Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Pluvicto

Active ingredient/s: Lutetium (^{177}Lu) vipivotide tetraxetan

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

October 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
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About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE(s)	Adverse event(s)
AML	Acute myeloid leukemia
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific annex
$AUC_{0\text{-}inf}$	Area under the concentration time curve from 0 to infinity
BMI	Body mass index
BSC	Best supportive care
BSoC	Best standard of care
CI	Confidence interval
CL	Clearance
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CrCl	Creatinine clearance
CT	Computed tomography
CYP	Cytochrome P450 enzymes
CV	Coefficient of variation
DCR	Disease control rate
DLP	Data lock point
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	United States Food and Drug Administration
GBq	Gigabecquerel
GM	Geometric mean
Gy	Gray
HR	Hazard ratio
IV	Intravenous
MBq	Megabecquerel
mCRPC	Metastatic castration resistant prostate cancer
MDS	Myelodysplastic syndrome

Abbreviation	Meaning
MRI	Magnetic resonance imaging
ORR	Overall response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PSMA	Prostate specific membrane antigen
RLT	Radioligand therapy
RMP	Risk management plan
rPFS	Radiographic progression-free survival
SAE(s)	Serious adverse event(s)
SSE	Symptomatic skeletal event
TEAE(s)	Treatment emergent adverse event(s)
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum concentration
Vz	Volume of distribution

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Pluvicto
Active ingredient:	Lutetium (^{177}Lu) vipivotide tetraxetan
Decision:	Approved
Date of decision:	16 July 2024
Date of entry onto ARTG:	17 July 2024
ARTG number:	410282
▼*Black Triangle Scheme*	Yes
for the current submission:	
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Limited 54 Waterloo Road Macquarie Park, NSW 2113
Dose form:	Solution for injection
Strength:	1000 megabecquerel (MBq)/mL
Container:	Vial
Pack size:	One vial
Approved therapeutic use for the current submission:	Pluvicto is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.
Route(s) of administration:	Intravenous
Dosage:	The recommended Pluvicto dose is 7,400 MBq intravenously every 6 weeks (± 1 week) for up to a total of 6 doses or until disease progression, or unacceptable toxicity. Medical castration with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in patients not surgically castrated. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	X Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Novartis Pharmaceuticals Australia Pty Limited (the sponsor) to register Pluvicto (lutetium (^{177}Lu) vipivotide tetraxetan) 1000 MBq/mL, solution for injection, vial for the following proposed indication:[1]

> *Pluvicto is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes.*

Disease or condition

Prostate cancer is the most commonly diagnosed cancer in Australia, and it is estimated that one in six males will be diagnosed by the time they are 85 years old. In 2022, there were approximately 24,000 males diagnosed with prostate cancer and the average age at diagnosis was 69 years. In 2014 to 2018, on average, 95.5% of males (all ages) diagnosed with prostate cancer survived five years after diagnosis. Despite this high 5-year survival, prostate cancer is still the second most common cause of cancer-related deaths in Australian males after lung cancer. Most patients present with localised disease and undergo initial surgical and/or radiological therapy. For those with advanced disease, androgen deprivation therapy is usually the first line option. While effective initially, the vast majority eventually progress while receiving hormonal therapies. It is reported that 10 to 20% of prostate cancer patients become castration-resistant within 5 years and >50% die within 3 years with historical standard therapies.[2] As metastatic castration resistant prostate cancer (mCRPC) will likely result in significant morbidity and ultimately the patient's death, there is an evident medical need for therapies that can improve quality of life and/or prolong survival.

Current treatment options

For patients with mCRPC, first line options include adding an androgen receptor pathway inhibitor (for example, abiraterone, enzalutamide, apalutamide and darolutamide) to androgen deprivation therapy.

Taxanes are the only cytotoxic chemotherapy agents that have significantly prolonged overall survival in clinical trials in males with mCRPC and no prior chemotherapy. Cytotoxic chemotherapy using docetaxel is generally reserved for patients with relatively rapidly progressing symptomatic disease for which less toxic approaches (for example, abiraterone,

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.
[2] Nassbaum, N. et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science, *Prostate Cancer and Prostatic Diseases*, 2016; 19: 111-121.

enzalutamide) may not be appropriate options. Docetaxel is used more commonly and cabazitaxel was designed for antitumor activity in docetaxel-resistant patients. These agents have typical chemotherapy side effects such as bone marrow suppression so are often not suitable for patients with significant comorbidities.

Sipuleucel-T is an immunotherapy and is an option for minimally symptomatic males who have slowly progressive disease not requiring a rapid response. The bone-targeted radiopharmaceutical radium-223 is an option for males with symptomatic bone metastases and no visceral disease.

Selected patients may be eligible for a poly ADP-ribose polymerase inhibitor (that is, those with homologous recombination repair deficiency) or an immune checkpoint inhibitor (pembrolizumab) if the tumour is deficient in mismatch repair or there is a high tumour mutational burden for whom there are no satisfactory alternatives or for those who cannot tolerate other forms of treatment.

Despite the broadening of therapeutic choices for mCRPC over the last decade, there are limited options for patients following progression on taxane-based chemotherapy, or when taxane-based chemotherapy is contraindicated.

Clinical rationale

Prostate specific membrane antigen (PSMA) is a type II membrane protein that is expressed in prostate tissue and in highly expressed in most prostate cancers. It is also expressed to a lesser extent in the peripheral and central nervous system, small intestinal and salivary gland tissues. It is this difference in expression that enables the therapeutics to be targeted primarily to the cancer cells.

The proposed product has a non-radioactive precursor molecule, PSMA-617 which contains the PSMA-binding ligand glutamate-urea-lysine linked to a DOTA-chelator. This is then complexed with the lutetium radionuclide which, via its radioactive nature, is responsible for the therapeutic activity of ^{177}Lu-PSMA-617. The mechanism of action of ^{177}Lu-PSMA-617 is to deliver therapeutic radiation to prostate cancer cells via its binding to PSMA.

The sponsor stated the following:

> *The binding of the ligand to PSMA leads to internalisation through endocytosis with sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003, Benešová et al 2015).[3, 4] This functional feature of PSMA allows for the development of low-molecular weight targeted radiopharmaceuticals with favourable pharmacokinetic and tumour penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).[5] In addition, while PSMA-617 has the capacity to chelate other radionuclides, Lu-177 is the radionuclide of choice for this application, based on its favourable radiochemical characteristics, including half-life and the path length of the β-particles (Sgouros et al 2020).[6]*

[3] Rajasekaran, S.A. et al. A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen, *Molecular Biology of the Cell*, 2003; 14: 4835-4845.

[4] Benešová, M. et al. Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor with Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer, *Journal of Nuclear Medicine,* 2015; 56: 914-920.

[5] Haberkorn, U. et al. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy, *Clinical Cancer Research,* 2016; 22: 9-15.

[6] Sgouros, G. et al. Radiopharmaceutical therapy in cancer: clinical advances and challenges, *Nature*, 2020; 19: 589-608.

The PSMA protein is also used as a target for diagnostic imaging in prostate cancer. In this situation the PSMA ligand is radiolabelled with gallium 68 and used to determine disease extent via positron emission tomography (PET) imaging.

It is noted that a positive PET/computed tomography (CT) scan was required for inclusion in the pivotal Phase III study. ^{177}Lu-PSMA-617 has been used as an experimental agent in the clinical setting for patients with mCRPC since 2013 with literature suggesting favourable results. Such products would have had different sources and preparation processes than the proposed radioligand product.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

This evaluation was facilitated through Project Orbis, an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA, and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	30 September 2021	Approved on 9 December 2022	*Pluvicto in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition 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 AR pathway inhibition and taxane-based chemotherapy (see section 5.1).*

Region	Submission date	Status	Approved indications
Great Britain	28 October 2021	Approved on 10 August 2022	*Pluvicto is indicated for the treatment of adult patients with prostate specific membrane antigen (PSMA)-positive metastatic castration resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes.*
United States of America	29 July 2021	Approved on 23 March 2022	*Pluvicto is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane based chemotherapy.*
Canada	28 January 2022	Approved on 25 August 2022	*Pluvicto (lutetium (^{177}Lu) vipivotide tetraxetan injection) is indicated for: The treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have received at least one androgen receptor pathway inhibitor (ARPI) and taxane based chemotherapy.*

Region	Submission date	Status	Approved indications
Singapore	22 August 2022	Approved on 18 December 2023	*Pluvicto is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibitor and taxane-based chemotherapy.*
Switzerland	23 November 2021	Approved on 24 February 2023	*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.*

