of patients. Rate of AEs leading to permanent discontinuation of BSC/BSoC was similar in both treatment arms (8.5% ^{177}Lu-PSMA-617 + BSC/BSoC and 7.8% BSC/BSOC only).

Safety topics of interest (STI), which were observed more frequently in the ^{177}Lu-PSMA-617 + BSC/BSoC arm compared to the BSC/BSOC only arm, were fatigue, myelosuppression, dry mouth, nausea, vomiting and renal toxicity. An increased rate of hepatotoxicity in the ^{177}Lu-PSMA-617 + BSC/BSoC arm was mainly related to low-grade events of increased levels of aspartate aminotransferase and alkaline phosphatase. There were no events of drug-induced liver injury in either treatment arm. Insufficient data are available to confirm an association between secondary primary malignancies or tumour lysis syndrome and ^{177}Lu-PSMA-617.

6.5 Final clinical and clinical pharmacology benefit risk assessment

Metastatic castration-resistant prostate cancer (mCRPC) is the last stage of prostate cancer and is associated with a dismal prognosis. Treatment of choice is taxane-based chemotherapy or novel androgen axis drug (NAAD) treatment, depending on the burden of disease and the frailty of the patient. According to the recent NCCN guidelines, in patients with disease progression after prior taxane therapy and prior NAAD therapy, cabazitaxel or re-challenge docetaxel are preferred treatment options, if patients are eligible for cytotoxic chemotherapy. NAADs such as abiraterone or enzalutamide are recommended treatment options as well, depending on prior exposure. Optimal

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sequencing of treatments available is unknown. After progression on/after standard of care taxane therapy and NAADs, patients have a median overall survival (OS) of 11-14 months with third-line therapy (CARD study, de Wit et al. 2019)[2].

Radiolabelled small molecules that bind to prostate-specific membrane antigen (PSMA), which is highly expressed in the majority of prostate cancers, provide a new treatment option. The applicant requests regular approval for ^{177}Lu-PSMA-617 in patients with mCRPC after prior taxanes and NAAD therapy and provides a pivotal randomised, open-label, phase 3 study (VISION) for evaluation of safety and efficacy.

The experimental drug was combined with best supportive care (BSC) and/or best standard of care (BSoC), which excluded cytotoxic chemotherapy, and was compared to BSC/BSoC only. Prior to study entry, patients had to undergo ^{68}Ga-PSMA-11 PET/CT scan to evaluate PSMA positivity. No information is available as to whether patients with PSMA expression otherwise established would benefit from ^{177}Lu-PSMA-617.

Due to the open-label design and the publicly available information on the potential efficacy of the experimental drug, a high early drop-out rate was observed in the control arm. Educational measures were implemented at the study sites to curtail this phenomenon. In addition, the primary analysis of the primary endpoint radiographic progression-free survival (rPFS) was performed on a special analysis set (= PFS full analysis set), which included only patients randomised on, or after, the date of implementation of the additional educational measures (05 Mar 2019). Overall survival (OS) analysis, as co-primary endpoint, was based on all randomised patients and sample size was increased accordingly. Overall, these changes were acceptable from a statistical point of view. Additional sensitivity analyses were performed to address the existing bias.

Beneficial effects

The study met its co-primary endpoints of rPFS and OS, and the type I error-controlled secondary endpoints of overall response rate (ORR), disease control rate (DCR) and time to first symptomatic skeletal event (SSE) were also statistically significant.

Results of rPFS and OS were consistent in various sensitivity analyses and in predefined subgroups.

Uncertainty in the knowledge about the beneficial effects

The major concern regarding the appropriateness of the control arm remains unsolved. Approximately 60% of patients in the VISION study had received only one prior taxane-containing regimen before study entry. According to the current guidelines, the recommended treatment option in these patients (if fit enough) would either be cabazitaxel or docetaxel re-challenge, which was not allowed per study design. An active control was potentially not included due to concerns regarding potential confounding of the treatment effect by “active” agents and the lack of safety data of these combinations, which is acknowledged in principle.

