ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Pluvicto 1 000 MBq/mL solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 1 000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.

The total amount of radioactivity per single-dose vial is 7 400 MBq ± 10% at the date and time of administration. Given the fixed volumetric activity of 1 000 MBq/mL at the date and time of calibration, the volume of the solution in the vial can range from 7.5 mL to 12.5 mL in order to provide the required amount of radioactivity at the date and time of administration.

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 photon radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (6.4%).

Excipient with known effect

Each mL of solution contains up to 0.312 mmol (7.1 mg) of sodium. Each vial contains up to 88.75 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless to slightly yellow solution, pH: 4.5 to 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Important safety instructions

Pluvicto should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

Radiopharmaceuticals, including Pluvicto, should be used by or under the control of healthcare professionals who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radiopharmaceuticals.

Patient identification

Patients should be identified for treatment by PSMA imaging.

Posology

The recommended treatment regimen of Pluvicto is 7 400 MBq intravenously every 6 weeks (±1 week) for up to a total of 6 doses, unless there is disease progression or unacceptable toxicity.

Medical castration with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in patients not surgically castrated.

Treatment monitoring
Laboratory tests should be performed before and during treatment with Pluvicto. Dosing may need to be modified based on the test results (see Table 1).

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

Dose modifications for adverse reactions
Recommended dose modifications of Pluvicto for adverse reactions are provided in Table 1. Management of severe or intolerable adverse reactions may require temporary dose interruption, dose reduction or permanent discontinuation of treatment with Pluvicto. If a treatment delay due to an adverse reaction persists for >4 weeks, treatment with Pluvicto must be discontinued. The dose of Pluvicto may be reduced by 20% to 5 900 MBq once; the dose should not be re-escalated. If a patient has further adverse reactions that would require an additional dose reduction, treatment with Pluvicto must be discontinued.

Table 1 Recommended dose modifications of Pluvicto for adverse reactions

Adverse reaction	Severity[a]	Dose modification
Dry mouth	Grade 3	Reduce Pluvicto dose by 20% to 5 900 MBq.
Gastrointestinal toxicity	Grade ≥3 (not amenable to medical intervention)	Withhold Pluvicto until improvement to grade 2 or baseline. Reduce Pluvicto dose by 20% to 5 900 MBq.
Myelosuppresion (anaemia, 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 haematinic levels (iron, B12 and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated.
	Grade ≥3	Withhold Pluvicto until improvement to grade 1 or baseline. Reduce Pluvicto dose by 20% to 5 900 MBq.
Renal toxicity	Defined as: • Confirmed serum creatinine increase (grade ≥2) • Confirmed CLcr <50 mL/min; calculate using Cockcroft-Gault with actual body weight	Withhold Pluvicto until improvement.
	Defined as: • Confirmed ≥40% increase from baseline serum creatinine and • Confirmed >40% decrease from baseline CLcr; calculate using Cockcroft-Gault with actual body weight	Withhold Pluvicto until improvement or return to baseline. Reduce Pluvicto dose by 20% to 5 900 MBq.
	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 stabilised and ECOG performance status has stabilised.
Fracture in weight-bearing bones	Any	Withhold Pluvicto until the fracture has been adequately stabilised/treated and ECOG performance status has stabilised.
Fatigue	Grade ≥3	Withhold Pluvicto until improvement to Grade 2 or baseline.
Electrolyte or metabolic abnormalities	Grade ≥2	Withhold Pluvicto until improvement to Grade 1 or baseline.

Non-haematological toxicity (clinically significant, not otherwise stated)	Grade ≥2	Withhold Pluvicto until improvement to Grade 1 or baseline.
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

Elderly

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

Renal impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment with baseline CLcr ≥50 mL/min by Cockcroft-Gault. Treatment with Pluvicto is not recommended in patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end-stage renal disease as the pharmacokinetic profile and safety of Pluvicto have not been studied in these patients (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment. Pluvicto has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population

There is no relevant use of Pluvicto in the paediatric population in the indication of treatment of PSMA-expressing prostate cancer.

Method of administration

Pluvicto is a ready-to-use solution for injection/infusion for single use only.

Administration instructions

The recommended dose of Pluvicto may be administered intravenously as an injection using the syringe method, as an infusion using the gravity method, or as an infusion using the peristaltic pump method.

When using the gravity or peristaltic pump method, Pluvicto should be infused directly from its original container.

The syringe method or the peristaltic pump method should be used when administering a reduced dose of Pluvicto following a dose modification for an adverse reaction. When using the gravity method for a reduced dose, the Pluvicto dose should be adjusted before the administration to avoid the delivery of an incorrect volume of Pluvicto.

Prior to administration, the intravenous catheter used exclusively for Pluvicto administration should be flushed with ≥10 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection to ensure patency and to minimise the risk of extravasation. Cases of extravasation should be managed as per institutional guidelines. Patients should be advised to remain well hydrated and to urinate frequently before and after administration of Pluvicto (see section 4.4).

For instructions on the method of preparation and intravenous methods of administration, see section 12.

For patient preparation, see section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

Risk from radiation exposure

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

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

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

After the procedure
Before the patient is released, the nuclear medicine physician or healthcare professional should explain the necessary radioprotection precautions that the patient should follow to minimise radiation exposure to others.

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

- Limit close contact (less than 1 metre) with others for 2 days or with children and pregnant women for 7 days.
- Refrain from sexual activity for 7 days.
- Sleep in a separate room from others for 3 days, from children for 7 days, or from pregnant women for 15 days.

Myelosuppression

In the VISION study, myelosuppression, including fatal cases, occurred more frequently in patients who received Pluvicto plus best standard of care (BSoC) compared to patients who received BSoC alone (see section 4.8).

Haematology laboratory tests, including haemoglobin, white blood cell count, absolute neutrophil count and platelet count, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced or permanently discontinued and patients should be clinically managed as deemed appropriate based on the severity of myelosuppression (see section 4.2).

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 4.8).

Before and after administration of Pluvicto, patients should be encouraged to increase oral fluids and urged to void as often as possible, especially after high activities, e.g. for radionuclide therapy. Kidney function laboratory tests, including serum creatinine and calculated CLcr, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced or permanently discontinued based on the severity of renal toxicity (see section 4.2).