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2023-02254-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	1 August 2023
Evaluation completed	24 April 2024
Advisory committee meeting	6 and 7 June 2024
Registration decision (Outcome)	16 July 2024
Registration in the ARTG completed	17 July 2024
Number of working days from submission dossier acceptance to registration decision*	197

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality evaluation summary

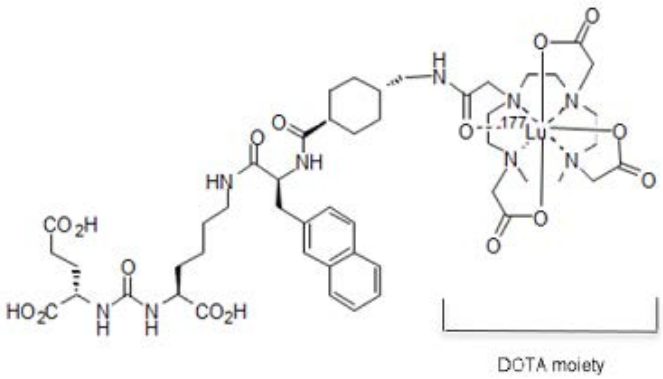
Pluvicto is a radiopharmaceutical and the active moiety is the radionuclide lutetium (^{177}Lu) which is linked to a targeting moiety that binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding to PSMA-expressing cancer cells, the beta radiation 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.

The product is a single use, sterile, clear, colourless to slightly yellow solution for injection or infusion. Given the fixed volumetric activity of 1,000 MBq/mL at the date and time of calibration (end of production), the volume of the solution in the vial can range from 7.5 mL to 12.5 mL to provide the required amount of radioactivity at the date and time of administration.

The product is manufactured in a continuous automatic process combining the radionuclide precursor ($^{177}LuCl_3$) with the chemical precursor (vipivotide tetraxetan) to form the drug substance (lutetium (^{177}Lu) vipivotide tetraxetan). The drug substance is not isolated and is directly formulated into the drug product.

The shelf life of the drug product is 120 hours (5 days) after calibration time (end of production).

Figure 1: Structure of lutetium (^{177}Lu) vipivotide tetraxetan



Biopharmaceutics

No bioequivalence studies were conducted for the proposed product as the formulation used in clinical development Study PSMA-617-01 (VISION) had only minor excipient differences in the overall composition compared to the proposed commercial formulation. The change in formulation is minor and does not affect the quality of the drug product and is unlikely to affect clinical performance.

Recommendation following quality evaluation

Approval is recommended for registration of the product from a pharmaceutical chemistry perspective.

Nonclinical evaluation summary

Deficiencies identified in the non-clinical dossier were primarily limited to the single rat repeat-dose toxicity study which utilised unlabelled vipivotide tetraxetan (not representative of the commercial formulation and toxicity of the lutetium component) and no toxicokinetic data. Given the renal toxicity observed in the acute study, repeated dosing with higher escalating doses of the proposed formulation and a longer dosing duration would have elucidated this finding further, more adequately assessed the potential for delayed toxicity and the toxicity of the lutetium component.

The nonclinical primary pharmacology and pharmacokinetic studies support the proposed indication 'treatment of (PSMA)-positive metastatic castration-resistant prostate cancer'.

The key concerns for patients identified from the nonclinical data are the potential for renal toxicity and injection site reactions.

While the toxicity investigations were limited, there are no nonclinical objections to registration of Pluvicto for the proposed indication provided safety has been adequately assessed by clinical data.

The nonclinical evaluation does not cover radiation protection aspects of the submission.

Clinical evaluation summary

Summary of clinical studies

The clinical dossier consisted of:

- Study PSMA-617-01 (VISION) – a randomised, open label, Phase III study in patients with progressive PSMA-positive mCRPC who were previously treated with 1 to 2 taxane-based chemotherapy regimens, and at least one novel androgen axis drug/androgen receptor pathway inhibitor.
- Study PSMA-617-01 Sub-study. This sub-study provided pharmacokinetics (PK), electrocardiogram (ECG), urine metabolites and dosimetry data.
  - There was one study report - Population PK modelling and exposure-response analyses on organ dosimetry and acute toxicity based on ^{177}Lu PSMA-617 sub-study data.
  - There were also several study reports located within the clinical study report of Study PSMA-617-01 Appendix 16. These reports included PK, urine metabolites, cardiac safety and dosimetry.
- Study PSMA-617-02 (RESIST-PC) – a Phase II, open label, randomised, uncontrolled study of two doses of ^{177}Lu-PSMA-617. (Study PSMA-617-02 was terminated early as it was not consistent with the overall strategy of the company. Efficacy data were not analysed and it only provided supportive safety data.)

Clinical Pharmacology

A sub-study within the Phase III Study PSMA-617-01 evaluated radiation dosimetry in 29 patients, and PK, ECGs and urine metabolites in 30 patients during Cycle 1 of treatment. In addition, a population PK analysis was undertaken using data from this sub-study. There were no data presented from healthy volunteers. Pharmacokinetic data were based on radioactivity detection in blood.

Following intravenous (IV) infusion of a single dose of ^{177}Lu-PSMA-617 it was widely distributed in tissues and volume of distribution (Vz) was 123 L (78.1% coefficient of variation (CV))

The organs with the largest absorbed doses were the lacrimal glands, salivary glands, colon/rectum and kidneys. The estimated absorbed dose after a full six cycles (44.4 gigabecquerel (GBq)) was calculated at 92 gray (Gy) for the lacrimal gland, 19 Gy for the kidneys and 1.5 Gy for the red marrow.

No metabolite was detected in significant amounts in the urine up to 48 hours, which given the geometric mean half-life of 41.6 hours, indicates excretion of unchanged parent compound during this time.

^{177}Lu-PSMA-617 is excreted predominantly through the kidneys as an intact molecule. approximately 50% of the administered activity was excreted by urine during the first 48 hours and approximately 1 to 5% of the injected ^{177}Lu-PSMA-617 activity was excreted through the faeces.

In the sub-study, the coefficient of variation for area under the concentration time curve from 0 to infinity ($AUC_{0\text{-}inf}$) was 31% and for maximum concentration (C_{max}) was 44%.

Pharmacokinetics

Following the IV injection/infusion of ^{177}Lu-PSMA-617 at Cycle 1 (dose of 7.4 GBq), the time to peak whole blood concentration (T_{max}) ranged from 0.0167 to 1.68 hours. The median T_{max} was 0.375 hours. The T_{max} was affected by variable infusion duration times. Whole blood concentrations followed a bi-exponential decline with a fast phase within the first 24 to 48 hours and a slower phase up to 144 hours, which resulted in a geometric mean terminal half-life of 41.6 hours (geometric mean (GM) CV 68.8%). The geometric mean total systemic clearance (CL) was 2.04 L/hr (GMCV 31.5%) and geometric mean apparent volume of distribution (Vz) was 123 L (GMCV 78.1%).

There have not been any studies in patients with hepatic impairment. ^{177}Lu-PSMA-617 is not metabolised by the liver, so no dose adjustment in patients with hepatic impairment has been proposed.

No dedicated renal impairment study for ^{177}Lu-PSMA-617 has been conducted. Based on simulations, renal impairment resulted in 20% increased $AUC_{0\text{-}inf}$ in mildly renally impaired patients and 42% increased $AUC_{0\text{-}inf}$ in moderately renally impaired patients. The population used for the model (n = 30) included only one patient with moderate renal impairment, 10 patients with mild renal impairment, and no patients with severe renal impairment. This limits the interpretability of the data. In addition, renal impairment resulted in a non-significant trend toward higher kidney dosimetry values. For patients with mild and moderate renal impairment, the absorbed doses for kidneys were on average 1.7-fold higher compared to patients with normal renal function.

Population pharmacokinetics analysis

Weight, body mass index (BMI), age and baseline creatinine clearance (CrCl) were investigated as covariates and CrCl had a significant effect on clearance.

PK interactions

^{177}Lu-PSMA-617 is not expected to cause any cytochrome P450 (CYP)- or transport-mediated drug interactions *in vivo*.

Pharmacokinetics conclusion

There were no healthy volunteer studies conducted. A sub-study of the Phase III trial included 30 patients who were assessed for the pharmacology endpoints. Only single dose (Cycle 1) data were collected.

Whole blood concentrations of ^{177}Lu- PSMA-617 were determined using a gamma counter to measure total radioactivity, and this was converted to ng/mL using specific activity and decay corrected radioactivity. Tissue distribution was evaluated by dosimetry.

