Summary Report of Benefit-Risk Assessment

PLUVICTO SOLUTION FOR INJECTION/INFUSION 1000 MBq/mL

NEW DRUG APPLICATION

Active Ingredient(s)	Lutetium (^{177}Lu) vipivotide tetraxetan
Product Registrant	Novartis (Singapore) Pte Ltd
Product Registration Number	SIN16917P
Application Route	Abridged evaluation
Date of Approval	18 December 2023

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A INTRODUCTION

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.

The active moiety of Pluvicto is the radionuclide lutetium-177 (^{177}Lu) which is linked to PSMA-617 (vipivotide tetraxetan), a targeting moiety that binds with high affinity to PSMA, resulting in internalisation and retention within the targeted prostate cancer cell. Upon the binding of Pluvicto to PSMA-expressing cancer cells, the beta-minus emission from lutetium-177 delivers therapeutic radiation to the targeted cell, as well as to surrounding cells, and induces DNA damage which can lead to cell death.

Pluvicto is available as radiopharmaceutical solution for injection/infusion containing 1000 Mbq/mL of Lutetium (^{177}Lu) vipivotide tetraxetan. Other ingredients in the vial are acetic acid, sodium acetate, gentisic acid, sodium ascorbate, pentetic acid, and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Lutetium (^{177}Lu) vipivotide tetraxetan and the drug product, Lutetium (^{177}Lu) vipivotide tetraxetan solution for injection 1000MBq/mL, are manufactured at Advanced Accelerator Applications S.R.L., Colleretto Giacosa, Italy.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance has been appropriately performed. The synthesis of the drug substance and its formulation into the drug product are part of a continuous process which is standard for radiopharmaceuticals. The drug substance is not isolated or stored, hence the quality control testing is performed at the finished product stage.

Drug product:

The manufacturing process utilises aseptic processing.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 120 hours (5 days) when stored at or below 30ºC. The container closure system is a colourless type I 30ml glass vial with bromobutyl rubber septum, capped with aluminium cap. The vial is enclosed within a lead shielded container.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Pluvicto for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibitor and taxane-based chemotherapy was based primarily on data from one pivotal Phase III study PSMA-617-01 (VISION).

The VISION study was a Phase III, randomised, open-label, multicentre study in patients with PSMA-positive mCRPC with at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, who have received at least one AR pathway inhibitor such as abiraterone acetate or enzalutamide, and 1 or 2 prior taxane-based chemotherapy regimens. Patients underwent a gallium (^{68}Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria.

Patients were randomised in a 2:1 ratio to receive either Pluvicto 7.4 GBq (200 mCi) every 6 weeks for up to a total of 6 doses plus best supportive care/best standard of care (BSC/BSoC) or BSC/BSoC alone. Randomisation was stratified by baseline lactate dehydrogenase (LDH), presence of liver metastases, Eastern Cooperative Oncology Group (ECOG) performance status score, and inclusion of an AR pathway inhibitor as part of BSC/BSoC at the time of randomisation. BSC/BSoC was administered at the physician's discretion, and included supportive measures, ketoconazole, radiation therapy in any external beam or seeded form to localised prostate cancer targets, bone-targeted agents (e.g., zoledronic acid, denosumab, bisphosphonates), AR pathway inhibitors, as well as androgen-reducing agents (including gonadotropin-releasing hormone [GnRH] analogues, corticosteroid and 5-alpha reductases). Patients continued treatment until evidence of tumour progression, unacceptable toxicity, use of prohibited treatment, non-compliance or withdrawal, or lack of clinical benefit.

The alternate primary efficacy endpoints were radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per Prostate Cancer Working Group 3 (PCWG3) criteria and overall survival (OS). Key secondary efficacy endpoints were overall response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, duration of response (DoR), disease control rate (DCR), and time to first symptomatic skeletal event (SSE), defined as first new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death from any cause, whichever occurred first.

The overall significance level for the study was 0.025 (one-sided), which was allocated between the alternate primary endpoints. For the study to be declared positive, it was required to reach statistical significance on either rPFS or OS at the respective allocated alpha level. The planned total sample size of 814 patients provided 84% power to detect a hazard ratio (HR) of 0.67, at a one-sided significance level of 0.004, in the analysis of rPFS after the occurrence of 364 events in 557 patients; and 90% power to detect a HR of 0.73, at a one-sided significance level of 0.025 (or 0.021 if the result in the rPFS analysis was not significant), in the analysis of OS after 508 deaths in 814 patients. If either alternate primary endpoint was met, key secondary endpoints were assessed using the Hochberg closed test procedure, to

control the overall Type I error rate. The analysis of OS included all the patients who had undergone randomisation (Full Analysis Set; FAS), whereas rPFS was analysed in a subgroup of patients who had undergone randomisation[1] (PFS-FAS). To assess the robustness of the primary endpoints, multiple sensitivity and supportive analyses were conducted. For rPFS, sensitivity analyses included analyses that accounted for additional categories of rPFS events, censoring of deaths following new anti-cancer therapy, and investigator assessment versus BICR. Supplementary analyses were performed using different population sets (FAS for rPFS and PFS-FAS for OS). Additional analyses were also conducted to assess the sensitivity of rPFS and OS to censoring due to dropouts.

A total of 831 patients were randomised into the study and included in the FAS – 551 in the Pluvicto+BSC/BSoC arm and 280 in the BSC/BSoC only arm. Of these 831 patients, 581 were randomised on or after 05 Mar 2019 (PFS-FAS) (385 in the Pluvicto+BSC/BSoC arm and 196 in the BSC/BSoC only arm). In the FAS, about half of the patients (50.6%) in the Pluvicto+BSC/BSoC arm discontinued Pluvicto treatment and 70.0% of patients in the control arm discontinued BSC/BSoC. The main reason (>10%) for discontinuing Pluvicto treatment was progressive disease (23.0%), while the main reasons for discontinuing BSC/BSoC treatment in the control arm were progressive disease (26.1%), no longer clinically benefitting (17.9%) and withdrawal of consent (12.9%).

The patient demographics and baseline disease characteristics were generally balanced between the treatment arms in both the FAS and PFS-FAS. In the FAS, the median age was 71 years (range: 40 to 94 years). The majority of patients were White (86.8%) and 2.4% were Asian. All patients (100.0%) had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two. At randomisation, 51.3% of patients had received one prior AR pathway inhibitor, 41.0% of patients received 2, and 7.7% of patients received 3 or more. During the randomised treatment period, 52.6% of patients in the Pluvicto+BSC/BSoC arm and 67.8% of patients in the BSC/BSoC only arm received at least one AR pathway inhibitor.

The study met its primary objectives for both alternate primary endpoints, rPFS per BICR and OS. The results demonstrated a statistically significant improvement in rPFS of 5.3 months for patients receiving Pluvicto+BSC/BSoC compared to patients receiving BSC/BSoC only. The median rPFS was 8.7 months (99.2% confidence interval [CI]: 7.9, 10.8) in the Pluvicto+BSC/BSoC arm and 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm (HR 0.40; 99.2% CI: 0.29, 0.57; p<0.001). The results of various sensitivity analyses for rPFS per BICR were consistent with the primary analysis results.