Renal/Hepatic impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Exposure (AUC) of lutetium (^{177}Lu) vipivotide tetraxetan is expected to increase with the degree of renal impairment (see section 5.2). Patients with mild or moderate renal impairment may be at greater risk of toxicity. Renal function and adverse reactions should be frequently monitored in patients with mild to moderate renal impairment (see section 4.2). Treatment with Pluvicto is not recommended in patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end-stage renal disease.

Fertility

Radiations of lutetium (^{177}Lu) vipivotide tetraxetan may potentially have toxic effects on male gonads and spermatogenesis. The recommended cumulative dose of 44 400 MBq of Pluvicto results in a radiation absorbed dose to the testes within the range where Pluvicto may cause infertility. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm can be discussed as an option for male patients before treatment (see section 4.6).

Contraception in males

Male patients are advised not to father a child and to use a condom for intercourse during treatment with Pluvicto and for 14 weeks after the last dose (see section 4.6).

Specific warnings

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

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies were performed.

4.6 Fertility, pregnancy and lactation

Contraception in males

Because of potential effects on spermatogenesis associated with radiations of lutetium (^{177}Lu) vipivotide tetraxetan, male patients are advised not to father a child and to use a condom for intercourse during treatment with Pluvicto and for 14 weeks after the last dose (see section 4.4).

Pregnancy

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-foetal development. However, all radioactive emissions, including those from Pluvicto, can cause foetal harm when administered to a pregnant woman.

Breast-feeding

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 breast-fed newborn/infant or on milk production.

Fertility

No studies were conducted to determine the effects of lutetium (^{177}Lu) vipivotide tetraxetan on fertility. Radiations of lutetium (^{177}Lu) vipivotide tetraxetan may potentially have toxic effects on male gonads and spermatogenesis. The recommended cumulative dose of 44 400 MBq of Pluvicto results in a radiation absorbed dose to the testes within the range where Pluvicto may cause infertility. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm can be discussed as an option for male patients before treatment (see section 4.4).

4.7 Effects on ability to drive and use machines

Pluvicto may have a minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

Unless otherwise stated, the frequency of listed adverse reactions is based on data from the VISION study in which 529 patients received at least one dose of 7 400 MBq (median number of doses was five).

The most common adverse reactions include: fatigue (48.0%), dry mouth (39.3%), nausea (35.7%), anaemia (31.9%), decreased appetite (21.4%) and constipation (20.2%). The most common grade 3 to 4 adverse reactions include: anaemia (12.9%), thrombocytopenia (7.9%), lymphopenia (7.8%) and fatigue (6.6%).

At the time of VISION final analysis, after a median follow-up duration of 14.2 months (range: 0.6 to 60.9 months), the overall safety profile remained consistent with that previously reported.

Tabulated list of adverse reactions

Adverse reactions (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse 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 2 Adverse reactions occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone in VISION[a]

System organ class Adverse reaction	Frequency category	All grades n (%)	Grades 3 to 4[b] n (%)
Infections and infestations			
Oral fungal infection[c]	Common	13 (2.5)	0 (0.0)
Blood and lymphatic system disorders			
Anaemia	Very common	169 (31.9)	68 (12.9)
Thrombocytopenia	Very common	91 (17.2)	42 (7.9)
Leukopenia[d]	Very common	83 (15.7)	22 (4.2)
Lymphopenia	Very common	75 (14.2)	41 (7.8)
Pancytopenia[e]	Common	9 (1.7)	7 (1.3)[b]
Bone marrow failure	Uncommon	1 (0.2)	1 (0.2)[b]
Nervous system disorders			
Dizziness	Common	44 (8.3)	5 (0.9)
Headache	Common	37 (7.0)	4 (0.8)
Dysgeusia[f]	Common	37 (7.0)	0 (0.0)
Eye disorders			
Dry eye	Common	16 (3.0)	0 (0.0)
Ear and labyrinth disorders			
Vertigo	Common	11 (2.1)	0 (0.0)
Gastrointestinal disorders			
Dry mouth[g]	Very common	208 (39.3)	0 (0.0)
Nausea	Very common	189 (35.7)	7 (1.3)
Constipation	Very common	107 (20.2)	6 (1.1)
Vomiting[h]	Very common	101 (19.1)	5 (0.9)
Diarrhoea	Very common	101 (19.1)	4 (0.8)
Abdominal pain[i]	Very common	61 (11.5)	7 (1.3)
Oesophageal disorder[j]	Common	18 (3.4)	1 (0.2)
Stomatitis	Common	9 (1.7)	1 (0.2)
Skin and subcutaneous tissue disorders			
Dry skin[k]	Common	8 (1.5)	0 (0.0)
Renal and urinary disorders			
Urinary tract infection[l]	Very common	63 (11.9)	20 (3.8)
Acute kidney injury[m]	Common	48 (9.1)	18 (3.4)

General disorders and administration site conditions			
Fatigue[n]	Very common	254 (48.0)	35 (6.6)
Decreased appetite	Very common	113 (21.4)	10 (1.9)
Weight decreased	Very common	58 (11.0)	2 (0.4)
Oedema peripheral[o]	Very common	53 (10.0)	2 (0.4)
Pyrexia	Common	37 (7.0)	2 (0.4)

Abbreviation: BSoC, best standard of care.

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

[b] Only includes grades 3 to 4 adverse reactions, with the exception of pancytopenia and bone marrow failure. Grade 5 (fatal) pancytopenia was reported in 2 patients who received Pluvicto plus BSoC. Grade 5 (fatal) bone marrow failure was reported in 1 patient who received Pluvicto plus BSoC.

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

[d] Leukopenia includes leukopenia and neutropenia.

[e] Pancytopenia includes pancytopenia and bicytopenia.

[f] Dysgeusia includes dysgeusia and taste disorder.

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

[h] Vomiting includes vomiting and retching.

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

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

[k] Dry skin includes dry skin and xeroderma.

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

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

[n] Fatigue includes fatigue and asthenia.