Following intravenous administration, ^{177}Lu-PSMA-617 is widely distributed in the tissues. The organs with the largest absorbed doses were the lacrimal glands, salivary glands, colon/rectum and kidneys.

The primary route of elimination is renal, and this is largely of the parent compound based on limited metabolites in the urine. Literature indicated that about 50% of the injected activity is eliminated by urine during the first 48 hours, with 1 to 5% excreted in faeces. A population PK model found baseline creatinine clearance had a significant impact on clearance. The model may have been hampered by the small sample size and data variability. The limited dosimetry data found increased kidney radiation exposure in patients with mild to moderate renal impairment. No renal impairment study has been conducted, and the Phase III study does not include patients with creatinine clearance <50 mL/min. No dose adjustment is recommended for patients with mild or moderate renal impairment.

Given the increased exposure in patients with mild renal impairment, the lack of data in patients with moderate or severe renal impairment and the fact that such patients may be in the proposed targeted population, further elucidation of PK and dosimetry in patients with moderate and severe renal impairment should be undertaken. A study examining this has been requested by the overseas regulator.

There have been no studies in hepatic impairment and the product is not metabolised by the liver.

Drug interactions are not anticipated given the preclinical data the sponsor quoted.

Pharmacodynamics

The dossier did not include any specific pharmacodynamic studies. Limited pharmacodynamic data were available from the sub-study of PSMA-617-01.

^{177}Lu-PSMA-617 at the studied dose had no observed clinically relevant effects on corrected QT interval or other ECG parameters, although a standard thorough QT study was not performed.

Limited dosimetry data from 29 patients found the highest values were in the lacrimal gland and then lower values in the salivary glands, rectum/colon, kidneys and bladder.

There was an indication that higher exposure led to a higher decrease from Baseline in creatinine clearance although the sample size was small and adverse effects data limited on which to base exposure-toxicity conclusions.

The positive relationship between exposure and increased kidney dosimetry could be confounded by baseline creatinine clearance.

Efficacy

The dossier included one clinical efficacy study, the pivotal PSMA-617-01 Phase III study, also known as VISION.[7]

Study PSMA-617-01 (VISION)

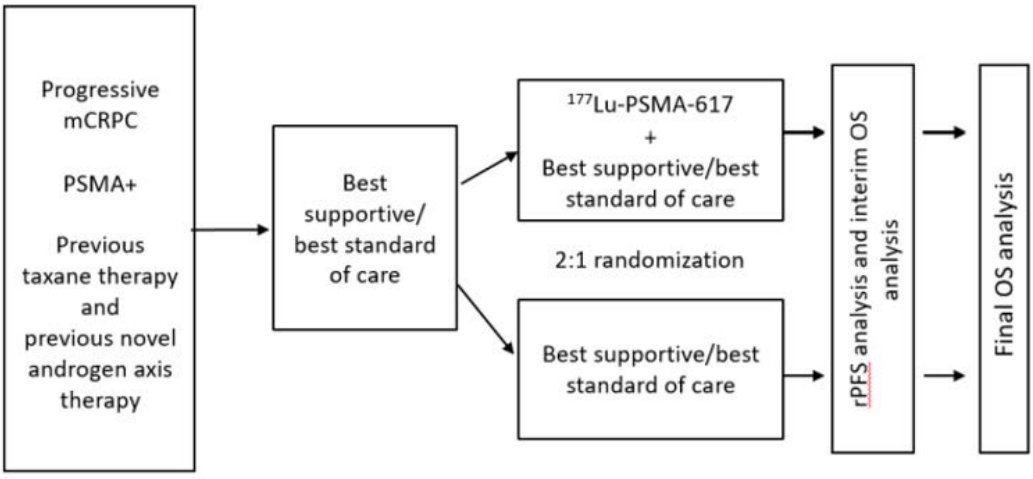
Study PSMA-617-01 (VISION) is an international, prospective, open-label, multicentre, randomised Phase III study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC).

The study commenced in May 2018, data cut off 27 January 2021. The study was conducted in the following countries (number of sites): Belgium (3), Canada (7), Denmark (3), France (6), Netherlands (4), Sweden (5), UK (9), US (45), and Germany (4, for the sub-study only). There were no study sites in Australia.

The primary objective of VISION was to compare radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC who received ^{177}Lu-PSMA-617 in addition to best supportive/best standard of care (BSC/BSoC) versus patients treated with BSC/BSoC only.

Key secondary objectives included overall response rate (ORR), disease control rate (DCR) and time to first symptomatic skeletal event (SSE). Other secondary objectives included safety and tolerability, health related quality of life, health economics and progression-free survival (PFS).

Figure 2: Study PSMA-617-01 design



Inclusion and exclusion criteria

Key inclusion criteria:

- Adult male.

[7] Sartor O, et al. VISION Investigators. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2021; 385(12): 1091-1103. doi: 10.1056/NEJMoa2107322.

- Histologically/pathologically, and/or cytologically confirmed prostate cancer.
- Progressive mCRPC (serum PSA progression, soft tissue progression or progression of bone disease).
- Received at least one novel anti-androgen drug.
- Previously treated with at least one but no more than 2 prior taxane regimens.
- Castrate level of serum testosterone (< 50 ng/dL or < 1.7 nmol/L).
- Positive 68Ga-PSMA-11 PET-CT scan.
- Eastern cooperative oncology group (ECOG) score 0-2.
- Life expectancy > 6 months.
- At least one metastatic lesion present on baseline CT, magnetic resonance imaging (MRI) or bone scan.
- Adequate bone marrow reserve, hepatic renal function (serum Cr ≤ 1.5 x upper limit of normal or CrCL ≥ 50 mLmin).

Key exclusion criteria:

- Previously treated with any of the following within 6 months of randomisation: Strontinum-89, Samarium-153, Rhenum-186, Rhenium-188, Radium-223 or hemi-body irradiation.
- Previously treated with PSMA-targeted radioligand therapy (RLT).
- Systemic anti-cancer therapy within 28 days prior to randomisation.
- Any investigational agents within 28 days prior to randomisation.
- History of central nervous system metastases who did not receive therapy and were neurologically unstable, symptomatic and receiving corticosteroids for purposes of maintaining neurologic integrity.
- Known hypersensitivity to the components of the study therapy or its analogues.
- Concurrent serious medical conditions, including New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the Investigator would impair study participation or co-operation.

Study treatments

Study treatment was ^{177}Lu-PSMA-617 (7.4 GBq +/- 10%) administered once every 6 weeks for a maximum of 6 cycles, plus BSC/BSoC. Patients were randomised 2:1 to ^{177}Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC only. Randomisation was stratified on the following factors: lactate dehydrogenase level (≤ 260 IU/L or > 260 UI/L), presence of liver metastases (yes or no), ECOG score (0-1 or 2) and inclusion of novel androgen axis drug in the BSC/BSoC (at time of randomisation, yes or no).

For both the treatment arm (AAA617 and BSC/BSoC) and the control arm (BSC/BSoC only), patients continued BSC/BSoC until they met one of the criteria for treatment discontinuation. BSC/BSoC was chosen by the patient's physician reflecting standard interventions. Where possible treatment was optimised prior to randomisation. It could be adapted during the study.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (for example, radium-223), or hemi-body radiotherapy treatment were prohibited.

Statistical methods

The design of the study was such that, to be declared positive, the study required statistical significance on either rPFS or OS at the allocated alpha level.

Radiographic progression-free survival distribution was estimated using the Kaplan-Meier method and 99.2% confidence intervals (CI) were presented. The two treatment groups were compared using a stratified (by randomisation stratification factors) log-rank test with a one-sided p value.

Overall survival in the treatment groups was compared using a log-rank test stratifying for the randomisation stratification factors. Overall survival distribution was estimated using the Kaplan-Meier method with 95% CIs. Supportive analyses for rPFS and OS used a stratified Cox regression model. A sensitivity analysis to assess the impact of COVID-19 included the primary OS analysis but censoring COVID-19 related deaths at the date of death.

Participant flow

The main reasons for discontinuing ^{177}Lu-PSMA-617 (50.6% patients) were progressive disease (23.0%), adverse events (AEs) (9.8%), and no longer clinically benefiting (6.5%).

The main reasons for discontinuing BSC/BSoC treatment were progressive disease (40.7% versus 26.1%), no longer clinically benefiting (13.1% versus 17.9%) and withdrawal of consent (9.3% versus 12.9%) (^{177}Lu-PSMA-617 plus BSC/BSoC versus BSC/BSoC only groups).