The applicant did not present any analyses to demonstrate potential frailty in the patients with only one prior taxane-containing regimen, which one would assume in order to justify the correct choice of therapy.

Overall, the issue persists. At least the proportion of patients with only one prior taxane-containing regimen was similar in both treatment arms (^{177}Lu-PSMA-617 + BSC/BSoC 58.9%; BSC/BSoC only: 55.7%), although this does not mean that a potential bias can be excluded.

Due to the high early drop-out rate, changes in the study conduct became necessary to minimise the existing bias. Sensitivity analyses showed robust results overall. However, especially in terms of rPFS, bias could not be entirely removed, given the higher number of missing assessments in the control arm. Overall, the remaining uncertainty is considered acceptable, and the treatment effect

[2] de Wit R et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019 Dec 26;381(26):2506-251

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especially in OS, which was less prone to bias, was convincing enough to establish efficacy compared to BSC/BSoC.

Patients had a median of two prior palliative treatments, thereby justifying the requested treatment line.

The currently requested indication was amended during the review process to include the term “progressive”, as requested per inclusion criterion. Further, the addition of “or ineligible for taxane therapy” was deleted given that all patients investigated had at least one prior taxane-containing regimen prior to study entry.

Dose selection was based on the published literature, with doses of 6-8 GBq ^{177}Lu-PSMA-617 every 6 weeks for 4 cycles being described as well tolerated. In view of positive reports of more than 4 cycles administered safely, 2 additional cycles of ^{177}Lu-PSMA-617 were incorporated into the protocol when benefit and tolerability were confirmed following the 4th cycle. However, due to missing randomisation into these groups of cycles, the adequacy of 4 vs. 6 cycles of ^{177}Lu-PSMA-617 cannot be assessed conclusively based on the data available due to the inherent selection bias. In addition, since none of the patients who received 4 cycles experienced a complete remission, the treatment with up to 6 cycles is considered appropriate.

The PK of ^{177}Lu-PSMA-617 was assessed in a subset of only 30 patients after administration of a single dose. The available data allow characterisation of the single-dose PK parameters. In addition, only a mild increase in ^{177}Lu-PSMA-617 in subjects with mild renal impairment was shown. PK data on patients with moderate or severe renal impairment are limited or missing. As ^{177}Lu-PSMA-617 is predominantly eliminated renally, and due to limited safety data in these patent groups, additional investigations in patients with moderate and severe renal impairment is required (stipulation).

Data on the excretion and metabolism of ^{177}Lu-PSMA-617 are incomplete. Data after multiple dose administration are missing. PK data on patients with any degree of hepatic impairment are missing. The uncertainties arising from this lack of data are mentioned in the information for healthcare professionals.

Unfavourable effects (risks)

Treatment toxicity was higher with ^{177}Lu-PSMA-617 + BSC/BSoC compared to BSC/BSoC only. The mechanism of action leads to adverse events in PSMA-expressing tissues such as salivary glands or kidneys. Myelosuppression, most likely caused by the effects of ionising radiation on sensitive precursor cells in circulation or in the bone marrow close to metastatic lesions, was reported frequently. High-grade adverse events were observed predominantly in the haematological system organ class, with anaemia and thrombocytopenia. However, even when taking into account the limitations of a cross-study comparison, the myelosuppressive effect appears to be less pronounced than with cabazitaxel therapy.

Uncertainty in the knowledge about the unfavourable effects

Although the rates of serious adverse events (SAE) leading to a fatal outcome were similar in both treatment arms, there were n=5 treatment-related fatal SAEs in the ^{177}Lu-PSMA-617 + BSC/BSoC arm compared to none in the BSC/BSoC arm. Further follow-up safety data are mandatory to fully assess the toxicity profile of ^{177}Lu-PSMA-617, especially to assess potential radiation-induced late effects.

The potential of ^{177}LU-PSMA-617 to cause prolongation of the QT interval was not assessed at maximal therapeutic concentrations (or supratherapeutic concentrations). However, model–based predictions indicate a risk for a prolongation beyond 10 msec (but <20 msec).