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

Description of selected adverse reactions

Myelosuppression

In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (all grades/grade ≥3): anaemia (31.9%/12.9%) versus (13.2%/4.9%); 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; bicytopenia (0.2%/0.2%) versus (0%/0%); and bone marrow failure (0.2%/0.2%) versus (0%/0%) including one fatal event of bone marrow failure in a patient who received Pluvicto plus BSoC.

Myelosuppression adverse reactions that led to permanent discontinuation in ≥0.5% of patients who received Pluvicto plus BSoC included: anaemia (2.8%), thrombocytopenia (2.8%), leukopenia (1.3%), neutropenia (0.8%) and pancytopenia (0.6%). Myelosuppression adverse reactions that led to dose interruptions/dose reductions in ≥0.5% of patients who received Pluvicto plus BSoC included: anaemia (5.1%/1.3%), 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 (5.7%/0.2%) versus (2.4%/0.5%); acute kidney injury (3.8%/3.2%) versus (3.9%/2.4%); renal failure (0.2%/0%) versus (0%/0%); and blood urea increased (0.2%/0%) versus (0%/0%).

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

Second primary malignancies
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself. As Pluvicto contributes to a patient's overall long-term radiation exposure, which is associated with an increased risk for cancer (see section 4.4), a potential risk of second primary malignancies cannot be ruled out for radiopharmaceuticals such as Pluvicto. At the time of the VISION primary analysis (cut-off date 27-Jan-2021), cases of squamous cell carcinoma (4 patients; 0.8%) and basal cell carcinoma, malignant melanoma and squamous cell carcinoma of the skin (1 patient each; 0.2% each) were reported in patients who received Pluvicto plus BSoC.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of administration of a radiation overdose with Pluvicto, the 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 dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Therapeutic radiopharmaceuticals, Other therapeutic radiopharmaceuticals, ATC code: V10XX05

Mechanism of action

The active moiety of Pluvicto is the radionuclide lutetium-177 which is linked to a small-molecule ligand that targets and 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.

Pharmacodynamic effects

Vipivotide tetraxetan does not have any pharmacodynamic activity.

Clinical efficacy and safety

VISION
The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC was evaluated in VISION, a randomised, multicentre, open-label phase III study. Eight hundred and thirty-one (N=831) adult patients were randomised (2:1) to receive either Pluvicto 7 400 MBq every 6 weeks for up to a total of 6 doses plus best standard of care (BSoC) (N=551) or BSoC alone (N=280). Patients who received 4 doses of Pluvicto were reassessed for evidence of response, signs of residual disease, and tolerability and could receive up to 2 additional doses per physician's discretion.

To maintain castration status, all patients continued to receive a GnRH analogue or had prior bilateral orchiectomy. Eligible patients were required to have progressive, PSMA-positive mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic and haematological function.

Eligible patients were also required to have received at least one AR pathway inhibitor, such as abiraterone acetate or enzalutamide, and 1 or 2 prior taxane-based chemotherapy regimens (with a regimen defined as a minimum exposure of 2 cycles of a taxane). Patients treated with only 1 prior taxane-based chemotherapy regimen were eligible if the patient was unwilling or the physician deemed the patient unsuitable to receive a second regimen. Patients with unstable symptomatic central nervous system metastases or symptomatic or clinically/radiologically impending spinal cord compression were not eligible for the study. Patients underwent a gallium (^{68}Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumour lesion with gallium (^{68}Ga) gozetotide uptake greater than in normal liver. Patients were excluded if any lesions exceeding size criteria in short axis (organs ≥1 cm, lymph nodes ≥2.5 cm, bones [soft-tissue component] ≥1 cm) had uptake less than or equal to uptake in normal liver.

BSoC administered at the physician's discretion included: supportive measures including pain management, hydration, blood transfusions, etc.; ketoconazole; radiation therapy (including seeded form or any external beam radiotherapy [including stereotactic body radiotherapy and palliative external beam]) to localised prostate cancer targets; bone-targeted agents including zoledronic acid, denosumab and any bisphosphonates; androgen-reducing agents including GnRH analogues, any corticosteroid, and 5-alpha reductases; AR pathway inhibitors. BSoC excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes and hemi-body radiotherapy treatment.

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

The primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS) as determined by blinded independent central review (BICR) per PCWG3 criteria. Among the secondary efficacy endpoints were overall response rate (ORR) as determined 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, tumour-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death from any cause, whichever occurred first. Radiographic imaging for tumour assessment (CT with contrast/MRI imaging and bone scan) was done every 8 weeks (±4 days) after the first dose for the first 24 weeks (independent of dose delays), then every 12 weeks (±4 days).

Demographic and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range: 40 to 94 years); 86.8% White; 6.6% Black or African American; 2.4% Asian; 92.4% had ECOG PS0-1; 7.6% had ECOG PS2. Randomisation was stratified by baseline lactate dehydrogenase (LDH ≤260 IU/L vs. >260 IU/L), presence of liver metastases (yes vs. no), ECOG PS score (0 or 1 vs. 2), and inclusion of an AR pathway inhibitor as part of BSoC at the time of randomisation (yes vs. no). At randomisation, all patients (100.0%) had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two; 97.1% of patients had received docetaxel and 38.0% of patients had received cabazitaxel. At randomisation, 51.3% of patients had received one prior AR pathway inhibitor, 41.0% of patients had received 2, and 7.7% of patients had received 3 or more. During the randomised treatment period, 52.6% of patients in the Pluvicto plus BSoC arm and 67.8% of patients in the BSoC alone arm received at least one AR pathway inhibitor.

Efficacy results for VISION are presented in Table 3 and Figures 1 and 2. The final analyses of OS and rPFS were event-driven and conducted after the occurrence of 530 deaths and 347 events, respectively.