At data cut-off, study discontinuation was 65.7% and 80.4% in the ^{177}Lu-PSMA-617 plus BSC/BSoC and BSC/BSoC only group, respectively. The main reasons were death (59.7% versus 59.6%) and withdrawal of consent (5.3% versus 18.9%).

As of the data cut-off date of 27 January 2021, the median study follow-up was 20.3 and 19.8 months ^{177}Lu-PSMA-617 plus BSC/BSoC and BSC/BSoC only groups, respectively.

Protocol deviations

The rate of at least one major protocol deviation was higher in the ^{177}Lu-PSMA-617 plus BSC/BSoC than the BSC/BSoC only group (50.6% versus 38.6%).

The main deviations (in the respective groups) were related to study procedure or assessment (23.2% versus 15.0%), inclusion/exclusion criteria (20.1% versus 15.7%), informed consent (8.9% versus 9.3%), study medication (6.7% versus 0.7%) and randomisation procedures (5.1% versus 2.5%).

The study ran during the COVID-19 pandemic however enrolment was completed on 23 October 2019 prior to the beginning of the pandemic in the study countries. Dosing with ^{177}Lu-PSMA-617 was completed on 26 June 2020. Six patients discontinued ^{177}Lu-PSMA-617 due to the pandemic, and it was reported that they all had already received at least of 4 cycles of study drug. The rate of major protocol deviations related to COVID-19 was 8.3% and 1.4% in the respective groups with the major deviation being missing imaging visit or assessment (7.1% versus 1.4%). There were three COVID-19 related deaths (one in the ^{177}Lu-PMSA-617 group and 2 in the control group). The sponsor reported that 'missed assessments or procedures due to the pandemic were estimated to represent less than 0.25% of the data to be collected'.

Baseline data

All patients were recruited from sites in Europe or North America. Demographic and baseline characteristics were balanced between treatment groups. The mean age was 70.0 years, 75.3% were aged ≥ 65 years, most subjects were White (86.8%) and the 92.4% had an ECOG performance status of 0-1.

The median time since cancer diagnosis was 7.4 years, 90.9% had an adenocarcinoma. Approximately 91% of patients had bone metastases and 12% had liver metastases. Cancer therapy was balanced between the groups. Most patients (76.1%) had at least one cancer-related radiotherapy. The mean number of prior systemic therapies was 5.3 (median 5.0) and the majority of patients (79.1%) had received 4 or more different categories of regimens. All patients had received prior taxane treatment and a prior AR pathway inhibitor.

Concomitant medications indicated as BSC/BSoC were most frequently gonadotropin releasing hormone analogues (88.5% versus 83.9% in ^{177}Lu-PSMA-617 plus BSC/BSoC group and BSC/BSoC only group, respectively). Noted between group differences were for ondansetron (49.3% versus 15.6%) and anti-androgens (34.4% versus 47.3%) (mainly enzalutamide 29.7% versus 42.4%). The clinical evaluation noted that given this imbalance, a sensitivity analysis was conducted to assess the impact of concurrent anti-androgen therapies on efficacy, with results showing that the rPFS and OS benefit of adding ^{177}Lu-PSMA-617 to BSC/BSoC was maintained even after excluding patients who received androgen pathway receptor inhibitors.

The mean duration of exposure to BSC/BSoC was 8.8 months and 3.5 months (median 7.6 versus 2.1 months) in the ^{177}Lu-PSMA-617 plus BSC/BSoC and BSC/BSoC only groups, respectively.

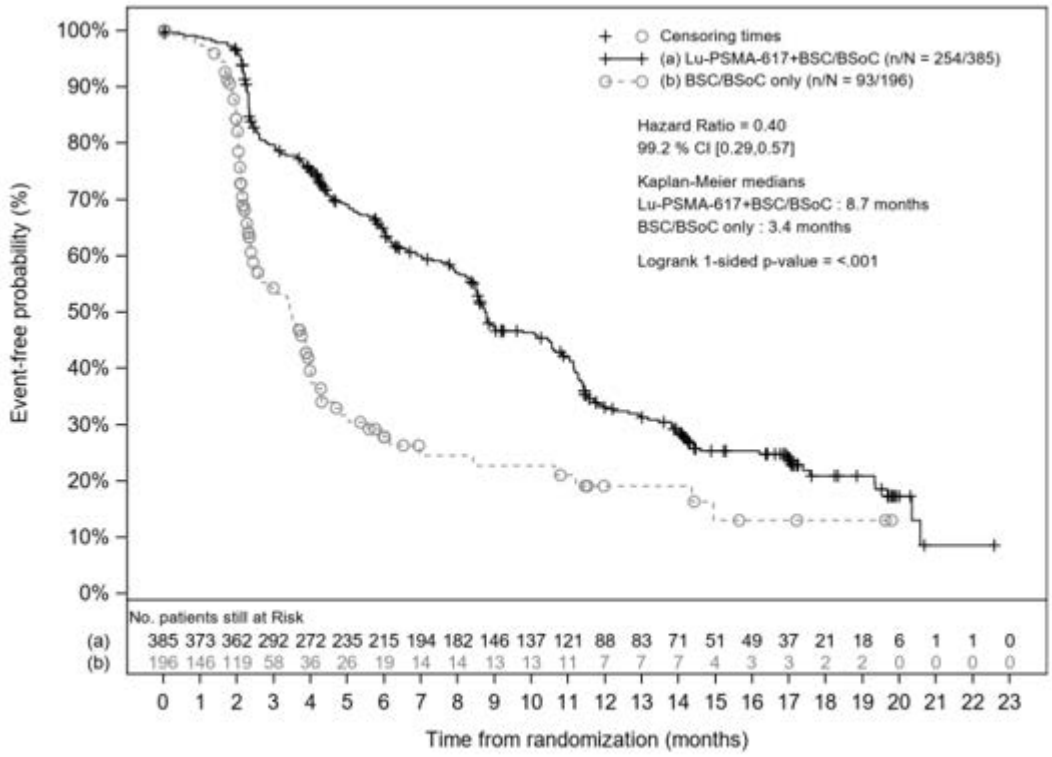
Results

The median PFS was 8.7 months (99.2% CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617 plus BSC/BSoC group to compared to 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only group, an increase of 5.3 months.

There was a 60% risk reduction in radiograph disease progression or death in the ^{177}Lu-PSMA-617 plus BSC/BSoC group (hazard ratio (HR) = 0.40, 99.2% CI: 0.29, 0.57, stratified log rank one-sided p value < 0.001).

There was a difference in the censoring rates between the 2 arms (34.0% versus 52.6%). The clinical evaluation noted that despite the change in analysis population, the rPFS data analysis was still subject to unbalanced censoring rates.

Figure 3: Kaplan-Meier plot of radiographic progression-free survival per independent central review (progression-free survival – full analysis set)



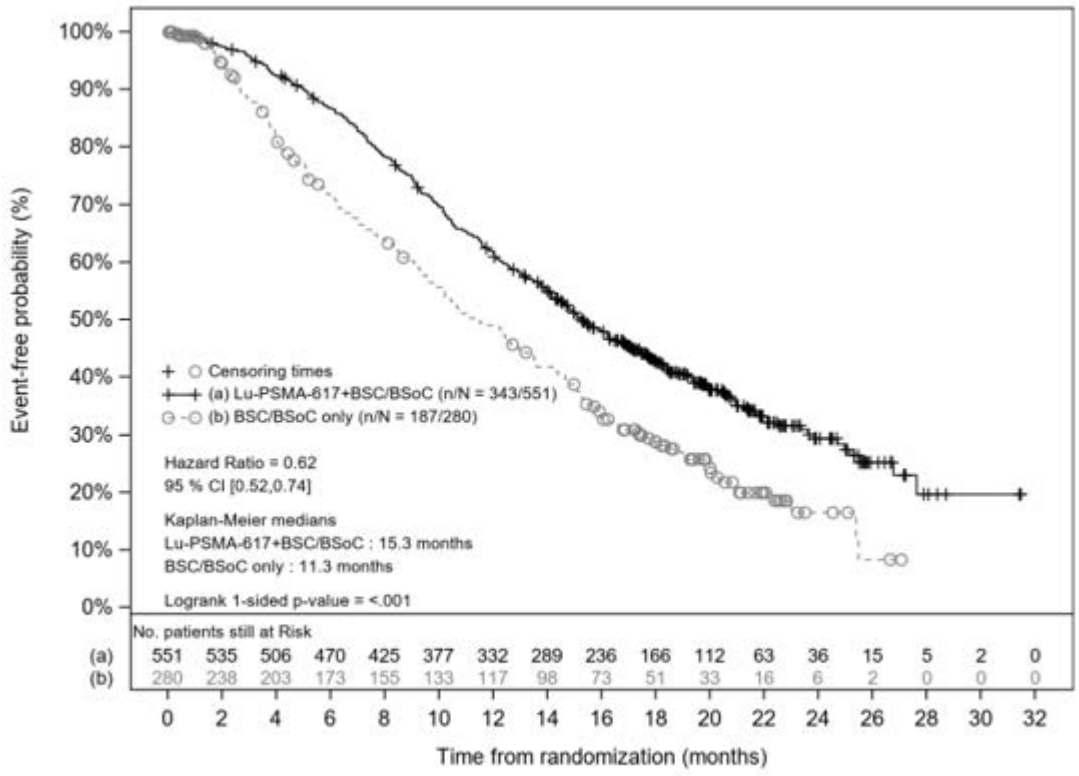
Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.