Benefit-risk assessment

Overall, there is sufficient evidence that ^{177}Lu-PSMA-617 provides a survival benefit in patients with mCRPC after progression on taxane and an NAAD compared to BSC/BSoC excluding

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chemotherapeutic agents. The issues raised during review were adequately addressed in general, and the benefit-risk ratio was assessed as positive.

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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.

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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.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.

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▼ 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®, 1,000 MBq/ml solution for injection/infusion

Pluvicto® CA, 1,000 MBq/ml solution for injection/infusion

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 taxane-based chemotherapy (see “Properties/Actions”).

Dosage/Administration

The medicinal product is intended exclusively for use in a hospital.
Pluvicto/Pluvicto CA must be administered only by persons permitted to handle radiopharmaceuticals in authorised settings and after evaluation of the patient by a qualified physician.
Radiopharmaceuticals, including Pluvicto/Pluvicto CA, should be used by or under the control of healthcare professionals 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 competent governmental agency authorised to license the use of radiopharmaceuticals.
The precautions of the Swiss Radiological Protection Ordinance must be followed.

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 up to a total 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)

These tests must be performed at least once within the 3 days before administration. It is also recommended to perform these tests 4 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 (extending the dosing interval by 4 weeks from 6 weeks to up to 10 weeks), dose reduction or permanent discontinuation of treatment with Pluvicto/Pluvicto CA.
If a treatment delay due to an adverse drug reaction persists for longer than 4 weeks, treatment with Pluvicto/Pluvicto CA must be discontinued. The dose of Pluvicto/Pluvicto CA may be reduced by 20% 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%.
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%.
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%.
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.

Adverse drug reaction	Severity[a]	Dose modification
	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%.
	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.
AST or ALT elevation	AST or ALT >5 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 has not been studied in these patients.

Elderly patients

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

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 a disposable syringe fitted with a syringe shield (with or without a syringe pump), as an infusion using the gravity method (with or without an infusion pump) or as an infusion from the vial (with a peristaltic infusion pump).
A reduced dose of Pluvicto/Pluvicto CA should be administered using the syringe method (with or without a syringe pump) or as an infusion from the vial (with a peristaltic infusion pump). Using the gravity method to administer a reduced dose of Pluvicto/Pluvicto CA is not recommended since it may result in delivery of the incorrect volume of Pluvicto/Pluvicto CA if the dose is not adjusted prior to administration.
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 (with or without a syringe pump)

1. After disinfecting the vial stopper, withdraw an appropriate volume of Pluvicto/Pluvicto CA solution to deliver the desired radioactivity by using a disposable syringe fitted with a syringe shield and a disposable sterile needle.
2. Administer Pluvicto/Pluvicto CA to the patient by slow intravenous push for approximately 1 to 10 minutes (either with a syringe pump or manually without a syringe pump) via a venous catheter that is pre-filled with 0.9% sterile sodium chloride solution and that is used exclusively for Pluvicto/Pluvicto CA administration to the patient.

3. Once the desired Pluvicto/Pluvicto CA dose has been administered, perform an intravenous flush of ≥10 ml of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

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

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 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 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 an infusion pump to regulate the flow of the sodium chloride solution via the short needle into the Pluvicto/Pluvicto CA vial (the sodium chloride solution entering the vial through the short needle will carry 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 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 infusion method from the vial (with a peristaltic infusion pump)

1. Insert a 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 infusion 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 infusion pump, following the pump 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 infusion 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 infusion pump and then change the position of the 3-way stopcock valve so that the peristaltic infusion pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic infusion pump and infuse an intravenous flush of ≥10 ml of 0.9% sterile sodium chloride solution through the 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 for Pluvicto in the VISION sub-study

	Absorbed dose per unit activity (Gy/GBq)[a] (N=29)		**Calculated absorbed dose for 7.4 GBq administration (Gy)[a]**		**Calculated absorbed dose for 6 x 7.4 GBq (44.4 GBq cumulative activity) (Gy)[a]**	
Organ	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.033	0.025	0.24	0.19	1.5	1.1
Brain	0.007	0.005	0.049	0.035	0.30	0.22
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] *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 household contacts 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 or healthcare professional 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