In terms of OS, treatment with Pluvicto+BSC/BSoC resulted in statistically significant improvement of 4.0 months compared to patients receiving BSC/BSoC only. The median OS was 15.3 months (95% CI: 14.2, 16.9) in the Pluvicto+BSC/BSoC arm and 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only arm (HR 0.62; 95% CI: 0.52, 0.74; p<0.001). Consistent OS benefit was demonstrated across sensitivity analyses.

Pre-specified subgroup analyses demonstrated generally consistent rPFS and OS benefits in all subgroups analysed, including use of AR pathway inhibitors as part of BSC/BSoC at time of randomisation (yes, no), baseline LDH (≤260 IU/L, >260 IU/L), presence of liver metastases

[1] After commencement of the study, a high rate of withdrawal of consent in the BSC/BSoC only arm was noted with the majority of these dropouts withdrawing consent to follow-up, hence rPFS data could not be collected for these patients. Enhanced study site education measures were implemented on 05 Mar 2019 to reduce the rate of withdrawal. To minimise the potential for bias in the analysis of rPFS due to the differential withdrawal of consent rate between the two treatment arms, the primary analysis of rPFS focused on patients randomised on or after 05 Mar 2019.

at baseline (yes, no), ECOG performance status score (0 or 1, 2), age (<65 years, ≥65 years), region (North America, Europe), baseline prostate specific antigen (PSA) (≤76 ng/mL, >76 ng/mL), baseline PSA doubling time (PSADT) (0 to ≤9 months, >9 months), number of prior AR pathway inhibitors (1, ≥2), number of prior immunotherapies (0, ≥1), number of prior taxanes (1, ≥2), number of prior non-taxanes (0, ≥1), prior bone sparing agents (yes, no), prior 223-Radium (yes, no), prior poly ADP-ribose polymerase (PARP) inhibitors (yes, no), concurrent AR pathway inhibitors (yes, no), concurrent radiation therapy (yes, no), and concurrent bone sparing agents (yes, no). It was observed that in the Asian subgroup the rPFS and OS showed an unfavourable trend for the Pluvicto+BSC/BSoC arm vs BSC/BSoC only arm with a HR of 1.50 (95% CI: 0.36, 6.19) and 1.04 (95% CI: 0.38, 2.81), respectively. Nonetheless, the results should be interpreted with caution as the sample size was very small for the Asian subgroup (≤11 patients per arm) and the 95% CIs were wide.

All key secondary objectives were also met. The ORR was statistically significant in favour of the Pluvicto+BSC/BSoC arm (29.8% vs 1.7%; odds ratio [OR] 24.99; 95% CI: 6.05, 103.24; p<0.001). The median DoR in responders was 9.8 months (95% CI: 9.1, 11.7) in the Pluvicto+BSC/BSoC arm. The median DoR in the BSC/BSoC only arm could not be meaningfully interpreted due to the very small number of responses (n = 2) with only 1 of the 2 patients who responded had RECIST radiographic progression or death. The DCR was statistically significant in favour of the Pluvicto+BSC/BSoC arm (89.0% vs 66.7%; OR 5.79; 95% CI: 3.18, 10.55; p<0.001). Time to first SSE also showed statistically significant benefits in favour of the Pluvicto+BSC/BSoC arm, with a HR of 0.50 (95% CI: 0.40, 0.62; p<0.001), and a median time to first SSE of 11.5 months (95% CI: 10.3, 13.2) in the Pluvicto+BSC/BSoC arm vs 6.8 months (95% CI: 5.2, 8.5) in the BSC/BSoC only arm.

Summary of key efficacy results

	Pluvicto+BSC/BSoC	**BSC/BSoC only**
Alternate primary efficacy endpoints		
rPFS (PFS-FAS), n	385	196
Events (progression or death), n (%)	254 (66.0%)	93 (47.4%)
Median rPFS (months) (99.2% CI)	8.7 (7.9, 10.8)	3.4 (2.4, 4.0)
HR (99.2% CI)[a]	0.40 (0.29, 0.57)	
One-sided p-value[b]	<0.001	
OS (FAS), n	551	280
Deaths, n (%)	343 (62.3%)	187 (66.8%)
Median OS (months) (95% CI)	15.3 (14.2, 16.9)	11.3 (9.8, 13.5)
HR (95% CI)[a]	0.62 (0.52, 0.74)	
One-sided p-value[b]	<0.001	
Key secondary efficacy endpoints		
ORR (Response Evaluable Analysis Set), n	319	120
ORR, n (%)	95 (29.8%)	2 (1.7%)
Odds ratio (95% CI)[c]	24.99 (6.05, 103.24)	
Two-sided p-value[d]	<0.001	
DCR (Response Evaluable Analysis Set), n	319	120
DCR, n (%)	284 (89.0%)	80 (66.7%)
Odds ratio (95% CI)[c]	5.79 (3.18, 10.55]	
Two-sided p-value[d]	<0.001	
DoR (Response Evaluable Analysis Set), n	319	120
Median DoR (months) (95% CI)	9.8 (9.1, 11.7)	10.6 (NE, NE)[e]
Time to first SSE (PFS-FAS), n	385	196
Events (SSE or death), n (%)	256 (66.5%)	137 (69.9%)
Median time to first SSE (months) (95% CI)	11.5 (10.3, 13.2)	6.8 (5.2, 8.5)
HR (95% CI)[a]	0.50 (0.40, 0.62)	
Two-sided p-value[b]	<0.001	

NE = Not evaluable

[a] Based on stratified Cox proportional hazards (PH) model

[b] Based on stratified log-rank test
[c] Based on stratified logistic regression model
[d] Based on Wald's Chi-Square test
[e] Median DoR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST radiographic progression or death.

Overall, the study met its primary objectives for both alternate primary endpoints and all key secondary objectives. The results adequately supported the efficacy of Pluvicto for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibitor and taxane-based chemotherapy.

D ASSESSMENT OF CLINICAL SAFETY

The safety evaluation was based on data from the pivotal study VISION, which comprised 529 patients in the Pluvicto+BSC/BSoC arm who were treated with at least one dose of Pluvicto and 205 patients in the BSC/BSoC only arm. The median duration of exposure to randomised treatment was longer in the Pluvicto+BSC/BSoC arm (7.8 months) than the BSC/BSoC only arm (2.1 months).

Overview of safety profile (VISION study)

	Pluvicto+BSC/BSoC (N=529)	**BSC/BSoC only (N=205)**
TEAE	519 (98.1%)	170 (82.9%)
Grade ≥3 TEAE	279 (52.7%)	78 (38.0%)
Drug-related TEAE	451 (85.3%)	59 (28.8%)
Drug-related grade ≥3 TEAE	150 (28.4%)	8 (3.9%)
SAE	192 (36.3%)	57 (27.8%)
Treatment-related SAE	49 (9.3%)	5 (2.4%)
TEAE leading to discontinuation Discontinuation of Pluvicto Discontinuation of BSC/BSoC	 63 (11.9%) 45 (8.5%)	 1 (0.5%)[a] 16 (7.8%)
Fatal TEAE	19 (3.6%)	6 (2.9%)

[a] Four patients randomised to Pluvicto+BSC/BSoC arm received BSC/BSoC only, and therefore contributed to the FAS safety analysis set of the BSC/BSoC arm.