Table 3 Efficacy results in VISION

Efficacy parameters	**Pluvicto plus BsoC**	**BSoC**
Alternate primary efficacy endpoints		
Overall survival (OS)[a]	N=551	N=280
Deaths, n (%)	343 (62.3%)	187 (66.8%)
Median, months (95% CI)[b]	15.3 (14.2; 16.9)	11.3 (9.8; 13.5)
Hazard ratio (95% CI)[c]	0.62 (0.52; 0.74)	
P-value[d]	<0.001	
Radiographic progression-free survival (rPFS)[e,f]	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)[b]	8.7 (7.9; 10.8)	3.4 (2.4; 4.0)
Hazard ratio (99.2% CI)[c]	0.40 (0.29; 0.57)	
P-value[d]	<0.001	
Secondary efficacy endpoints		
Time to first symptomatic skeletal event (SSE)[f]	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)[b]	11.5 (10.3; 13.2)	6.8 (5.2; 8.5)
Hazard ratio (95% CI)[c]	0.50 (0.40; 0.62)	
P-value[g]	<0.001	
Best overall response (BOR)		
Patients with evaluable disease at baseline	N=319	N=120
Complete response (CR), n (%)	18 (5.6%)	0 (0%)
Partial response (PR), n (%)	77 (24.1%)	2 (1.7%)
Overall response rate (ORR)[h,i]	95 (29.8%)	2 (1.7%)
P-value[j]	<0.001	
Duration of response (DOR)[h]		
Median, months (95% CI)[b]	9.8 (9.1; 11.7)	10.6 (NE; NE)[k]

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] Analysed on an intent-to-treat (ITT) basis in all randomised patients.

[b] Based on Kaplan-Meier estimate.

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

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

[e] By BICR per PCWG3 criteria. The primary analysis of rPFS included censoring of patients who had ≥2 consecutive missed tumour assessments immediately prior to progression or death. Results for rPFS with and without censoring for missed assessments were consistent.

[f] Analysed on an ITT basis in all patients randomised on or after 05-Mar-2019, when actions were implemented to mitigate early drop-out from BSoC arm.

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

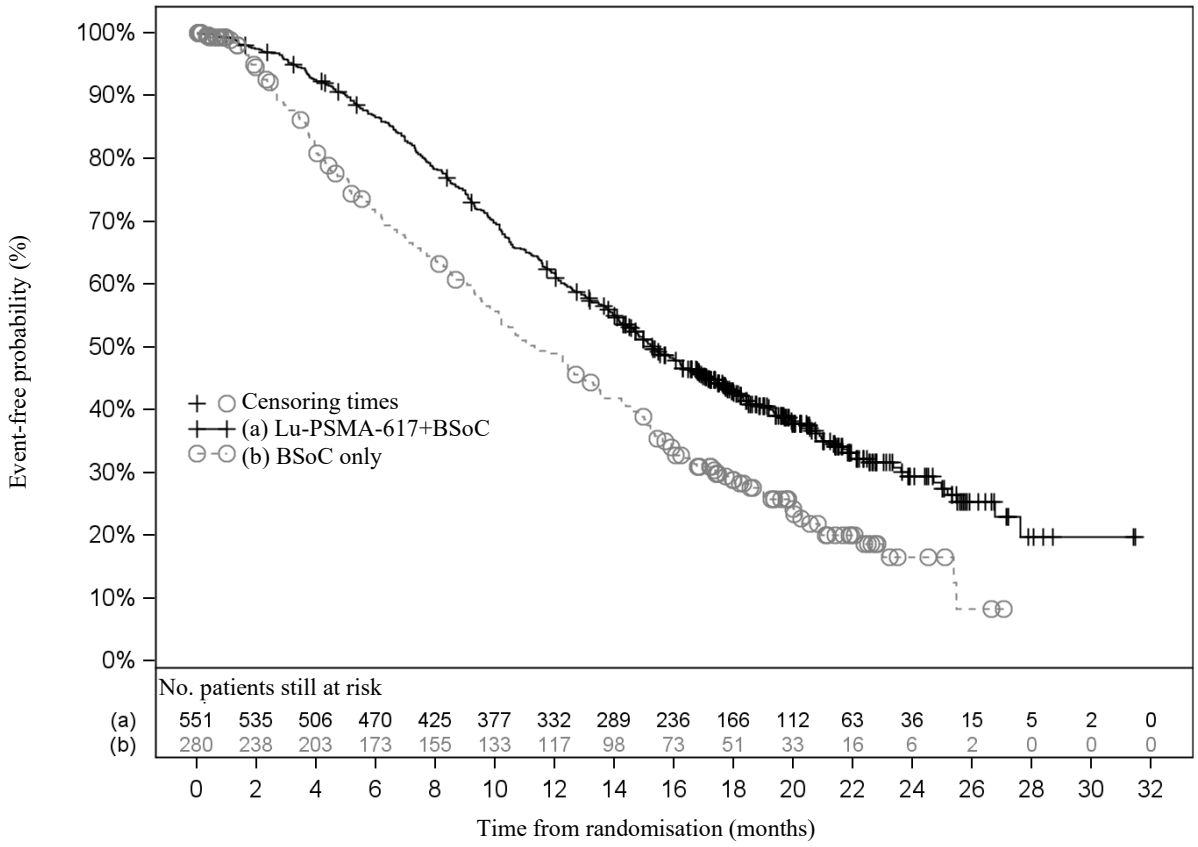
[h] By BICR per RECIST v1.1.