In the VISION study myelosuppression, including fatal cases, occurred more frequently in patients who were treated with Pluvicto/Pluvicto CA plus best standard of care (BSoC) than in patients who received BSoC alone (see "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

In the VISION study renal toxicity occurred more frequently in patients who received Pluvicto/Pluvicto CA plus BSoC than in patients who received BSoC alone (see "Adverse effects"). Patients should be informed that they should remain well hydrated and to 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) of Pluvicto is expected to increase with the degree of renal impairment (see "Pharmacokinetics in special populations"). 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”).

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. The recommended cumulative dose of 44,400 MBq of Pluvicto/Pluvicto CA results in a radiation absorbed dose to the testes within a range where Pluvicto/Pluvicto CA may cause infertility.

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

Summary of the safety profile

The safety of Pluvicto was evaluated in the phase III VISION study in patients with progressive, PSMA-positive mCRPC. Of the 831 patients randomised, 734 patients received at least one dose of randomised treatment. Patients received at least one dose of either 7,400 MBq of Pluvicto administered every 6 to 10 weeks plus BSoC (N=529) or BSoC alone (N=205).
Among patients who received Pluvicto plus BSoC the mean number of doses of Pluvicto received was 5 (range: 1 to 6), with 67.7% of patients receiving at least 4 doses of Pluvicto and 46.5% of patients receiving a total of 6 doses of Pluvicto. The median cumulative Pluvicto dose was 37,500 MBq (range: 7,000 to 48,300). The median duration of randomised treatment was 7.8 months (range: 0.3 to 24.9) in patients who received Pluvicto plus BSoC and 2.1 months (range: 0.0 to 26.0) for patients who received BSoC alone.
Table 3 provides an overview of the frequency of adverse drug reactions. The most common adverse drug reactions (≥20%) occurring more frequently in patients who received Pluvicto plus BSoC than in patients who received BSoC alone include: fatigue (43.1%), dry mouth (39.3%), nausea (35.3%), anaemia (31.8%), decreased appetite (21.2%) and constipation (20.2%). The most common grade 3 to 4 adverse drug reactions (≥5%) occurring more frequently in patients who received Pluvicto plus BSoC than in patients who received BSoC alone include: anaemia (12.9%), thrombocytopenia (7.9%), lymphopenia (7.8%) and fatigue (5.9%).

Tabulated summary of adverse drug reactions

Adverse drug reactions (**Table 3**) are ordered by MedDRA system organ class and frequency according to the following convention: 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 occurring more frequently in patients who received Pluvicto plus BSoC than in patients who received BSoC alone in VISION[a]

	Pluvicto plus BSoC (N=529)		
Adverse effects	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**
Blood and lymphatic system disorders			
Anaemia	168 (31.8%)	Very common	68 (12.9%)
Thrombocytopenia	91 (17.2%)	Very common	42 (7.9%)
Leukopenia[c]	83 (15.7%)	Very common	22 (4.2%)
Lymphopenia	75 (14.2%)	Very common	41 (7.8%)
Pancytopenia[d]	9 (1.7%)	Common	7 (1.3%)[b]
Nervous system disorders			
Dizziness	44 (8.3%)	Common	5 (0.9%)
Headache	37 (7.0%)	Common	4 (0.8%)
Dysgeusia[e]	37 (7.0%)	Common	0
Eye disorders			
Dry eye	16 (3.0%)	Common	0
Ear and labyrinth disorders			
Vertigo	11 (2.1%)	Common	0
Gastrointestinal disorders			
Dry mouth[f]	208 (39.3%)	Very common	0
Nausea	187 (35.3%)	Very common	7 (1.3%)
Constipation	107 (20.2%)	Very common	6 (1.1%)
Vomiting[g]	101 (19.1%)	Very common	5 (0.9%)
Diarrhoea	100 (18.9%)	Very common	4 (0.8%)
Abdominal pain[h]	59 (11.2%)	Very common	6 (1.1%)
Renal and urinary disorders			
Urinary tract infection[i]	61 (11.5%)	Very common	20 (3.8%)
Acute kidney injury[j]	45 (8.5%)	Common	17 (3.2%)
General disorders and administration site conditions			
Fatigue	228 (43.1%)	Very common	31 (5.9%)
Decreased appetite	112 (21.2%)	Very common	10 (1.9%)
Decreased weight	57 (10.8%)	Very common	2 (0.4%)
Peripheral oedema[k]	52 (9.8%)	Common	2 (0.4%)
Pyrexia	36 (6.8%)	Common	2 (0.4%)