Treatment-emergent adverse events (TEAEs) were reported more frequently in Pluvicto+BSC/BSoC arm compared to the BSC/BSoC only arm (98.1% vs 82.9%). The TEAEs with differences ≥10% between the two treatment arms (Pluvicto+BSC/BSoC arm vs BSC/BSoC only arm) were fatigue (43.1% vs 22.9%), dry mouth (38.8% vs 0.5%), nausea (35.3% vs 16.6%), anaemia (31.8% vs 13.2%), diarrhoea (18.9% vs 2.9%), vomiting (18.9% vs 6.3%), thrombocytopenia (17.2% vs 4.4%), lymphopenia (14.2% vs 3.9%), leukopenia (12.5% vs 2.0%) and urinary tract infection (11.0% vs 1.0%).

The most frequent Grade ≥3 TEAEs (≥5%) occurring at higher incidences in the Pluvicto+BSC/BSoC arm vs the BSC/BSoC only arm were anaemia (12.9% vs 4.9%), thrombocytopenia (7.9% vs 1.0%), lymphopenia (7.8% vs 0.5%) and fatigue (5.9% vs 1.5%).

The most frequently reported drug-related TEAEs (≥20%) in the Pluvicto+BSC/BSoC arm (vs BSC/BSoC only arm) were dry mouth (35.9% vs 0%), fatigue (31.2% vs 6.8%), nausea (28.0% vs 3.9%) and anaemia (25.5% vs 2.9%).

The drug-related grade ≥3 TEAEs that were reported with the highest incidences in the Pluvicto BSC/BSoC arm (vs BSC/BSoC only arm) were anaemia (9.6% vs 0.5%), thrombocytopenia

(6.8% vs 0%) and lymphopenia (6.8% vs 0%). All other drug-related grade ≥3 TEAEs were reported in less than 5.0% of the patients.

The incidence of serious adverse events (SAEs) was higher in the Pluvicto+BSC/BSoC arm compared to the BSC/BSoC only arm (36.3% vs 27.8%). In both arms, the incidences of individual SAEs were generally low (<2%) except for anaemia (2.8% vs 0.5%), urinary tract infection (2.5% vs 0.5%), haematuria (2.1% vs 0.5%) and spinal cord compression (1.1% vs 4.9%).

TEAEs leading to discontinuation of Pluvicto were reported in 63 (11.9%) patients in the Pluvicto+BSC/BSoC arm. The most frequent events were myelosuppression related events, including anaemia (2.8%), thrombocytopenia (2.8%), leukopenia (1.3%), neutropenia (0.8%) and pancytopenia (0.6%). All other events were reported in ≤0.5% of the patients.

The incidence of deaths due to TEAE was 3.6% in the Pluvicto+BSC/BSoC arm and 2.9% in the BSC/BSoC only arm. Three on-treatment deaths were considered by the Investigator to be related to study treatment: 2 deaths due to pancytopenia and 1 death due to bone marrow failure, all in the Pluvicto+BSC/BSoC arm. Warnings on the risk of life-threatening myelosuppression have been included in the package insert (PI).

The adverse events of special interest (AESIs) included fatigue, myelosuppression, dry mouth, nausea and vomiting, and renal toxicity. The AESIs occurred more frequently in the Pluvicto+BSC/BSoC arm compared to the BSC/BSoC only arm: fatigue (49.1% vs 29.3%), myelosuppression (47.4% vs 17.6%), dry mouth (39.3% vs 1.0%), nausea and vomiting (39.3% vs 17.1%), renal toxicity (8.7% vs 5.9%). Most of these events were drug-related. Of note, myelosuppression-related events led to withdrawal of Pluvicto in 7.0% of the patients, while treatment discontinuation due to fatigue, dry mouth, nausea and vomiting, and renal toxicity were low (0.4%, 0.2%, 0.2% and 0.2%, respectively).

Myelosuppression-related events included anaemia (31.8% in the Pluvicto+BSC/BSoC arm vs 13.2% in the BSC/BSoC only arm), thrombocytopenia (17.2% vs 4.4%), lymphopenia (14.2% vs 3.9%), leukopenia (12.5% vs 2.0%) and neutropenia (8.5% vs 1.5%). The PI has included warnings on myelosuppression and recommendations for monitoring of haematology laboratory tests, as well as dose modifications based on the severity of myelosuppression.

For renal toxicity, the most frequent events were blood creatinine increased (5.3% in the Pluvicto+BSC/BSoC arm vs 2.4% in the BSC/BSoC only arm) followed by acute kidney injury (3.6% vs 3.9%). One event of renal failure was reported in the Pluvicto+BSC/BSoC arm. Recommendations for management of renal toxicity have been included in the PI, including adequate hydration, frequent urination, regular monitoring of kidney function, and appropriate dose modifications based on the severity of renal toxicity.

Overall, the safety profile of Pluvicto treatment was consistent with that of other radioligand therapies (RLTs), characterised by myelosuppression, renal toxicity, fatigue, and gastrointestinal AEs such as nausea, vomiting and dry mouth. Adequate warnings and recommendation for management of the AEs, including laboratory monitoring and dose modifications, have been included in the PI to mitigate the risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Patients with metastatic prostate cancer who become castration-resistant have a poor prognosis with an estimated median survival of 9 to 13 months. Treatment options for patients who have received AR pathway inhibitors and taxane-based chemotherapy are limited, hence there is a medical need for effective therapies in this patient population.

The clinical benefit of Pluvicto in patients with PSMA-positive mCRPC who have been treated with AR pathway inhibitor and taxane-based chemotherapy has been demonstrated based on statistically significant and clinically meaningful prolongation of OS (median OS 15.3 vs 11.3 months; HR 0.62; 95% CI: 0.52, 0.74; p<0.0001) and rPFS (median rPFS 8.7 vs 3.4 months; HR 0.40; 99.2% CI: 0.29, 0.57; p<0.001) with Pluvicto+BSC/BSoC compared to the BSC/BSoC only arm.

The ORR (29.8% vs 1.7%; OR 24.99; 95% CI: 6.05, 103.24; p<0.001), DCR (89.0% vs 66.7%; OR 5.79; 95% CI: 3.18, 10.55; p<0.001) and time to first SSE (median time to first SSE 11.5 vs 6.8 months; HR 0.50; 95% CI: 0.40, 0.62; p<0.001) were also statistically significant in favour of the Pluvicto+BSC/BSoC arm compared to the BSC/BSoC only arm.