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

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

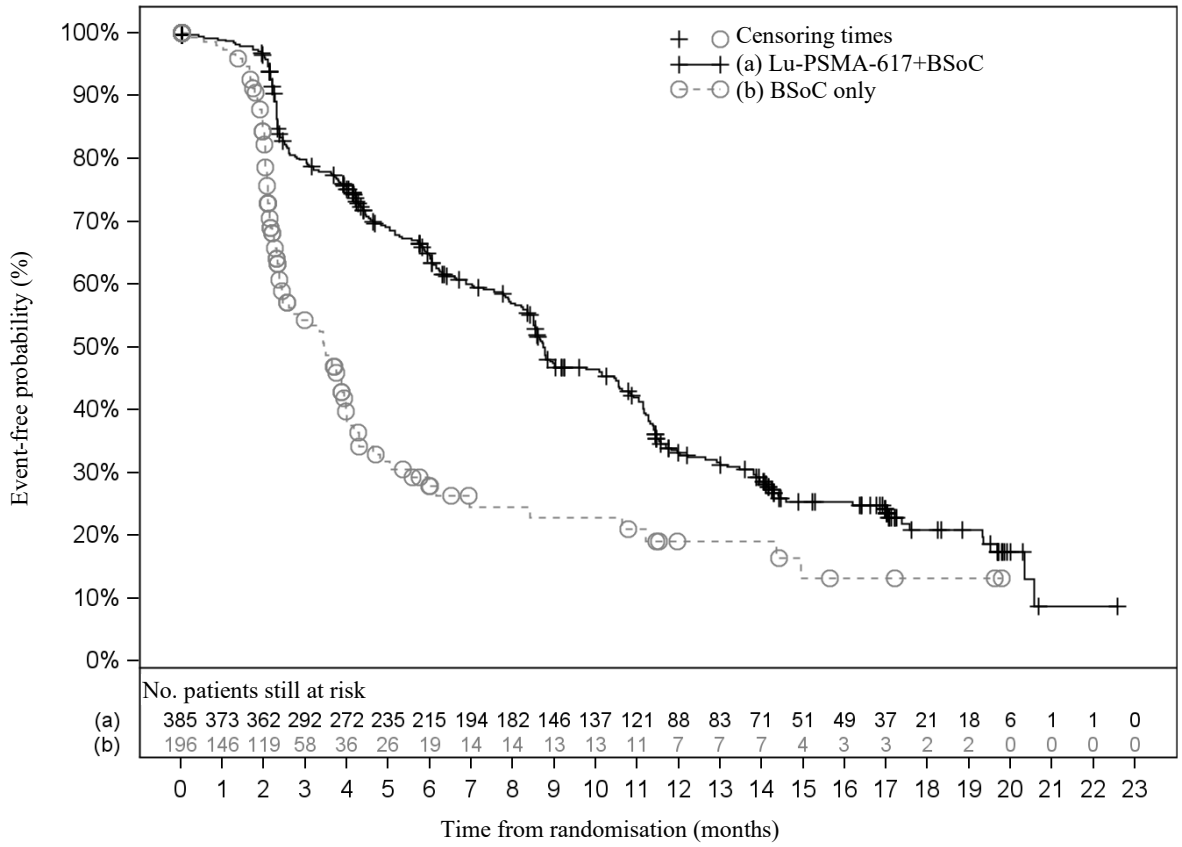
[k] Median DOR in the BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST v1.1 radiographic progression or death.

Figure 1 Kaplan-Meier plot of OS 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 randomisation.
n/N: Number of events/number of patients in treatment arm.

Figure 2 Kaplan-Meier plot of BICR-assessed rPFS in VISION



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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Pluvicto in all subsets of the paediatric population in the treatment of PSMA-expressing prostate cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

Pluvicto is administered intravenously and is immediately and completely bioavailable.

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

Distribution

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

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

Organ uptake

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

Elimination

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

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

Half-life

Pluvicto shows a bi-exponential elimination with a geometric mean terminal elimination half-life ($t_{½}$) of 41.6 hours (CV 68.8%).

Biotransformation

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

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*.

Special populations

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

Renal impairment
Exposure (AUC) of lutetium (^{177}Lu) vipivotide tetraxetan increased by 20% in patients with mild renal impairment compared to normal renal function. Kidney dosimetry half-life also increased in patients with mild renal impairment compared to normal renal function, 51 hours vs. 37 hours, respectively. Patients with mild or moderate renal impairment may be at greater risk of toxicity (see section 4.4). No pharmacokinetic data are available for patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end-stage renal disease.

5.3 Preclinical safety data

No toxicological effects were observed in safety pharmacology or single-dose toxicity studies in rats and minipigs administered a non-radioactive formulation containing vipivotide tetraxetan and lutetium

(^{175}Lu) vipivotide tetraxetan, or in repeat-dose toxicity studies in rats administered 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Sodium acetate
Gentisic acid
Sodium ascorbate
Pentetic acid
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in sections 4.2 and 12.

6.3 Shelf life

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

6.4 Special precautions for storage

Do not freeze.
Store in the original package in order to protect from ionising radiation (lead shielding).

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

6.5 Nature and contents of container

Clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal.

Each vial contains a volume of solution that can range from 7.5 mL to 12.5 mL corresponding to a radioactivity of 7 400 MBq ±10% at the date and time of administration.

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

6.6 Special precautions for disposal and other handling

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For instructions on preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this medicinal product the integrity of the lead container or the vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

This preparation is likely to result in a relatively high radiation dose to most patients. The administration of Pluvicto may result in significant environmental hazard. This may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered. Suitable precautions in accordance with national regulations should be taken concerning the activity eliminated by the patients in order to avoid any contaminations.

Lutetium-177 for Pluvicto may be prepared using two different sources of stable nuclides (either lutetium-176 or ytterbium-176). Lutetium-177 for Pluvicto prepared using the stable isotope lutetium-176 ("carrier added") requires special attention with regard to waste management due to the presence of the long-lived metastable lutetium-177 (^{177m}Lu) impurity with a half-life of 160.4 days. Lutetium-177 for Pluvicto is prepared using ytterbium-176 ("non-carrier added") unless otherwise communicated on the product batch release certificate. The user must consult the product batch release certificate provided before using Pluvicto to ensure appropriate waste management.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1703/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 December 2022

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

Radiation dose to specific organs, which may not be the target organ of therapy, can be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

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 absorbed doses to different organs for adult patients receiving Pluvicto are shown in Table 4. The organs with the highest 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 Estimated absorbed dose[a] for Pluvicto in the VISION sub-study