Abbreviation: BSoC: best standard of care.

	Pluvicto plus BSoC (N=529)		
Adverse effects	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**

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

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

[c] Leukopenia includes leukopenia and neutropenia.

[d] Pancytopenia includes pancytopenia and bicytopenia.

[e] Dysgeusia includes dysgeusia and taste disorder.

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

[g] Vomiting includes vomiting and retching.

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

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

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

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

Description of specific adverse effects and additional information

Myelosuppression

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 (31.8%/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; and bicytopenia (0.2%/0.2%) versus (0%/0%).

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 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

(5.3%/0.2%) versus (2.4%/0.5%); acute kidney injury (3.6%/3.0%) versus (3.9%/2.4%); renal failure (0.2%/0%) versus (0%/0%); and 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.

Reporting suspected adverse effects after 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 0.498 MeV (79%) and photonic radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (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	

Radiation	Energy (keV)	Iβ-%	Iγ%
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
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
1,080 (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.
Unlabelled vipivotide tetraxetan does not exhibit any pharmacodynamic activity.

Clinical efficacy

The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC was established in VISION, 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.
Eligible patients had PSMA-positive mCRPC, an 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. 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 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 of 2 cycles of a taxane). Patients with unstable symptomatic central nervous system metastases or symptomatic or clinically/radiologically impending spinal cord compression were not eligible for the study. Patients underwent a gallium (^{68}Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have at least one PSMA-positive lesion identified by this scan and no CT/MRI-measurable lesions that showed poor or no gallium (^{68}Ga) gozetotide uptake on the PET scan.
BSoC administered at the physician's discretion included: supportive measures such as pain medications, hydration, blood transfusions, etc.; ketoconazole; radiotherapy in localised prostate cancer; bone-targeted agents; androgen-reducing agents; AR pathway inhibitors.

The alternate primary efficacy endpoints were overall survival (OS) and radiological progression-free survival (rPFS) by blinded independent central review (BICR) as per PCWG3 criteria. An additional secondary efficacy endpoint was overall response rate (ORR) by BICR as per Response Evaluation Criteria in Solid Tumors (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% 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 lactase dehydrogenase (LDH), presence of liver metastases, ECOG PS score and intake of an AR pathway inhibitor as part of BSoC at the time of randomisation. At randomisation all patients (100.0%) had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two. 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 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**. 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 6: 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; BICR: blinded independent central review; RECIST: Response Evaluation Criteria in Solid Tumors.

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

Organ uptake

The biodistribution of lutetium (^{177}Lu) vipivotide tetraxetan shows primary uptake in 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

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.
Aseptic technique and radiation shielding should be used when handling or administering Pluvicto/Pluvicto CA, using tongs as needed to minimise radiation exposure.
The vial should be visually examined behind a shielded screen for particulate matter and discolouration prior to administration. The vial should be discarded if particulates or discolouration are present. If at any time during the handling of this medicinal product the integrity of the container or vial is compromised, it must not be used.
Pluvicto/Pluvicto CA is a ready-to-use solution for single use. The Pluvicto/Pluvicto CA solution should not be injected directly into any other intravenous solution.
The amount of radioactivity delivered to the patient should be confirmed with an appropriately calibrated activity measurement device prior to and after Pluvicto/Pluvicto CA administration.
This preparation results in a relatively high radiation dose to most patients. 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 isotope 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.

Swissmedic number

68684, 69027

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

Advanced Accelerator Applications International SA, 1204 Geneva

Information last revised

September 2022