The safety profile of Pluvicto was considered acceptable for the intended population given the severity of the disease. The most notable safety concerns with Pluvicto were fatigue, gastrointestinal AEs (dry mouth, nausea, vomiting), myelosuppressive AEs (anaemia, thrombocytopenia, lymphopenia, leukopenia) and renal toxicity, which are known and expected AEs of RLT. Given the observed toxicities, warnings and recommendations for dose modifications are included in the PI as risk mitigation measures.

Overall, the benefits of Pluvicto outweighed the risks for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibitor and taxane-based chemotherapy.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Pluvicto for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibitor and taxane-based chemotherapy was deemed favourable and approval of the product registration was granted on 18 December 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

1 Tradename(s)

Pluvicto® 1 GBq/mL (27 mCi/mL) solution for injection/infusion

2 Description and composition

Pharmaceutical form

Solution for injection/infusion.

Clear, colorless to slightly yellow solution.

pH: 4.5 to 7.0.

Active substance

One mL of solution contains 1 GBq (27 mCi) of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.

The total amount of radioactivity per single-dose vial is 7.4 GBq (200 mCi) ± 10% at the date and time of administration. Given the fixed volumetric activity of 1 GBq/mL (27 mCi) 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.

Physical characteristics

Lutetium-177 decays to a stable hafnium-177 with a physical half-life of 6.647 days by emitting beta-minus 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 2-1.

Table 2-1 Lutetium-177 Main Radiations

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

Radiation	Energy (keV)	Iβ-%	Iγ%
γ	321.3		0.22

External radiation

Table 2-2 summarizes the radioactive decay properties of lutetium-177.

Table 2-2 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
1080 (45 days)	0.009

Excipients

Acetic acid (0.30 mg/mL), sodium acetate (0.41 mg/mL), gentisic acid (0.39 mg/mL), sodium ascorbate (50.0 mg/mL), pentetic acid (0.10 mg/mL), water for injections (q.s. to 1 mL).

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

3 Indications

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

4 Dosage regimen and administration

Important safety instructions

Pluvicto is a radiopharmaceutical and should be handled with appropriate safety measures to minimize radiation exposure (see section 6 Warnings and precautions). Waterproof gloves and effective radiation shielding should be used when handling Pluvicto.

Radiopharmaceuticals, including Pluvicto, should be used by or under the control of healthcare providers who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals.

Patient identification

Patients should be identified for treatment by PSMA imaging.

Dosage regimen

The recommended Pluvicto dose is 7.4 GBq (200 mCi) intravenously every 6 weeks (± 1 week) for a total of 6 doses.

Treatment monitoring

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

- Hematology (hemoglobin, white blood cell count, absolute neutrophil count, platelet count)
- Kidney function (serum creatinine, calculated creatinine clearance [CLcr])
- Liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood serum albumin, total blood bilirubin)

Dose modifications for adverse drug reactions

Recommended dose modifications of Pluvicto for adverse drug reactions are provided in Table 4-1. Management of severe or intolerable adverse drug reactions may require temporary dose interruption (extending the dosing interval by 4 weeks from 6 weeks up to 10 weeks), dose reduction or permanent discontinuation of treatment with Pluvicto. If a treatment delay due to an adverse drug reaction persists for >4 weeks, treatment with Pluvicto must be discontinued. The dose of Pluvicto 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 must be discontinued.

Table 4-1 Recommended dose modifications of Pluvicto for adverse drug reactions

Adverse drug reaction	Severity[a]	Dose modification
Dry mouth	Grade ≥3	Reduce Pluvicto dose by 20%.
Gastrointestinal toxicity	Grade ≥3 (not amenable to medical intervention)	Withhold Pluvicto until improvement to Grade 2 or baseline. Reduce Pluvicto dose by 20%.
Anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia	Grade 2	Withhold Pluvicto until improvement to Grade 1 or baseline. Manage as deemed appropriate. The use of growth factors is permitted but should be discontinued once improved to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated.
	Grade ≥3	Withhold Pluvicto until improvement to Grade 1 or baseline. Reduce Pluvicto dose by 20%.
Renal toxicity	Defined as: • Confirmed serum creatinine increase (Grade ≥2)	Withhold Pluvicto until improvement.

Adverse drug reaction	Severity[a]	Dose modification
	• Confirmed CLcr <30 mL/min; calculate using Cockcroft-Gault with actual body weight	
	Defined as: • Confirmed ≥40% increase from baseline serum creatinine and • Confirmed >40% decrease from baseline CLcr; calculate using Cockcroft-Gault with actual body weight	Withhold Pluvicto until improvement or return to baseline. Reduce Pluvicto dose by 20%.
	Recurrent renal toxicity (Grade ≥3)	Permanently discontinue Pluvicto.
Spinal cord compression	Any	Withhold Pluvicto until the compression has been adequately treated and any neurological sequela have stabilized and ECOG performance status has stabilized.
Fracture in weight-bearing bones	Any	Withhold Pluvicto until the fracture has been adequately stabilized/treated and ECOG performance status has stabilized.
AST or ALT elevation	AST or ALT >5 times ULN in the absence of liver metastases	Permanently discontinue Pluvicto.

Abbreviations: CLcr, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

Grading according to most current Common Terminology Criteria for Adverse Events (CTCAE).

[a]The same thresholds are also applicable to baseline values at the time of treatment initiation with Pluvicto.

Special populations

Renal impairment

Exposure of Pluvicto is expected to increase with the degree of renal impairment. Patients with mild or moderate renal impairment may be at greater risk of toxicity. No dose adjustment is recommended for patients with mild renal impairment (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault); however, insufficient data are available for drawing a conclusion for patients with moderate renal impairment (CLcr 30 to 59 mL/min). Renal function and adverse reactions should be monitored frequently in patients with mild to moderate renal impairment. The pharmacokinetic profile and safety of Pluvicto have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease.

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment.

Pediatric patients (below 18 years of age)

The safety and effectiveness of Pluvicto in pediatric patients have not been established.

Geriatric patients (65 years of age or older)

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

Method of administration

Preparation instructions

- Aseptic technique and radiation shielding should be used when handling or administering Pluvicto, using tongs as needed to minimize radiation exposure.
- The vial should be visually inspected under a shielded screen for particulate matter and discoloration prior to administration. The vial should be discarded if particulates or discoloration are present.
- Pluvicto is a ready-to-use solution for single use only. The Pluvicto solution should not be injected directly into any other intravenous solution.
- The amount of radioactivity delivered to the patient should be confirmed with an appropriately calibrated dose calibrator prior to and after Pluvicto administration.
- Any unused medicinal product or waste material should be disposed of in accordance with national regulations.

Administration instructions

The recommended dose of Pluvicto may be administered intravenously as an injection using a disposable syringe fitted with a syringe shield (with or without a syringe pump), as an infusion using the gravity method (with or without an infusion pump), or as an infusion using the vial (with a peristaltic infusion pump).