	Absorbed dose per unit activity (mGy/MBq) (N=29)		**Calculated absorbed dose for 7 400 MBq administration (Gy)**		**Calculated absorbed dose for 6 x 7 400 MBq (44 400 MBq cumulative activity) (Gy)**	
Organ	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.033	0.026	0.25	0.19	1.5	1.1
Brain	0.0069	0.0051	0.051	0.038	0.30	0.23
Eyes	0.022	0.025	0.16	0.18	0.98	1.1
Gallbladder wall	0.028	0.026	0.21	0.19	1.3	1.2
Heart wall	0.17	0.12	1.3	0.88	7.8	5.3
Kidneys	0.42	0.19	3.1	1.4	19	8.4
Lacrimal glands	2.1	0.48	15	3.6	92	21
Left colon	0.58	0.14	4.3	1.0	26	6.1
Liver	0.093	0.050	0.69	0.37	4.1	2.2
Lungs	0.11	0.11	0.78	0.83	4.7	5.0
Oesophagus	0.025	0.026	0.18	0.19	1.1	1.2
Osteogenic cells	0.036	0.029	0.26	0.21	1.6	1.3
Pancreas	0.027	0.026	0.20	0.19	1.2	1.2
Prostate	0.027	0.026	0.20	0.19	1.2	1.2
Rectum	0.56	0.14	4.1	1.1	25	6.3
Red marrow	0.035	0.020	0.26	0.15	1.5	0.91
Right colon	0.32	0.079	2.4	0.58	14	3.5
Salivary glands	0.63	0.37	4.6	2.7	28	16
Small intestine	0.071	0.031	0.52	0.23	3.1	1.4
Spleen	0.061	0.028	0.45	0.21	2.7	1.2
Stomach wall	0.025	0.026	0.19	0.19	1.1	1.2
Testes	0.023	0.025	0.17	0.19	1.0	1.1
Thymus	0.024	0.026	0.18	0.19	1.1	1.2
Thyroid	0.26	0.37	1.9	2.8	11	17
Total body	0.037	0.027	0.28	0.20	1.7	1.2
Urinary bladder wall	0.32	0.025	2.4	0.19	14	1.1
Effective dose[b]	0.12 mSv/MBq	0.043 mSv/MBq	0.89 Sv	0.315 Sv	5.3 Sv	1.9 Sv

[a] Absorbed dose estimates were derived using OLINDA v2.4. Values have been calculated based on dosimetry estimates at full precision and rounded to relevant digits.

[b] Derived according to ICRP Publication 103.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The user must consult the product batch release certificate provided before using Pluvicto to ensure appropriate waste management (see section 6.6).

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single-dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

Preparation instructions

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

Intravenous methods of administration

Instructions for the syringe method

- Withdraw an appropriate volume of Pluvicto solution to deliver the desired radioactivity by using a disposable syringe fitted with a syringe shield and a disposable sterile needle that is 9 cm, 18 gauge (long needle). To aid the withdrawal of the solution, a filtered 2.5 cm, 20 gauge needle (short venting needle) can be used to reduce the resistance from the pressurised vial. Ensure that the short needle does not touch the Pluvicto solution in the vial.
- If using a syringe pump, fit the syringe into the shielded pump and include a 3-way stopcock valve between the syringe and an intravenous catheter primed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection and used for Pluvicto administration to the patient.
- Administer Pluvicto to the patient by slow intravenous push within approximately 1 to 10 minutes (either with a syringe pump or manually without a syringe pump) via an intravenous catheter that is primed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection and that is used exclusively for Pluvicto administration to the patient.
- When the desired Pluvicto radioactivity has been delivered, stop the syringe pump and then change the position of the 3-way stopcock valve to flush the syringe with 25 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection. Restart the syringe pump.
- After the flush of the syringe has been completed, perform an intravenous flush of ≥10 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection through the intravenous catheter to the patient.

Instructions for the gravity method

- Insert a 2.5 cm, 20 gauge needle (short needle) into the Pluvicto vial and connect via a catheter to 500 mL sterile sodium chloride 9 mg/mL (0.9%) solution for injection (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 sterile sodium chloride 9 mg/mL (0.9%) solution for injection to flow into the Pluvicto vial prior to the initiation of the Pluvicto infusion and do not inject the Pluvicto solution directly into the sterile sodium chloride 9 mg/mL (0.9%) solution for injection.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Pluvicto vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is primed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection 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 sterile sodium chloride 9 mg/mL (0.9%) solution for injection via the short needle into the Pluvicto vial (the sterile sodium chloride 9 mg/mL (0.9%) solution for injection 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 sterile sodium chloride 9 mg/mL (0.9%) solution for injection line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an intravenous flush of ≥10 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection through the intravenous catheter to the patient.

Instructions for the peristaltic pump method

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

Quality control

The solution should be visually inspected for damage and contamination before use, and only clear solutions free of visible particles should be used. The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes. The vial must not be opened.

If at any time in the preparation of this medicinal product the integrity of the lead container or the vial is compromised, it should not be used.

The amount of radioactivity in the vial must be measured prior to administration using a suitable radioactivity calibration system in order to confirm that the actual amount of radioactivity to be administered is equal to the planned amount at the administration time.

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Advanced Accelerator Applications (Italy) S.R.L.
Via Ribes 5
10010
Colleretto Giacosa (TO)
Italy

Advanced Accelerator Applications Ibérica, S.L.U.
Polígono Industrial la Cuesta – Sector 3
Parcelas 1 y 2 La Almunia de Doña Godina
50100 Zaragoza
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Pluvicto in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the patient guide, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The patient guide is aimed to reduce the risk of inadvertent radiation exposure.

The MAH shall ensure that, in each Member State where Pluvicto is marketed, patients have access to the patient guide.

The Pluvicto patient guide contains the following key elements:
- What Pluvicto is and how it works
- Description of risk guidance on:
    - Hydration
    - Close contacts
    - Care givers
    - Sexual activity and contraception
    - Toilet use
    - Showering and laundry
    - Waste disposal

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LEAD SHIELDING CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Pluvicto 1 000 MBq/mL solution for injection/infusion
lutetium (^{177}Lu) vipivotide tetraxetan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One mL contains 1 000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at calibration time.
Volumetric activity at calibration time: 1 000 MBq/mL - {DD/MM/YYYY hh:mm UTC}

3. LIST OF EXCIPIENTS

Acetic acid, sodium acetate, gentisic acid, sodium ascorbate, pentetic acid, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion

1 single-dose vial

Vial no.: {X}
Volume: {Y} mL
Activity at administration time: {Z} MBq - {DD/MM/YYYY hh:mm UTC}

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY



8. EXPIRY DATE

EXP: {DD/MM/YYYY hh:mm UTC}

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Store in the original package in order to protect from ionising radiation (lead shielding).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1703/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pluvicto 1 000 MBq/mL solution for injection/infusion
lutetium (^{177}Lu) vipivotide tetraxetan
Intravenous use