The median OS in the ^{177}LuPSMA-617 plus BSC/BSoC group was 15.3 months (95% CI: 14.2, 16.9) compared to 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only group, an increase of 4.0 months

The median OS follow-up times were similar between groups (20.3 versus 19.8 months). The risk reduction in death was 38% with a HR of 0.62 (95% CI: 0.52, 0.74, stratified log rank test $p < 0.001$).

Censoring rates for OS were 37.7% versus 33.2% in the respective groups.

Figure 4: Kaplan-Meier plot of overall survival (full analysis set)



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

The sponsor undertook further sensitivity analyses to assess the impact of censoring due to drop outs. The extreme case analysis considered all drop outs in the ^{177}Lu-PSMA-617 plus BSC/BSoC arm as events. The two best case analyses imputed data for drop outs in the control arm based on the HR in the 20% of patients with the longest survival either overall or in the BSC/BSoC only arm. Results of these analyses for rPFS and OS showed consistency with the primary analysis

The clinical evaluation noted that upon review of the disproportionate drop out in the BSoC arm compared to the ^{177}Lu-PSMA-617, ascertainment of many of the OS events from withdrawn patients as well as multiple sensitivity analyses that considered extreme cases and the possibility of informative censoring continued to support the statistically significant primary analysis results for both OS and rPFS

There was no formal statistical testing for sub-group analyses and the numbers in some groups were small.

Efficacy conclusion

The efficacy of ^{177}Lu-PSMA-617 was based on a single, Phase III, randomised, controlled study. The study was open label due to anticipated toxicity.[8]

The patient population was those with progressive mCRPC who have previously received treatment with taxane chemotherapy (at least one but not more than two regimens) and at least one novel anti-androgen drug. The inclusion criteria are consistent with the proposed indication metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. However, the proposed

[8] Sponsor clarification: The study was open label because blinding of the investigational agent was not feasible due to the ease with which both patients and site personnel may be able to determine if they were receiving a radioactive dose.

indication includes patients who are not medically suitable for taxanes and this group was not included in the clinical trial.

Trial patients had a 68Ga-PSMA-11 PET/CT scan at screening and were only included if this was positive as determined by a central reader. The criteria were strict and excluded patients if one lesion was not PSMA positive.[9] There were no data on the efficacy of the product in patients with PSMA-negative lesions and the sponsor has a US post marketing commitment to assess this population.

The study was positive with improvement on both alternate endpoints of rPFS by blinded independent central review and OS. Results were supported by key secondary endpoints of ORR, DCR and time to first SSE, by subgroup analyses and also multiple sensitivity analyses. There was a complete response rate of 5.6% (versus 0% in the control group).

Overall survival is a robust and clinically relevant endpoint and changes in the analysis strategy and populations relating to rPFS would not necessarily impact on its reliability given the ascertainment of survival status in the full population. The 4.0 months (11.3 to 15.3 months) improvement in median OS is felt clinically meaningful. The data on rPFS are not felt to be as reliable due to the smaller analysis population, the high degree of censoring (even with the change in analysis population) and the lesser meaningfulness of the outcome. It is noted in the overseas regulator review that the focus on efficacy was also on the OS endpoint and the US label does not include the rPFS data.

The time to first SSE (endpoint includes SSE and deaths) hazard ratio was driven by the differential in overall survival. The rate of non-death SSE was 15.6% and 17.3% in the respective groups. Given this, the actual effect of treatment on time to symptomatic skeletal events is less clear and its inclusion in the draft Product Information (PI) is not supported.

Safety

The safety evaluation for ^{177}Lu-PSMA-617 was primarily based on data from the single, open-label, randomised Phase III Study PSMA-617-01 in patients with PSMA-positive mCRPC. Safety data was derived from 529 patients who received from 1 to 6 doses of the 7.4 GBq ^{177}Lu-PSMA-617 on top of BSC/BSoC. The median duration of exposure to ^{177}Lu-PSM-617 was 6.9 months (mean 6.3 months, range 0.3-10.2 months). By comparison, the median duration of exposure to BSC/BSoC in the control group was 2.1 months (mean 3.5 months, range 0 to 26 months) and this could bias to a more favourable outcome in the BSC/BSoC only group.

The sample size is felt to be sufficient for this evaluation. The open label nature of the study may have affected the reporting of safety data particularly the assessment of relatedness to treatment. In addition, safety of ^{177}Lu-PSMA-617 was assessed while patients received concomitant anti-cancer therapies and the imbalance in the use of certain therapies, in particular anti-androgens (mainly enzalutamide 30% versus 43%) could have had some impact on results in favour of the ^{177}Lu-PSMA-617 group.

The safety data from the Phase II Study PSMA-617-02, which assessed 6.0 and 7.4 GBq doses, were not pooled with the Phase III study and provided little additional value due to the design differences and methodological issues (small sample size, inconsistent use of concomitant best standard of care, variable collection of laboratory data, differing classification of AEs and early

[9] Sponsor clarification: Patients should be considered eligible for lutetium Lu 177 vipivotide tetraxetan therapy if at least one tumor lesion is positive and all lesions on anatomical imaging larger in short axis than size criteria are also positive (size criteria: organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm). Patients should be considered ineligible for lutetium Lu 177 vipivotide tetraxetan therapy if all lesions are negative or any one lesion larger than size criteria is negative.

termination). Consequently, it is not possible to comment reliably on the comparative safety of the two doses.

In the Phase III study, 67.7% of patients received at least 4 cycles of ^{177}Lu-PSMA-617 while 46.5% of patients received 6 cycles. Overall, there was no specific safety concerns in patients who received the higher number of treatment cycles compared to those who received ≤ 4 cycles. However, due to patients requiring tolerability to progress to Cycle 5 and 6, a comparison between these patients may be biased. In addition, given the drop off in patient numbers, the safety profile presented may not be an accurate reflection on the safety of a full 6 cycles of therapy that are proposed in the posology in draft product information.

The data provided did not sufficiently address the long-term safety of the product and this has been queried. The median duration of follow up for OS in the full analysis set was 20.3 months in the ^{177}Lu-PSMA-617 plus BSC/BSoC group. This timeframe may not be sufficient time to assess delayed effects of radiation exposure (for example, nephrotoxicity, development of myelodysplastic syndrome or second primary malignancies). Assessment of long-term safety may need to be conducted in patients with longer life expectancy that is, in an earlier disease setting. It is noted there is a post marketing requirement from the overseas regulator for further characterisation of long-term safety as spontaneous post-marketing reports are not deemed sufficient to assess the serious risks of the therapy.

As expected, the addition of ^{177}Lu-PSMA-617 on top of BSC/BSoC led to higher rates of treatment emergent adverse events (TEAEs), Grade ≥ 3 TEAEs, treatment-related TEAEs and serious adverse events (SAEs).

Table 3: Overview of treatment emergent adverse events during randomised treatment in VISION

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
TEAE	519 (98.1)	170 (82.9)
Serious TEAE	192 (36.3)	57 (27.8)
Grade 3/4/5 TEAE	279 (52.7)	78 (38.0)
Drug-related TEAE	451 (85.3)	59 (28.8)
Serious drug-related TEAE	49 (9.3)	5 (2.4)
Drug-related grade 3/4/5 TEAE	150 (28.4)	8 (3.9)
TEAE leading to reduction of ^{177}Lu-PSMA-617	30 (5.7)	0
TEAE leading to reduction of BSC/BSoC	17 (3.2)	7 (3.4)
TEAE leading to interruption of ^{177}Lu-PSMA-617	85 (16.1)	2 (1.0)[1]
TEAE leading to interruption of BSC/BSoC	50 (9.5)	14 (6.8)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	63 (11.9)	1 (0.5)[1]
TEAE leading to discontinuation of BSC/BSoC	45 (8.5)	16 (7.8)
Fatal TEAE	19 (3.6)	6 (2.9)

Drug-related is related to any study drug (^{177}Lu-PSMA-617 or BSC/BSoC) as assessed by the investigator.
[1] Four patients randomized to ^{177}Lu-PSMA-617+BSC/BSoC arm received BSC/BSoC only, and therefore contribute to the FAS safety analysis set of the BSC/BSoC arm, see [Study PSMA-617-01-Section 10.1.2].
Source: [Study PSMA-617-01-Table 14.3.2.1]

The most notable TEAEs that were more common in the ^{177}Lu-PSMA-617 group were fatigue, dry mouth, nausea, anaemia, diarrhoea, vomiting, thrombocytopaenia, lymphopaenia, leukopaenia and urinary tract infection. Exposure-adjusted incidence rates were calculated and there remained higher rates in the ^{177}Lu-PSMA-617 group for all these events apart from fatigue.

The highest absorbed dose of radiation from the dosimetry data was in the lacrimal gland followed, at a lower level, by the salivary glands. The rate of dry eyes was less than might be expected (3.0% versus 1.0%) and all but one case were Grade 1 in severity. By contrast, dry

mouth was frequent (39.3% versus 1.0%), although severity was Grade 1 or 2 and it rarely led to dose reduction or discontinuation.

The most common treatment-related adverse events occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617 plus BSC/BSoC were dry mouth, fatigue, nausea, anaemia, thrombocytopaenia, decreased appetite and vomiting. The rate of Grade ≥ 3 treatment related adverse events (AEs) was higher in the ^{177}Lu-PSMA-617 group (28.4% versus 3.9%) and Grade ≥ 3 events of note included anaemia (9.6% versus 0.5%), thrombocytopenia and lymphopenia (6.8% versus 0% each).

Most deaths while on randomised treatment were related to disease progression. Serious adverse events with a fatal outcome were slightly more frequent in the ^{177}Lu-PSMA-617 group (3.6% versus 2.9%). There were three fatal AEs associated with concomitant myelosuppression and two due to bleeding (intracranial haemorrhage and subdural haematoma) in patients with concurrent thrombocytopaenia.

A higher rate of SAEs occurred in the ^{177}Lu-PSMA-617 arm compared to the BSC group (36.3% versus 27.8%) with treatment-related SAEs in also more frequent (9.3% versus 2.4%). The most common SAEs in the ^{177}Lu-PSMA-617 plus BSC/BSoC group were anaemia (2.8% versus 0.5%), urinary tract infection (2.5% versus 0.5%) and haematuria (2.1% versus 0.5%). There was higher rate of spinal cord compression in the BSC/BSoC group (1.1% versus 4.9%).

Discontinuation of ^{177}Lu-PSMA-617 due to a TEAE occurred in 12% of patients and was generally related to myelosuppression - anaemia (2.8%), thrombocytopaenia (2.8%), leukopaenia (1.3%), neutropaenia (0.8%) and pancytopaenia (0.6%). Dose interruption was necessary in 16.1% and dose reduction in 5.7%, with haematologic adverse events being the main reason.

The most common laboratory abnormalities that worsened from Baseline in the ^{177}LuPSMA-617 plus BSC/BSoC group were decreases in haemoglobin, lymphocytes, leukocytes and platelets. Liver function parameters did not reveal any hepatic safety concerns while there was a slightly higher rate of increased creatinine (29.7% versus 22.9%).

Renal events were slightly higher in ^{177}Lu-PSMA-617 treated patients (8.7% versus 5.9%) although only one led to treatment withdrawal. The kidney is the main route of excretion, and it is also a PSMA expressing tissue so nephrotoxicity is a potential concern. The Phase III study did not include patients with a creatinine clearance of < 50 mL/min so use in this population, together with longer term renal safety, are important areas of missing safety information. This gap has also been identified by the overseas regulator. Therefore, a post marketing study is required in patients with moderate or severe renal impairment.

There was a trend for higher incidence and severity of AEs in patients with increasing age, ECOG score of 2, renal impairment, abnormal epidermal growth factor receptor, proteinuria and concurrent radiation therapy.

No specific clinical drug-drug interaction studies were conducted. The quoted data were not suggestive of potential interactions.

The addition of ^{177}Lu-PSMA-617 to best standard of care in this advanced cancer population was reasonably tolerated. Haematologic toxicity with myelosuppression was the most notable safety issue particularly as this patient population may have reduced bone marrow reserve due to metastases or prior chemotherapy.

Post marketing data to March 2023 reported an estimated 4198 patients exposed to Pluvicto and a cumulative clinical trial exposure of 1330 patients. There have been 1572 cases reported including risks of myelosuppression, renal toxicity and intracranial haemorrhage. Bone and

fracture events have been assessed, and risk is difficult to separate from underlying disease. The risks of second primary malignancy and the risk in patients with renal impairment still require further data. The potential safety risk of inadvertent radiation exposure has not been reported to date in post marketing data.

Safety conclusion

Treatment with Pluvicto was not without safety risks and 12% of patients discontinued therapy due to an adverse event, with bone marrow toxicity and resultant myelosuppression being the most notable. As the patient population may have diffuse metastatic disease infiltrating the bone marrow, and have all received taxane chemotherapy, they would be predisposed to this haematologic toxicity.

Given the renal excretion of the product, the risk of long-term kidney toxicity, the potential for increased radiation exposure in patients with renal impairment, and the lack of clinical data in this patient group, there is evident need for further assessment in this area. The overseas regulator has a post marketing requirement for Study CAAA617A12202, which aims to determine the 'kidney biodistribution, dosimetry, pharmacokinetics, and safety of lutetium (^{177}Lu) vipivotide tetraxetan and assess the potential for higher drug exposure and the resultant risk of increased serious toxicities in patients with moderate and severe renal impairment'. The study will assess long-term toxicities in these patients and follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first. The clinical study report is expected to be available in quarter 4 of 2026 and data should result in optimisation of the labelling recommendations. Until these data are available, the Product Information needs to fully outline the renal risks including the lack of data in patients with creatinine clearance < 50 mL/min.

Given the relatively short follow up of patients in the pivotal study there is a lack of long-term safety data. The overseas regulator has another post marketing requirement to further delineate potential long-term risks. It was stated that the sponsor needs to:

> *Conduct an integrated safety analysis to further characterize the long term outcome of the known serious risk of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications; the potential serious signals of secondary malignancies including myelodysplastic syndrome and acute myeloid leukemia (MDS/AML); and other serious adverse reactions in patients receiving lutetium (^{177}Lu) vipivotide tetraxetan in the VISION study and its sub-study, Trial CAAA617C12301 (NCT04720157), Trial CAAA617B12302 (NCT04689828) and other clinical trials as appropriate. Capture data prospectively in amended case report forms to include incidence, grade, date of onset and resolution of the adverse reaction, predisposing factors and outcomes, date and quantity of red cell and platelet transfusion, use of growth factors for myelosuppression, subsequent antineoplastic therapies, radiation therapy, and hospital admissions. Follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first.*

The expected final report is due March 2034.

Pluvicto is a radioactive therapeutic agent with a novel mechanism of action targeting an indication where there is a definite unmet clinical need. In patients with progressive, PSMA-positive mCRPC who have been treated with androgen reception pathway inhibition and taxane-based chemotherapy, treatment with ^{177}Lu-PSMA-617 resulted in an improvement in overall survival of four months compared to treatment with best standard of care. While safety risks, particularly bone marrow toxicity, are present, they are outweighed by the potential for clinically meaningful improved survival in this population with a life-threatening condition. As such, the benefit–risk balance is positive.

Recommendation following the clinical evaluation

Approval of Pluvicto is recommended subject to:

- Revision of the indication as follows:

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

- Provision of data from the post marketing study in patients with moderate or severe renal impairment when available.
- Provision of data from the integrated safety analysis/post marketing study characterising the long-term safety of patients who have received Pluvicto when available.

Risk management plan

Novartis Pharmaceuticals Australia Pty Ltd has submitted European Union (EU)- risk management plan (RMP) version 1.2 (date 11 October 2022; data lock point (DLP) 27 January 2021) and Australian-specific annex (ASA) version 1.0 (dated 20 June 2023) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 4: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Myelosuppression	✓	–	✓	-
	Renal toxicity	✓	✓†	✓	–
Important potential risks	Intracranial hemorrhage	✓*	–	-	–
	Inadvertent radiation exposure	✓	-	✓	–
	Second primary malignancies	✓	✓†	-	–
Missing information	Patients with severe renal impairment	✓	–	✓	–

* Targeted follow – up.

† PSMA-617-01 (VISION) study

The summary of safety concerns in the ASA aligns with the EU-RMP and is acceptable from an RMP perspective.

The sponsor has proposed routine pharmacovigilance activities for all safety concerns, which includes a general checklist for cerebral haemorrhage as specific adverse drug reactions follow

up form, for the important potential risk of intracranial haemorrhage. Additional pharmacovigilance activity has been proposed in the form of an extended 12-month long-term follow-up study to assess the survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies. The sponsor has committed to provide the outcomes of the completed study to the TGA for review when available.

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

Risk-benefit analysis

Delegate's considerations

Few therapeutic options exist for patients with mCRPC who have previously received a novel androgen receptor inhibitor and taxane-based chemotherapy; there remains an unmet medical need for effective new treatment options in this setting.

Lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu-PSMA-617) is a prostate-specific membrane antigen (PSMA) inhibitor which has been used experimentally for several years for the treatment of patients with mCRPC; consequently, published data on efficacy and safety of ^{177}Lu-PSMA-617 in patients with mCRPC is available from many centres.

Benefits

The pivotal data for efficacy come from Study PSMA-617-01 (VISION). This was a prospective, open-label, multicentre, randomised Phase III study of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC who had previously received taxane-based chemotherapy regimens and at least one androgen receptor pathway inhibitor, and who had a 68Ga-PSMA-11 PET/CT scan that determined eligibility for inclusion. Patients were randomised 2:1 to receive either 7.4 GBq (± 10%) ^{177}Lu-PSMA-617 plus BSC/BSoC or to receive BSC/BSoC only.

At final analysis (data cut-off 27 January 2021), with a median follow-up time for OS of approximately 20 months, both alternate primary efficacy objectives in the VISION study of rPFS and OS were met.

Treatment with ^{177}Lu-PSMA-617 showed an improvement in both primary endpoints of rPFS by blinded independent central review and OS compared with treatment with BSC/BSoC, of which the OS benefit is considered clinically relevant.

- rPFS: treatment with ^{177}Lu-PSMA-617 showed a statistically significant improvement in rPFS compared with BSC/BSoC: HR = 0.40 (99.2% CI: 0.29, 0.57); $p < 0.001$; median rPFS 8.7 months (95% CI: 7.9; 10.8) versus 3.4 months (95% CI: 2.4; 4.0).
- OS: treatment with ^{177}Lu-PSMA-617 showed a statistically significant improvement in OS compared with BSC/BSoC: HR = 0.62 (95% CI: 0.52; 0.74); $p < 0.001$; median OS 15.3 months (95% CI: 14.2; 16.9) versus 11.3 months (95% CI: 9.8; 13.5).

All performed sensitivity/supportive analyses support the OS primary analysis and subgroup analyses for OS provided results consistent with this analysis.

For the key secondary endpoints (ORR, DCR and time to first SSE), treatment with ^{177}Lu-PSMA-617 showed a statistically significant improvement compared with BSC/BSoC; the rPFS result and the results for the key secondary endpoints provide support for the OS result.

Uncertainties of benefit

The reliability of reported patient reported outcome (PRO) results which favoured treatment with ^{177}Lu-PSMA-617 plus BSC/BSoC is low, in view of the lower recurrence rate of the PROs-questionnaires and the open design, limiting the interpretation of the effect on quality of life for the treatment regimen.

Homogeneity and consistency of the alternate primary endpoints rPFS and OS was not demonstrated across patient subgroups of Asians, African Americans or Blacks, and baseline prostate specific antigen doubling time > 9 months, due to small patient numbers.

Risks

The main safety evaluation was based on safety data from Study PSMA-617-01 (VISION). Supportive safety data are derived from the Phase II Study PSMA-617-02 using a different dose regimen (6.0 GBq or 7.4 GBq, every 8 weeks for 4 cycles).

Adding ^{177}Lu-PSMA-617 to BSC leads to a more unfavourable safety profile compared with BSC alone, with higher numbers of treatment-related AEs, severe AEs, SAEs, and treatment-related deaths. This may partly be attributed to the imbalance in treatment duration with a significantly shorter treatment exposure in the BSC/BSoC arm, leading to a bias to the disadvantage of ^{177}-Lu-PSMA-617.

Serious adverse events:

- PSMA: 36.3% versus BSC: 27.8%.

Drug-related SAEs:

- PSMA: 9.3% versus BSC: 2.4%.

Grade 3 or higher AEs:

- Mainly haematological events.
- PSMA: 52.7% versus BSC: 38.0%.
- Drug related Grade 3 or higher AEs: 28.4% versus 3.9%
- Incidence of each individual Grade ≥ 3 AE was low.

Deaths:

- 85 patients died while on-treatment.
- PSMA: 12.5% versus BSC: 9.3%.
- Most deaths were due to disease progression (PSMA: 8.3% versus BSC: 6.8%).
- However, three deaths were reported to be related to study treatment by the investigator: 2 deaths due to pancytopenia and one death due to bone marrow failure, all in the PSMA arm. In a trial with a comparison with BSC/BSoC this may be expected but may indicate also a higher risk due to the additional treatment.

Dose reduction due to TEAE:

- 5.7% of patients in the PSMA arm had TEAEs that led to dose reduction.

Treatment discontinuation due to TEAE:

- 11.9% of the patients discontinued ^{177}Lu-PSMA-617 due to TEAEs.

- The most frequent TEAEs leading to discontinuation of ^{177}Lu-PSMA-617 were related to myelosuppression.

Adverse events: the greatest differences (≥ 20%) between the two treatment arms were observed for:

- Gastrointestinal disorders (PSMA: 75.4% versus BSC: 31.7%).
- General disorders and administration site conditions (PSMA: 61.2% versus BSC: 38.5%).
- Blood and lymphatic system disorders (PSMA: 47.8% versus BSC: 18.0%).
- Urinary tract infections were also more frequent (PSMA: 11.0% versus BCS: 1.0%).

Adverse events of special interest included:

- Fatigue (PSMA: 49.1% patients versus BSC: 29.3% patients).
- Myelosuppression (47.4% patients versus 17.6% patients) (Grade ≥ 3: 23.4% versus 6.8%).
- Dry mouth (39.3% patients versus 1.0% patients).
- Nausea and vomiting (39.3% patients versus 17.1% patients).

Drug related TEAEs (as assessed by the investigator) were clearly more frequent in the PSMA arm (85.3% patients) as compared to the BSC arm (28.8% patients) as would be expected:

- High Grade (≥ 3) events were reported with highest incidence in this arm for anaemia (9.6% patients), thrombocytopenia and lymphocytopenia (6.8% each).
- Dry mouth, fatigue and nausea, that were the most reported drug-related events in this arm, were usually low grade (≤ 2) in severity and only led to permanent discontinuation of ^{177}Lu-PSMA-617 in ≤ 0.5% of patients.
- Myelosuppression, this is a known risk for ^{177}Lu-PSMA-617; myelosuppression-related events (including anaemia, thrombocytopenia, lymphocytopenia, leukopenia, neutropenia) was consistently higher in the PSMA arm (47.4%) compared with the BSC arm (17.6%).
- Renal toxicity is also a known risk for ^{177}Lu-PSMA-617; renal events in general were observed slightly more frequent with 8.7% of patients in the PSMA arm than in the BSC arm (5.9%). Renal toxicity was predominantly low-grade comprising creatinine increases that were manageable and reversible. Nevertheless, Grade ≥ 3 events were reported.
- Patients with moderate renal impairment (CrCl < 50 mL/min) may bear an inherent risk of increase in AEs and treatment with ^{177}Lu-PSMA-617 is not recommended in this population. The differences between renally impaired versus non-impaired groups were greater for high grade TEAEs (77.4% patients versus 50.5% patients), and serious TEAEs (67.7% patients versus 32.9% patients). Similar difference (50.0% patients versus 26.4% patients) was noted in the BSC/BSoC only arm for the serious TEAEs. The incidence of fatal TEAEs, though low in number overall, was 4 times more in the impaired group as compared with the non-impaired (12.9% patients versus 3.0% patients) in the PSMA arm and more than 2 times in the impaired group as compared with the non-impaired in the BSC arm (7.1% patients versus 2.7% patients).
- Hepatotoxicity was slightly higher for the PSMA arm (PSMA: 10.2% versus BSC: 7.8%).
- Non-haematological TEAEs: although the TEAEs such as dry mouth (38.8% versus 0.5%), nausea (35.3% versus 16.6%), diarrhea (18.9% versus 2.9%), vomiting (18.9 versus 6.3%) and urinary tract infections (11% versus 1%) were also more frequent in the

^{177}Lu-PSMA-617 plus BSC/BSoC arm; however, they were usually low grade (≤ 2) in severity, and only led to permanent discontinuation of ^{177}Lu-PSMA-617 in ≤ 0.5% of patients.

- Despite the high apparent radiation exposure, incidences of lacrimal toxicities, that is, dry eye and blurred vision were infrequent and were mostly low grade (Grade 1-2) in the PSMA-617-01 study. Two (0.4%) patients in the PSMA arm had high grade (≥ 3) events of blurred vision.
- Second primary malignancies as consequence of the radiation were infrequent events in both arms (2.1% patients versus 1.0% patient). The events were skin cancers and metastases to the brain or meninges. However, one case of acute myeloid leukemia (AML) was reported outside of the treatment emergent period, after the 30-day post-treatment follow-up, but before capture of long-term follow-up events.

Uncertainties of risk

The safety profile presented may not fully reflect the treatment risks of the applied posology, as more than the half of the full analysis set safety population included in this assessment was not exposed to the planned treatment course of 6 cycles and the intended full dose of ^{177}Lu-PSMA-617. An underestimation of the toxicity may even be presumed also, since frequency and particularly severity of adverse events of special interest are likely to depend on the total dose administered and may increase during longer treatment.

The open-label design of the pivotal study may have affected safety reporting, and the imbalance of drug-related AEs, as assessed by the investigator, needs to be interpreted with caution. Many patients were already receiving BSC/BSoC before randomisation and standard of care might have not been systematically considered as study drug by some investigators.

The uncertainty that there may be a potential for ameliorated tolerability at a lower dose level remains. However, it is unknown whether this would maintain similar clinical benefit.

Myelosuppression events in the ^{177}Lu-PSMA-617 arm occurred frequently and these events have a large impact on the toxicity, tolerability and on treatment-related deaths. It is unclear whether risk minimalisation measures were taken/were effective on this subject.

The risk of haematological malignancies particularly for leukemia/myelodysplastic syndromes and other malignancies is clearly a well-known complication of all types of radiation treatment and probably beside the risks derived from bone marrow impairment (bleeding, infection) the most severe adverse event of RLT. A case of AML is already reported. However, it is acknowledged that in patients with mCRPC with a limited life-expectancy the relevance of these events may reasonably be balanced by the improvement in overall survival. As in other RLTs before this important risk remains not fully evaluable from the data submitted, further data from longer follow-up is recommended.

It is not known whether AEs related to the safety topics resolved over time as these data were not collected by the sponsor. The sponsor has meanwhile committed that these data will be submitted at the time they become available via the post-marketing requirement of the overseas regulator, which is intended to collect data including the risks of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications, and potential of secondary malignancies.

Benefit/Risk balance

The benefit-risk balance is considered to be favourable in patients with progressive, PSMA-positive mCRPC, who have received ≥ 1 novel androgen receptor inhibitor and had previously been treated with 1 to 2 taxane-based chemotherapy regimens, treatment with

^{177}Lu-PSMA-617 showed a statistically significant and clinically relevant improvement in OS compared to treatment with BSC/BSoC.

As expected, a more unfavourable safety profile was reported for patients in the ^{177}Lu-PSMA-617 arm compared to those who received BSC/BSoC alone. However, the safety profile of ^{177}Lu-PSMA-617, although non-negligible, is outweighed by the efficacy outcomes in the context of this disease setting and patient population.

The clinical evaluation has recommended removing the phrase 'who are not medically suitable for taxanes' from the indication, as the VISION trial did not include this patient group. The sponsor did not agree.

In theory, there does not appear to be any biologic reason to suggest that the efficacy or safety of ^{177}Lu-PSMA-617 in patients who are unsuitable for taxanes would be significantly different to patients who have previously received these agents in this context. However, the intended population of VISION was that of patients with progressive disease following previous treatment with an androgen receptor pathway inhibitor and docetaxel +/- cabazitaxel (that is, those who have no other (currently) available life-prolonging therapeutic options), this is reflected in the VISION inclusion criteria. As such, there is no trial data to support a favourable clinical benefit-risk profile of this therapy, at present, for the patient group 'who are not medically suitable for taxanes'.

The Delegate awaits with interest the results of currently active trials (that is, PSMAfore NCT04689828, patients with mCRPC with progressive disease following one prior second generation androgen receptor inhibitor therapy; PSMAddition NCT04720157) which is expected to provide information on the clinical efficacy and safety of Pluvicto in an earlier treatment setting for patients with metastatic prostate cancer.

Given the lack of clinical data in the chemotherapy naïve population, the delegate's preliminary (pre-ACM) view is in alignment with the recommendation with the clinical evaluation, with support for the following indication:

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

The Delegate will refer this issue to the ACM to seek their view on whether they support the use of Pluvicto in the Australian clinical setting for the less restrictive indication as proposed by the sponsor.

Proposed action

The benefit risk assessment for Pluvicto is considered to be favourable; the Delegate supports registration of Pluvicto for the following indication:

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

Advisory committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***Does ACM support the use of Pluvicto in the Australian clinical setting for the less restrictive indication as proposed by the sponsor (that is, for the treatment of adult patients with PSMA positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes)?***

The ACM advised that the VISION trial included only patients who had had prior treatment with androgen receptor pathway inhibition and a taxane.

The ACM considered that it was likely that patients considered 'not medically suitable for a taxane' would likely have failed other inclusion criteria for the VISION trial.

The ACM noted that long-term toxicity (such as radiation risk and second cancers) from Pluvicto is unknown and risk may increase with longer survival if Pluvicto is used earlier in the course of the disease.

While it is likely clinical benefit would be seen in the 'not medically suitable for a taxane' patients, benefit over risk has not been established, and more data are required.

Advisory committee conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

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

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Pluvicto (lutetium (^{177}Lu) vipivotide tetraxetan) 1000 MBq/mL, solution for injection, vial indicated for:

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

Specific conditions of registration

- Pluvicto (Lutetium (^{177}Lu) vipivotide tetraxetan) is to be included in the Black Triangle Scheme. The PI and CMI for Pluvicto must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Pluvicto EU-Risk Management Plan (RMP) (version 1.2, dated 11 October 2022, and, DLP 27 January 2021), with Australian specific annex (version 1.0, dated 20 June 2023), included with submission PM-2023-02254-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

- Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.
- The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Conduct an integrated safety analysis to further characterise the long term outcome of the known serious risk of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications; the potential serious signals of secondary malignancies including myelodysplastic syndrome and acute myeloid leukemia (MDS/AML); and other serious adverse reactions in patients receiving lutetium (^{177}Lu) vipivotide tetraxetan in the VISION study and its sub-study, Trial CAAA617C12301 (NCT04720157), Trial CAAA617B12302 (NCT04689828) and other clinical trials as appropriate. Capture data prospectively in amended case report forms to include incidence, grade, date of onset and resolution of the adverse reaction, predisposing factors and outcomes, date and quantity of red cell and platelet transfusion, use of growth factors for myelosuppression, subsequent antineoplastic therapies, radiation therapy, and hospital admissions. Follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first.
- Conduct a clinical trial to determine the kidney biodistribution, dosimetry, pharmacokinetics, and safety of lutetium (^{177}Lu) vipivotide tetraxetan and assess the potential for higher drug exposure and the resultant risk of increased serious toxicities in patients with moderate and severe renal impairment. Assess long-term toxicities in these patients. Follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first. Include risk mitigation strategies to reduce potential toxicities in the final report. Design and conduct the trial in accordance with FDA Guidance for Industry titled Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing.
- Conduct a clinical trial to evaluate the efficacy and safety of lutetium (^{177}Lu) vipivotide tetraxetan in patients with advanced/metastatic prostate cancer who have at least one lesion with PSMA expression higher than that in normal liver parenchyma on PSMA-11 PET scan and at least one lesion with PSMA expression less than or equal to uptake in normal liver, with the following size criteria in short axis: size criteria in short axis: organs > 1 cm, lymph nodes > 2.5 cm, bones (soft tissue component) > 1cm. Alternatively, add cohorts of these patients to ongoing trials. Include an analysis of these safety and efficacy data.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

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