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

Prior to administration, flush the intravenous catheter used exclusively for Pluvicto administration with ≥10 mL of 0.9% sterile sodium chloride solution to ensure patency and to minimize 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)

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

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

- Insert a 2.5 cm, 20 gauge needle (short needle) into the Pluvicto vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport the Pluvicto solution during the infusion). Ensure that the short needle does not touch the Pluvicto solution in the vial and do not connect the short needle directly to the patient. Do not allow

the sodium chloride solution to flow into the Pluvicto vial prior to the initiation of the Pluvicto infusion and do not inject the Pluvicto solution directly into the sodium chloride solution.

- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Pluvicto vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is pre-filled with 0.9% sterile sodium chloride solution and that is used exclusively for the Pluvicto infusion into the patient.
- Use a clamp or an infusion pump to regulate the flow of the sodium chloride solution via the short needle into the Pluvicto vial (the sodium chloride solution entering the vial through the short needle will carry the Pluvicto solution from the vial to the patient via the intravenous catheter connected to the long needle within approximately 30 minutes).
- During the infusion, ensure that the level of solution in the Pluvicto vial remains constant.
- Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the vial method (with a peristaltic infusion pump)

- Insert a 2.5 cm, 20 gauge needle (short venting needle) into the Pluvicto vial. Ensure that the short needle does not touch the Pluvicto solution in the vial and do not connect the short needle directly to the patient or to the peristaltic infusion pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Pluvicto vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic infusion pump following the pump manufacturer's instructions.
- Pre-fill the line by opening the 3-way stopcock valve and pumping the Pluvicto solution through the tubing until it reaches the exit of the valve.
- Pre-fill the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the pre-filled intravenous catheter to the patient and set the 3-way stopcock valve such that the Pluvicto solution is in line with the peristaltic infusion pump.
- Infuse an appropriate volume of Pluvicto solution at approximately 25 mL/h to deliver the desired radioactivity.
- When the desired Pluvicto radioactivity has been delivered, stop the peristaltic infusion pump and then change the position of the 3-way stopcock valve so that the peristaltic infusion pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic infusion pump and infuse an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Radiation dosimetry

Dosimetry of lutetium (^{177}Lu) vipivotide tetraxetan was collected in 29 patients in the Phase III VISION sub-study, in order to calculate whole body and organ radiation dosimetry. The mean and standard deviation (SD) of the estimated radiation absorbed doses to different organs for

adult patients receiving Pluvicto are shown in Table 4-2. The organs with the highest radiation absorbed doses are lacrimal glands and salivary glands.

The maximum penetration of lutetium-177 in tissue is approximately 2 mm and the mean penetration is 0.67 mm.

Table 4-2 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
Esophagus	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.

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 2 Description and composition.

6 Warnings and precautions

Risk from radiation exposure

Pluvicto contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Radiation exposure to patients, medical personnel, and household contacts should be minimized during and after treatment with Pluvicto consistent with institutional good radiation safety practices, patient management procedures, and instructions to the patient for follow-up radiation protection at home.

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

Before the patient is released, the nuclear medicine physician or healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimize radiation exposure to others.

Following administration of Pluvicto, patients should be advised to:

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

Myelosuppression

Pluvicto can cause severe and life-threatening myelosuppression, including anaemia, thrombocytopenia, leukopenia, and neutropenia. In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus best standard of care (BSoC) compared to patients who received BSoC alone (see section 7 Adverse drug reactions).

Hematology laboratory tests, including hemoglobin, white blood cell count, absolute neutrophil count, and platelet count, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced, or permanently discontinued and patients should be clinically managed as deemed appropriate based on the severity of myelosuppression (see section 4 Dosage regimen and administration).

Renal toxicity

In the VISION study, renal toxicity occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (see section 7 Adverse drug reactions).

Patients should be advised to remain well hydrated and to urinate frequently before and after administration of Pluvicto. Kidney function laboratory tests, including serum creatinine and calculated CLcr, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced, or permanently discontinued based on the severity of renal toxicity (see section 4 Dosage regimen and administration).

7 Adverse drug reactions

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 randomized, 734 patients received at least one dose of randomized treatment. Patients received at least one dose of either Pluvicto 7.4 GBq (200 mCi) administered every 6 to 10 weeks plus BSoC (N = 529) or BSoC alone (N = 205).

Among patients who received Pluvicto plus BSoC, the median number of doses of Pluvicto received was 5 (range: 1 to 6), with 67.7% of patients who received at least 4 doses of Pluvicto and 46.5% of patients who received a total of 6 doses of Pluvicto. The median cumulative dose of Pluvicto was 37.5 GBq (range: 7.0 to 48.3). The median duration of exposure to randomized treatment was 7.8 months (range: 0.3 to 24.9) for patients who received Pluvicto plus BSoC and 2.1 months (range: 0.0 to 26.0) for patients who received BSoC alone.

Table 7-1 summarizes the incidence of adverse drug reactions. The most common adverse drug reactions (≥20%) occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone include: fatigue (43.1%), dry mouth (39.3%), nausea (35.3%), anaemia (31.8%), decreased appetite (21.2%), and constipation (20.2%). The most common Grade 3 to 4 adverse drug reactions (≥5%) occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to 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 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone in VISION[a]

	Pluvicto plus BSoC (N = 529)			BSoC (N = 205)		
Adverse drug reactions	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**	**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%)	27 (13.2%)	Very common	10 (4.9%)
Thrombocytopenia	91 (17.2%)	Very common	42 (7.9%)	9 (4.4%)	Common	2 (1.0%)
Leukopenia[c]	83 (15.7%)	Very common	22 (4.2%)	4 (2.0%)	Common	1 (0.5%)
Lymphopenia	75 (14.2%)	Very common	41 (7.8%)	8 (3.9%)	Common	1 (0.5%)
Pancytopenia[d]	9 (1.7%)	Common	7 (1.3%)[b]	0		0
Nervous system disorders						
Dizziness	44 (8.3%)	Common	5 (0.9%)	9 (4.4%)	Common	0
Headache	37 (7.0%)	Common	4 (0.8%)	4 (2.0%)	Common	0
Dysgeusia[e]	37 (7.0%)	Common	0	3 (1.5%)	Common	0
Eye disorders						
Dry eye	16 (3.0%)	Common	0	2 (1.0%)	Uncommon	0
Ear and labyrinth disorders						
Vertigo	11 (2.1%)	Common	0	0		0
Gastrointestinal disorders						
Dry mouth[f]	208 (39.3%)	Very common	0	1 (0.5%)	Uncommon	0
Nausea	187 (35.3%)	Very common	7 (1.3%)	34 (16.6%)	Very common	1 (0.5%)
Constipation	107 (20.2%)	Very common	6 (1.1%)	23 (11.2%)	Very common	1 (0.5%)
Vomiting[g]	101 (19.1%)	Very common	5 (0.9%)	13 (6.3%)	Common	1 (0.5%)
Diarrhoea	100 (18.9%)	Very common	4 (0.8%)	6 (2.9%)	Common	1 (0.5%)
Abdominal pain[h]	59 (11.2%)	Very common	6 (1.1%)	13 (6.3%)	Common	1 (0.5%)
Renal and urinary disorders						
Urinary tract infection[i]	61 (11.5%)	Very common	20 (3.8%)	2 (1.0%)	Uncommon	1 (0.5%)
Acute kidney injury[j]	45 (8.5%)	Common	17 (3.2%)	12 (5.9%)	Common	6 (2.9%)
General disorders and administration site conditions						
Fatigue	228 (43.1%)	Very common	31 (5.9%)	47 (22.9%)	Very common	3 (1.5%)
Decreased appetite	112 (21.2%)	Very common	10 (1.9%)	30 (14.6%)	Very common	1 (0.5%)
Weight decreased	57 (10.8%)	Very common	2 (0.4%)	18 (8.8%)	Common	0

	Pluvicto plus BSoC (N = 529)			BSoC (N = 205)		
Adverse drug reactions	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**
Oedema peripheral[k]	52 (9.8%)	Common	2 (0.4%)	14 (6.8%)	Common	(0.5%)
Pyrexia	36 (6.8%)	Common	2 (0.4%)	7 (3.4%)	Common	0

Abbreviation: BSoC, best standard of care.

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

[b]Only includes Grades 3 to 4 adverse 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, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

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

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

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

Description of selected adverse drug reactions

Myelosuppression

In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (all Grades/Grade ≥3: anemia (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 events of pancytopenia in patients who received Pluvicto plus BSoC; and bicytopenia (0.2%/0.2%) versus (0%/0%).

Myelosuppression adverse drug reactions that led to permanent discontinuation in ≥0.5% of patients who received Pluvicto plus BSoC included: anemia (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: anemia (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 compared to patients who received BSoC alone (all Grades/Grades 3 to 4): blood creatinine increased (5.3%/0.2%) versus (2.4%/0.5%); acute kidney injury (3.6%/3.0%) versus (3.9%/2.4%); renal failure (0.2%/0%) versus (0%/0%); and blood urea increased (0.2%/0%) versus (0%/0%).

Renal adverse drug reactions that led to permanent discontinuation in ≥0.2% of patients who received Pluvicto plus BSoC included: blood creatinine increased (0.2%). Renal adverse drug reactions that led to dose interruptions /dose reductions in ≥0.2% of patients who received Pluvicto plus BSoC included: blood creatinine increased (0.2%/0.4%) and acute kidney injury (0.2%/0%).

8 Interactions

No clinical drug interaction studies were performed.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

The safety and efficacy of Pluvicto have not been established in females as Pluvicto is not indicated for use in females. No animal studies using lutetium (^{177}Lu) vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including Pluvicto, have the potential to cause fetal harm. Based on its mechanism of action, Pluvicto can cause fetal harm when administered to a pregnant woman (see section 11 Clinical pharmacology).

9.2 Lactation

Risk summary

The safety and efficacy of Pluvicto have not been established in females as Pluvicto is not indicated for use in females. There are no data on the presence of lutetium (^{177}Lu) vipivotide tetraxetan in human milk or its effects on the breastfed child or on milk production.

9.3 Females and males of reproductive potential

Contraception

Males

Based on its mechanism of action, male patients should be advised not to father a child and to use condoms for intercourse during treatment with Pluvicto and for 14 weeks after the last dose (see section 11 Clinical pharmacology, section 13 Non-clinical safety data).

Infertility

No studies were conducted to determine the effects of lutetium (^{177}Lu) vipivotide tetraxetan on fertility. The recommended cumulative dose of 44.4 GBq of Pluvicto results in a radiation absorbed dose to the testes within the range where Pluvicto may cause infertility.

10 Overdosage

In the event of administration of a radiation overdose with Pluvicto, the radiation absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective radiation dose that was applied.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10XX05

Mechanism of action (MOA)

The active moiety of Pluvicto 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 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 (PD)

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

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

Unlabeled vipivotide tetraxetan does not have any pharmacodynamic activity.

Cardiac electrophysiology

The ability of Pluvicto to prolong the QTc interval at the recommended dose was assessed in 30 patients in the Phase III VISION sub-study. Pluvicto did not prolong the QT/QTc interval.

Pharmacokinetics (PK)

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

Absorption

Pluvicto is administered intravenously and is immediately and completely bioavailable.

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

Distribution

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

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

Organ uptake

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

Elimination

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

Half-life

Pluvicto shows a bi-exponential elimination with a geometric mean terminal elimination half-life (T½) of 41.6 hours (CV 68.8%).

Metabolism

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

Excretion

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

Special populations

Geriatric patients (65 years of age or older)

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

Age/Body weight

No clinically significant effects on the pharmacokinetic parameters of lutetium (^{177}Lu) vipivotide tetraxetan were identified for the following covariates assessed in 30 patients in the Phase III VISION sub-study: age (median: 67 years; range: 52 to 80 years) and body weight (median: 88.8 kg; range: 63.8 to 143.0 kg).

Renal impairment

Based on population pharmacokinetic analysis, exposure of lutetium (^{177}Lu) vipivotide tetraxetan is expected to increase with the degree of renal impairment. Patients with mild or moderate renal impairment may be at greater risk of toxicity. No dose adjustment is recommended for patients with mild renal impairment (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault); however, insufficient data are available for drawing a conclusion on patients with moderate renal impairment (CLcr 30 to 59 mL/min). Renal function and adverse reactions should be monitored frequently in patients with mild to moderate renal impairment. The effect of severe renal impairment (baseline CLcr 15 to 29 mL/min) or end-stage renal disease on lutetium (^{177}Lu) vipivotide tetraxetan pharmacokinetics has not been studied.

In vitro evaluation of drug interaction potential

CYP450 enzymes

Vipivotide tetraxetan is not a substrate of cytochrome P450 (CYP450) enzymes. It does not induce cytochrome P450 (CYP) 1A2, 2B6 or 3A4, and it does not inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 *in vitro*.

Transporters

Vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2, and it is not an inhibitor of BCRP, P-gp, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 *in vitro*.

12 Clinical studies

The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC was established in VISION, a randomized, multicenter, open-label Phase III study. Eight hundred and thirty-one (N = 831) patients were randomized (2:1) to receive either Pluvicto 7.4 GBq (200 mCi) every 6 weeks for up to a total of 6 doses plus BSoC (N = 551) or BSoC alone (N = 280).

Eligible patients were required to have PSMA-positive mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic and hematological function. Eligible patients were also required to have received at least one AR pathway inhibitor, such as abiraterone acetate or enzalutamide, and 1 or 2 prior taxane-based chemotherapy regimens (with a regimen defined as a minimum exposure of 2 cycles of a taxane). Patients with unstable symptomatic central nervous system metastases or symptomatic or clinically/radiologically impending spinal cord compression were not eligible for the study. Patients underwent a gallium (^{68}Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have at least one PSMA-positive lesion identified by this scan, 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 including pain medications, hydration, blood transfusions, etc.; ketoconazole; radiation therapy (including seeded form or any external beam radiotherapy [including stereotactic body radiotherapy and palliative external beam]) to localized prostate cancer targets; bone-targeted agents including zoledronic acid, denosumab, and any bisphosphonates; androgen-reducing agents including any corticosteroid and 5-alpha reductases; AR pathway inhibitors.

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

The alternate primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per PCWG3 criteria. Additional secondary efficacy endpoints were overall response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and time to first symptomatic skeletal event (SSE) defined as first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death from any cause, whichever occurred first.

Demographic and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range: 40 to 94 years); 86.8% White; 6.6% Black or African American; 2.4% Asian; 92.4% had ECOG PS0-1; 7.6% had ECOG PS2. Randomization was stratified by baseline lactase dehydrogenase (LDH), presence of liver metastases, ECOG PS score and inclusion of an AR pathway inhibitor as part of BSoC at the time of randomization. At randomization, all patients (100.0%) had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two. At randomization, 51.3% of patients had received one prior AR pathway inhibitor, 41.0% of patients received 2, and 7.7% of patients had received 3 or more. During the randomized 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 12-1 and Figures 12-1 and 12-2. The final analyses of OS and rPFS were event-driven and conducted after the occurrence of 530 deaths

and 347 events, respectively. Treatment with Pluvicto plus BSoC demonstrated a statistically significant improvement in OS and rPFS by BICR compared to treatment with BSoC alone. The primary efficacy results are supported by a statistically significant difference between the treatment arms in the time to first SSE (p <0.001) and ORR (p <0.001). There was an estimated 38% risk reduction of death, an estimated 60% risk reduction of radiographic disease progression or death, and an estimated 50% risk reduction of SSE or death based on hazard ratios in favor of Pluvicto plus BSoC treatment.

Table 12-1 Efficacy results in VISION

Efficacy parameters	Pluvicto plus BSoC	BSoC
Alternate primary efficacy endpoints		
Overall survival (OS)	N = 551	N = 280
Deaths, n (%)	343 (62.3%)	187 (66.8%)
Median, months (95% CI)[a]	15.3 (14.2, 16.9)	11.3 (9.8, 13.5)
Hazard ratio (95% CI)[b]	0.62 (0.52, 0.74)	
P-value[c]	<0.001	
Radiographic progression-free survival (rPFS)[d]	N = 385	N = 196
Events (progression or death), n (%)	254 (66.0%)	93 (47.4%)
Radiographic progressions, n (%)	171 (44.4%)	59 (30.1%)
Deaths, n (%)	83 (21.6%)	34 (17.3%)
Median, months (99.2% CI)[a]	8.7 (7.9, 10.8)	3.4 (2.4, 4.0)
Hazard ratio (99.2% CI)[b]	0.40 (0.29, 0.57)	
P-value[c]	<0.001	
Secondary efficacy endpoints		
Time to first symptomatic skeletal event (SSE)	N = 385	N = 196
Events (SSE or death), n (%)	256 (66.5%)	137 (69.9%)
SSEs, n (%)	60 (15.6%)	34 (17.3%)
Deaths, n (%)	196 (50.9%)	103 (52.6%)
Median, months (95% CI)[a]	11.5 (10.3, 13.2)	6.8 (5.2, 8.5)
Hazard ratio (95% CI)[b]	0.50 (0.40, 0.62)	
P-value[e]	<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%)
Stable disease (SD), n (%)	68 (21.3%)	30 (25.0%)
Non-CR/Non-PD, n (%)	121 (37.9%)	48 (40.0%)
Progressive disease (PD), n (%)	33 (10.3%)	35 (29.2%)
Unknown, n (%)	2 (0.6%)	5 (4.2%)
Overall response rate (ORR)[f,g]	95 (29.8%)	2 (1.7%)
P-value[h]	<0.001	
Duration of response (DOR)[f]		
Number of responders	n = 95	n = 2
Events (progression or death), n (%)	46 (48.4%)	1 (50.0%)
Radiographic progressions, n (%)	29 (30.5%)	1 (50.0%)
Deaths, n (%)	17 (17.9%)	0 (0%)
Median, months (95% CI)[a]	9.8 (9.1, 11.7)	10.6 (NE, NE)[i]

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

[a]*Based on Kaplan-Meier estimate.*

Efficacy parameters	Pluvicto plus BSoC	BSoC

[b]*Hazard ratio based on the stratified Cox PH model. Hazard ratio <1 favors Pluvicto plus BSoC.*

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

[d]*By BICR per PCWG3 criteria.*

[e]*Stratified log-rank test two-sided p-value.*

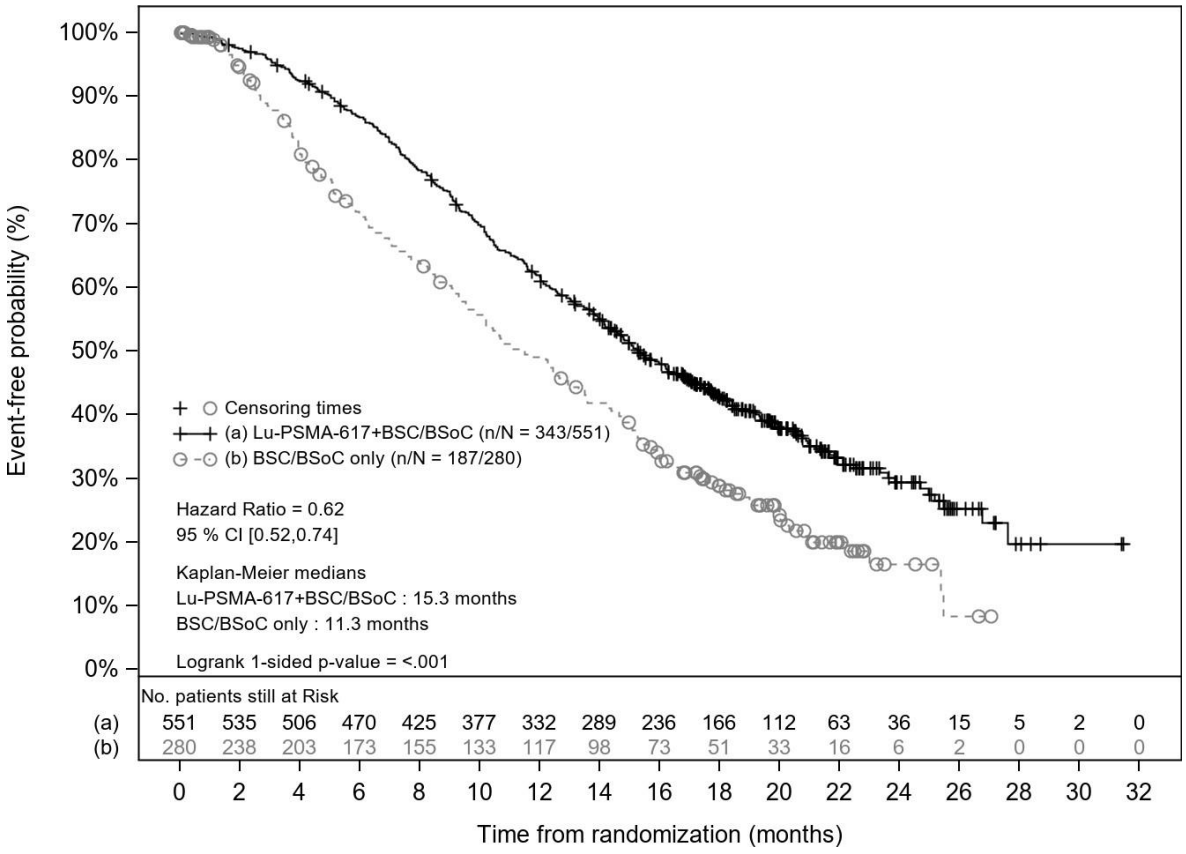
[f]*By BICR per RECIST v1.1.*

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

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

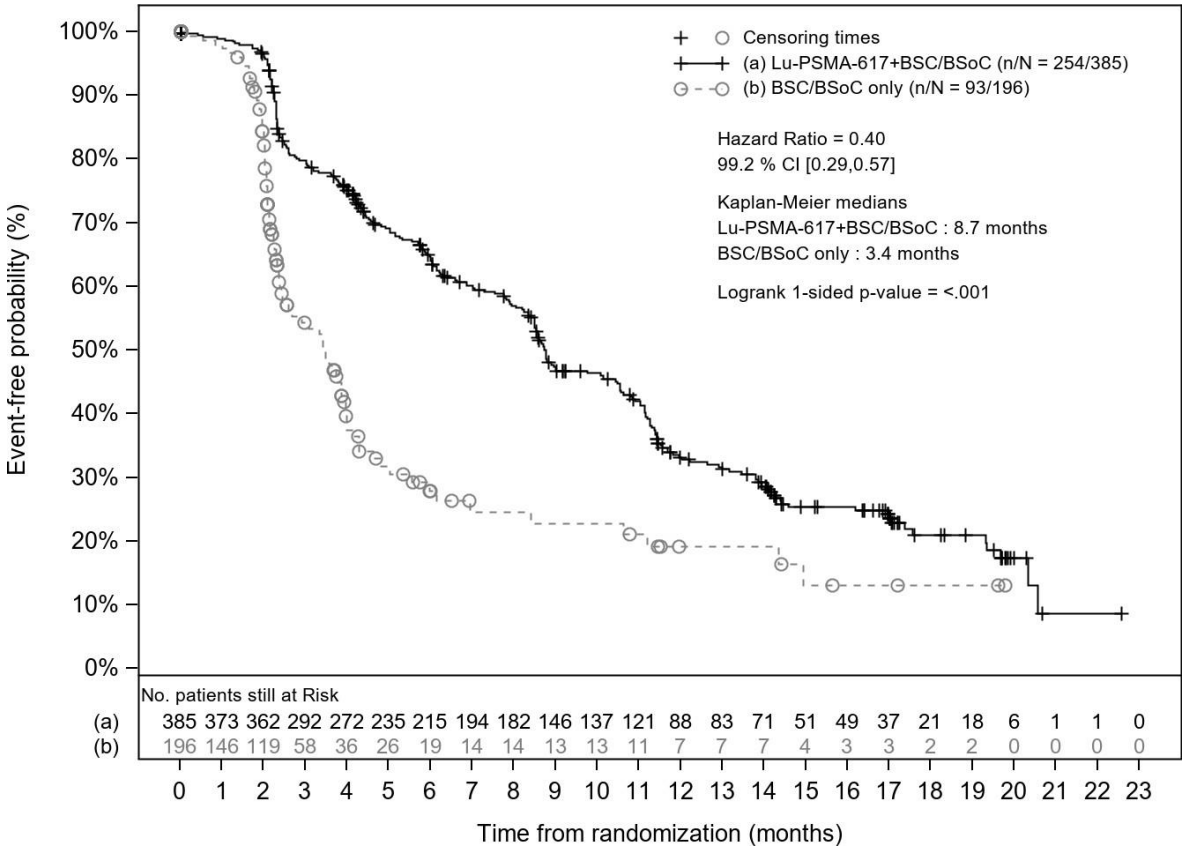
[i]*Median DOR in the BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST v1.1 radiographic progression or death.*

Figure 12-1 Kaplan-Meier plot of overall survival in VISION



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

Figure 12-2 Kaplan-Meier plot of BICR-assessed radiographic progression-free survival (rPFS) in VISION



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

Mean and median baseline prostate-specific antigen (PSA) levels were similar in both treatment arms. Serum PSA levels decreased by ≥50% from baseline in 177 of 385 (46.0%) patients who received Pluvicto plus BSoC and in 14 of 196 (7.1%) patients who received BSoC alone.

FACT-P total score showed an estimated 46% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favor of Pluvicto plus BSoC, indicating patient stabilization and delay in time to deterioration while on Pluvicto plus BSoC treatment. Specifically, time to worsening of the FACT-P total score was delayed by 3.5 months for Pluvicto plus BSoC with a median time to deterioration of 5.7 months (95% CI: 4.8, 6.6) compared to 2.2 months (95% CI: 1.8, 2.8) for BSoC alone. BPI-SF pain intensity scale showed an estimated 48% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favor of Pluvicto plus BSoC, indicating patient stabilization and less pain while on Pluvicto plus BSoC treatment. Specifically, time to worsening of the BPI-SF pain intensity scale was delayed by 3.7 months for Pluvicto plus BSoC with a median time to deterioration of 5.9 months (95% CI: 4.8, 6.9) compared to 2.2 months (95% CI: 1.8, 2.8) for BSoC alone. The results of these patient-reported outcomes (PRO) should be interpreted with caution in the context of the open-label study design. The proportion of patients with post-baseline PRO data available is higher in the Pluvicto plus BSoC arm as compared to the BSoC alone arm (e.g. 92.7% vs. 77.0% at Cycle 1, 88.1% vs. 52.0% at Cycle

2, 77.1% vs 27.6% at Cycle 3, 63.4% vs 16.3% at Cycle 4, 51.7% vs 10.7% at Cycle 5, and 44.7% vs. 6.6% at Cycle 6); these imbalances are related to shorter period of time on study treatment in the BSoC alone arm.

13 Non-clinical safety data

Safety pharmacology and animal toxicology

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

For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4 Dosage regimen and administration.

Shelf life

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

Special precautions for storage

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

Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

Do not use Pluvicto after the expiry date and time which are stated on the label after EXP.

Nature and contents of container

Clear, colorless type I glass vial, closed with a bromobutyl rubber stopper and aluminum seal.

Each vial contains a volume of solution that can range from 7.5 mL to 12.5 mL corresponding to a radioactivity of 7.4 GBq (200 mCi) ± 10% at the date and time of administration.

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

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with national regulations.

Lutetium-177 may be prepared using two different sources of stable isotopes (either lutetium-176 or ytterbium-176) that require different waste management. Lutetium-177 is prepared using ytterbium-176 ("non-carrier added") unless otherwise communicated on the product batch release certificate.

Manufacturer:
See folding box.

® = registered trademark

Product owner

Advanced Accelerator Applications International SA

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