2. METHOD OF ADMINISTRATION

Single-dose vial

3. EXPIRY DATE

EXP: {DD/MM/YYYY hh:mm UTC}

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Vial no.: {X}
Volume: {Y} mL
Volumetric activity at calibration time: 1 000 MBq/mL - {DD/MM/YYYY hh:mm UTC}
Activity at administration time: {Z} MBq - {DD/MM/YYYY hh:mm UTC}

6. OTHER



Manufacturer

Advanced Accelerator Applications (Italy) S.R.L.
Via Ribes 5
10010
Colleretto Giacosa (TO)
Italy

Advanced Accelerator Applications Ibérica, S.L.U.
Polígono Industrial la Cuesta – Sector 3
Parcelas 1 y 2 La Almunia de Doña Godina
50100 Zaragoza
Spain

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Pluvicto 1 000 MBq/mL solution for injection/infusion
lutetium (^{177}Lu) vipivotide tetraxetan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise the procedure.
- If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pluvicto is and what it is used for
2. What you need to know before Pluvicto is used
3. How Pluvicto is used
4. Possible side effects
5. How Pluvicto is stored
6. Contents of the pack and other information

1. What Pluvicto is and what it is used for

What Pluvicto is
Pluvicto contains lutetium (^{177}Lu) vipivotide tetraxetan. This medicine is a radiopharmaceutical product for therapy only.

What Pluvicto is used for
Pluvicto is used to treat adults with progressive castration-resistant prostate cancer that has spread to other parts of the body (metastatic) and has already been treated with other cancer treatments. Castration-resistant prostate cancer is a cancer of the prostate (a gland of the male reproductive system) that does not respond to treatment that reduces male hormones. Pluvicto is used if the prostate cancer cells have a protein on their surface called prostate-specific membrane antigen (PSMA).

How Pluvicto works
Pluvicto binds to PSMA found on the surface of the prostate cancer cells. Once bound, the radioactive substance in Pluvicto, lutetium-177, gives off radiation that causes the prostate cancer cells to die.

Your doctor will carry out tests to see if PSMA is present on the surface of the cancer cells. Your cancer is more likely to respond to treatment with Pluvicto if the test result is positive.

The use of Pluvicto involves exposure to amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

If you have any questions about how Pluvicto works or why this medicine has been prescribed for you, ask your nuclear medicine doctor.

2. What you need to know before Pluvicto is used

Follow all instructions given by your nuclear medicine doctor carefully. They may differ from the general information contained in this leaflet.

Pluvicto must not be used
- if you are allergic to lutetium (^{177}Lu) vipivotide tetraxetan or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
If any of these apply to you, tell your nuclear medicine doctor before receiving Pluvicto:
- if you have low levels of certain types of cells in the blood (red blood cells, white blood cells, neutrophils, platelets)
- if you have or have had tiredness, weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or bleeding for longer than normal, or frequent infections with signs such as fever, chills, sore throat or mouth ulcers (possible signs of myelosuppression [a condition in which the bone marrow cannot make enough blood cells])
- if you have or have had kidney problems
- if you have or have had any other type of cancer or treatment for cancer, as Pluvicto contributes to your overall long-term cumulative radiation exposure

Before administration of Pluvicto you should:
- drink plenty of water so that you remain hydrated and urinate as often as possible during the first hours after administration

Children and adolescents
The safety and efficacy of this medicine have not been established in children and adolescents under 18 years of age. This medicine should not be given to children or adolescents aged under 18 years because no data are available in this age group.

Pregnancy, breast-feeding and fertility
Pluvicto is not intended for use in women.

Before you receive Pluvicto, tell your nuclear medicine doctor if you are sexually active as all radioactive emissions, including those from Pluvicto, can cause harm to an unborn baby.

Fertility
Pluvicto may cause infertility. Please ask your nuclear medicine doctor how this may affect you, especially if you are planning to have children in the future. You may wish to seek advice on preservation of sperm before treatment starts.

Contraception in males
- You should avoid sexual activity for 7 days after administration of Pluvicto.
- You should not father a child and should use a condom during intercourse throughout treatment with Pluvicto and for 14 weeks after your last dose.
- Tell your nuclear medicine doctor immediately if you father a child at any time during this time period.

Driving and using machines
It is considered unlikely that Pluvicto will affect your ability to drive or use machines.

Pluvicto contains sodium
This medicine contains up to 88.75 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 4.4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Pluvicto is used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Pluvicto will only be used in special controlled areas. This radiopharmaceutical product will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this radiopharmaceutical product and will keep you informed of their actions.

How much Pluvicto is given
The recommended treatment regimen of Pluvicto is 7 400 MBq (megabecquerel, the unit used to express radioactivity), which is given approximately every 6 weeks for up to a total of 6 doses.

Administration of Pluvicto and conduct of the procedure
Pluvicto is administered directly into a vein.

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure.

If you have questions about how long you will receive Pluvicto, talk to your nuclear medicine doctor.

Treatment monitoring
Your nuclear medicine doctor will do blood tests before and during treatment to check your condition and to detect any side effects as early as possible. Based on the results, your nuclear medicine doctor may decide to delay, change or stop your treatment with Pluvicto if necessary.

After administration of Pluvicto, you should:
- drink plenty of water for 2 days so that you remain hydrated and urinate as often as possible to eliminate the radiopharmaceutical product from your body

Because this medicine is radioactive, you will have to follow the instructions described below to minimise radiation exposure to others unless otherwise instructed by your nuclear medicine doctor.

<u>Contact with others, children, and/or pregnant women</u>
- Limit close contact (less than 1 metre) with:
  - others for 2 days
  - children and pregnant women for 7 days
- Sleep in a separate room from:
  - others for 3 days
  - children for 7 days
  - pregnant women for 15 days
- Avoid sexual activity for 7 days
- Do not father a child and do use a condom during intercourse throughout treatment with Pluvicto and for 14 weeks after your last dose

<u>Use of toilets</u>
Take special precautions to avoid contamination for 2 days after administration:
- You must always sit when using the toilet.
- It is essential that you use toilet paper every time you use the toilet.
- Always wash your hands well after using the toilet.
- Flush all wipes and/or toilet paper down the toilet immediately after use.
- Flush any tissues or any other items that contain bodily waste, such as blood, urine and faeces down the toilet. Items that cannot be flushed down the toilet, such as bandages, must be placed in separate plastic waste disposal bags (according to “Waste disposal recommendations” below).
- Any special medical equipment that could be contaminated by your bodily fluids (e.g. catheter bags, colostomy bags, bedpans, water nozzles) must be emptied immediately into the toilet and then cleaned.

Showering and laundry
- Take a shower every day for at least 7 days after administration.
- Wash your underwear, pyjamas, sheets and any clothes that contain sweat, blood or urine separately from the laundry of others in your household, using a standard washing cycle. You do not need to use bleach and you do not need extra rinses.

Care givers
For 2-3 days after administration:
- People who are confined to bed or have reduced mobility will preferably receive assistance from a care giver. It is recommended that when providing assistance in the bathroom, the care giver wears disposable gloves.
- Care givers who clean up vomit, blood, urine or faeces should wear plastic gloves, which should be disposed of in a separate plastic waste disposal bag (see "Waste disposal recommendations" below).

Waste disposal recommendations
- All items to be thrown away should be discarded in a separate plastic waste disposal bag to be used only for this purpose.
- Keep the plastic waste disposal bags separate from the other household waste and away from children and animals.
- A member of the hospital staff will tell you how and when to get rid of these waste disposal bags.

Hospitalisation and emergency care
- If for any reason you require emergency medical assistance or are unexpectedly admitted to the hospital during the first 7 days after administration, you should inform the healthcare professionals about the name, date and dose of your radioactive treatment.

Other precautions
- The nuclear medicine doctor will inform you if you need to take any other special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

If you have been given more Pluvicto than you should
An overdose is unlikely because you will only receive Pluvicto in doses that are precisely controlled by the nuclear medicine doctor supervising the procedure. However, in the event of an overdose, you will receive the appropriate treatment.

If you forget to receive Pluvicto
If you miss an appointment to receive Pluvicto, contact your nuclear medicine doctor as soon as possible to reschedule.

Should you have any further questions on the use of Pluvicto, please ask the nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious
If you experience any of the following serious side effects, **tell your nuclear medicine doctor right away**.

Very common: may affect more than 1 in 10 people
- tiredness, weakness, pale skin or shortness of breath (possible signs of low levels of red blood cells [*anaemia*])

- bleeding or bruising more easily than normal or bleeding for longer than normal (possible signs of low levels of platelets [*thrombocytopenia*])
- frequent infections with signs such as fever, sore throat or mouth ulcers (possible signs of low levels of white blood cells [*leukopenia, lymphopenia*])

Common: may affect up to 1 in every 10 people
- passing urine less often or in much smaller amounts than usual (possible sign of kidney problems [*acute kidney injury*])
- tiredness, weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or bleeding for longer than normal or frequent infections with signs such as fever, chills, sore throat or mouth ulcers (possible signs of low levels of blood cells [*pancytopenia*])

Uncommon: may affect up to 1 in every 100 people
- Weakness, pale skin, bleeding or bruising more easily than normal or difficulty to stop bleeding and frequent infections with signs such as fever, chills, sore throat or mouth ulcers (bone marrow failure)

Other possible side effects
Other side effects include the following listed below. If these side effects become severe, please tell your nuclear medicine doctor.

Very common: may affect more than 1 in 10 people
- tiredness (*fatigue*)
- dry mouth
- nausea
- loss of appetite
- changes in bowel movements (constipation or diarrhoea)
- vomiting
- frequent urination with pain or burning sensation (*urinary tract infection*)
- abdominal pain
- weight loss
- swollen hands, ankles or feet (*peripheral oedema*)

Common: may affect up to 1 in every 10 people
- dizziness
- headache
- disturbed sense of taste (*dysgeusia*)
- fever (*pyrexia*)
- trouble swallowing and/or heartburn (*oesophageal disorder*)
- dry eyes
- oral fungal infection
- dizziness, with a spinning sensation (*vertigo*)
- mouth sores (*stomatitis*)
- dry skin

Reporting of side effects
If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How Pluvicto is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulations on radioactive materials.

The following information is intended for the specialist only:
- Keep this medicine out of the sight and reach of children.
- Do not freeze.
- Store in the original package in order to protect from ionising radiation (lead shielding).
- Pluvicto must not be used after the expiry date and time which are stated on the lead shielding container and vial labels after EXP.
- Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Pluvicto contains
- The active substance is lutetium (^{177}Lu) vipivotide tetraxetan. One mL of solution contains 1 000 MBq lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.
- The other ingredients are: acetic acid, sodium acetate, gentisic acid, sodium ascorbate, pentetic acid, water for injections (see "Pluvicto contains sodium" in section 2).

What Pluvicto looks like and contents of the pack
Pluvicto is a clear, colourless to slightly yellow solution supplied in a clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal.
Each vial contains a volume of solution that can range from 7.5 mL to 12.5 mL corresponding to a radioactivity of 7 400 MBq ±10% at the date and time of administration.
The vial is enclosed within a lead container for protective shielding.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Advanced Accelerator Applications (Italy) S.R.L.
Via Ribes 5
10010
Colleretto Giacosa (TO)
Italy

Advanced Accelerator Applications Ibérica, S.L.U.
Polígono Industrial la Cuesta – Sector 3
Parcelas 1 y 2 La Almunia de Doña Godina
50100 Zaragoza
Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Sverige AB
Tlf.: +46 8 732 32 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
ΒΙΟΚΟΣΜΟΣ ΑΕΒΕ
Τηλ: +30 22920 63900
ή
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Novartis Sverige AB
Sími: +46 8 732 32 00

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
ΒΙΟΚΟΣΜΟΣ ΑΕΒΕ
Τηλ: +30 22920 63900
ή
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Suomi/Finland
Novartis Sverige AB
Puh/Tel: +46 8 732 32 00

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

---

The following information is intended for healthcare professionals only:

The complete SmPC of Pluvicto is provided as a separate document in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC.