NOVARTIS

Chief Medical Office & Patient Safety

Lutetium (^{177}Lu) vipivotide tetraxetan

AAA617

EU Safety Risk Management Plan

Active substance(s) (INN or common name)	lutetium (^{177}Lu) vipivotide tetraxetan
Product(s) concerned (brand name(s)):	Pluvicto
Document status:	Final
Version number:	1.2
Data lock point for this RMP	27-Jan-2021
Date of final sign off	11-Oct-2022

Rationale for submitting an updated RMP:

This EU RMP v1.2 is updated to address Day 180 and Day 180+x List of outstanding issues by CHMP dated 21-Jul-2022 and 28-Sep-2022 respectively following the initial submission to European Medicines Agency (EMA) on 30-Aug-2021 (EMEA/H/C/005483).

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 1.1
Part I	Indication is updated.
Part II	None
Part III	Milestone date of PSMA-617-01 (VISION) study has been updated
Part IV	No changes
Part V	Routine risk minimization measures have been updated for the risk of second primary malignancies. Targeted follow-up checklist has been included. Patient guide for inadvertent radiation exposure has been added.
Part VI	RMP summary was updated in line with the updates made to the earlier sections
Part VII	Annex-6 has been updated with patient guide for inadvertent radiation exposure. Annex-8 of the RMP updated in line with the recommended changes

Other RMP versions under evaluation

None

Details of the currently approved RMP:

Not applicable for initial marketing authorization application submission.

QPPV name: Dr. David Lewis, BSc (Hons), PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
AR	Androgen receptor
ATC	Anatomical Therapeutic Chemical classification system (WHO drug dictionary)
AVM	Arteriovenous malformations
BMI	Body mass index
CBC	Complete blood count
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
CYP450	Cytochrome P450
DTP	Drug-treatable populations
EEA	European Economic Area
EMA/ EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GPRD	General Practice Research Database
HA	Health Authority
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International normalized ratio
MA	Marketing Authorization
mCRPC	Metastatic castration-resistant prostate cancer
mCRPCTT	mCRPC targeted therapy
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-effect-level
PSMA	Prostate-specific membrane antigen
PSUR	Periodic safety update report
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Pharmacovigilance

RISM	Radiation-induced second malignancies
RMP	Risk Management Plan
RoW	Rest of world
SAE	Serious adverse event
SD	Sprague Dawley
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA queries
SREs	Skeletal-related events
THIN	The Health Improvement Network
ULN	Upper limit of normal

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Lutetium (^{177}Lu) vipivotide tetraxetan
Pharmacotherapeutic group(s) (ATC Code)	V10XX05
Marketing Authorization Holder	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Pluvicto
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: Pluvicto is a therapeutic radiopharmaceutical
	Summary of mode of action: Lutetium (^{177}Lu) vipivotide tetraxetan is a radioligand therapy that is comprised of the therapeutic radionuclide lutetium-177 linked to a small molecule that binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of lutetium (^{177}Lu) vipivotide tetraxetan to PSMA-expressing cancer cells, the beta 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.
	Important information about its composition: Lutetium (^{177}Lu) vipivotide tetraxetan is composed of 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 in mCRPC
Hyperlink to the Product Information	[Proposed SmPC]
Indication(s) in the EEA	**Current:** 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.
Dosage in the EEA	**Current:** The recommended lutetium (^{177}Lu) vipivotide tetraxetan dose is 7400 MBq intravenously every 6 weeks (± 1 week) for up to a

	total of 6 doses, or until disease progression, or unacceptable toxicity.
Pharmaceutical form(s) and strengths	**Current:** Lutetium (^{177}Lu) vipivotide tetraxetan 1000 MBq/ml solution for injection/ infusion. One ml of solution contains 1000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration. The total amount of radioactivity per single-dose vial is 7400 MBq ± 10% at the date and time of administration. Given the fixed volumetric activity of 1000 MBq/mL at the date and time of calibration, the volume of the solution in the vial is adjusted between 7.5 mL and 12.5 mL to provide the required amount of radioactivity at the date and time of administration.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication and target population

2.1 Indication

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.

PSMA is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but also has restricted and several hundred-fold lower expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease (Ross et al 2003). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with metastatic castration-resistant prostate cancer (mCRPC).

When conducted, calculations were based on the assumption that all cases of mCRPC occurred in men aged ≥40 years.

Incidence:

Within the published data, one study was found reporting the incidence (per 100,000 men) of mCRPC in Europe (Thurin et al 2020) and three studies were found reporting number of

incident cases (n) in Europe (Marteau et al 2014), the UK (Morgan et al 2010) and in the USA (Scher et al 2015).

Thurin et al 2020 estimated the incidence of mCRPC in 2014 using the French nationwide healthcare database (SNDS) by a SNDS extraction of men covered by the general healthcare insurance (86% of the French population), and aged ≥40 year. Age-standardized incidence of mCRPC was estimated as 21 cases per 100,000 men in 2014. Less than one mCRPC case per 100,000 was observed in men aged 40-49 and maximum mCRPC incidence was in men aged 80-89 (175 per 100,000).

In a study by Marteau et al 2014, the incidence of mCRPC patients was assessed in 8 European countries and Australia using several sources including national cancer registries, a literature review, and an ad-hoc chart review. Across all 9 countries, 76,200 new patients were diagnosed mCRPC over one year. Of those patients, 35% (26,400 patients) went to supportive care without receiving any mCRPC targeted therapy (mCRPCTT) while 65% (49,800 patients) received a first line mCRPCTT.

One retrospective study by Morgan et al 2010 reported incidence of mCRPC in the UK using the Health Improvement Network (THIN) data collected between 1998 and 2008. Based on an extrapolation, the study estimated an annual incidence of 820 mCRPC cases from 2003 to 2007 in the UK. Assuming the UK population of men aged ≥40 year was ~14,000,000 in 2007, the annual incidence would be ~5.8 per 100,000 men aged ≥40.

Based on a dynamic transition model, Scher et al 2015 estimated the future mCRPC incidence in the USA, which was expected to increase by 19% in the base case scenario from 36,100 in 2009 to 42,970 in 2020. The majority (86%) of new mCRPC cases were from progression of nmCRPC. Assuming the USA population of men aged ≥40 years was ~67,000,000 in 2009 and ~160,000,000 in 2020, corresponding estimated annual incidence per 100,000 men was 53.9 and 26.9, respectively.

Prevalence:

Within the published data, only one study was found to report the prevalence of mCRPC in Europe (Thurin et al 2020). Five retrospective studies reported the number of prevalent cases in different regions (i.e., worldwide (Parihar 2018), the UK (Hirst et al 2012, Morgan et al 2010), USA (Fuld et al 2018, Scher et al 2015).

Thurin et al (2020) estimated the prevalence of mCRPC in 2014 by a SNDS extraction of men covered by the general healthcare insurance (86% of the French population), and aged ≥40. The age-standardized prevalence of mCRPC was estimated as 62 cases per 100,000 men in 2014. Less than one mCRPC prevalent case per 100,000 was observed in men aged 40-49 and the maximum mCRPC prevalence was in men aged 80-89 (500 per 100,000).

In a study using country-specific cancer registries from 45 countries, Parihar 2018 estimated the first-line mCRPC drug-treatable populations (DTP) by global geographic/economic regions over the period 2017-2027. They found an estimated 331,000 first-line mCRPC DTP worldwide in 2017 and projected that the first-line mCRPC DTP worldwide will increase by 30% over the period 2017-2027, with higher growth across lower-income countries (40%), than across high-income countries (14%).

One retrospective study by Morgan et al 2010 reported the prevalence of mCRPC in the UK using THIN data between 1998 and 2008. Based on an extrapolation, the study estimated that the annual prevalence of mCRPC was 1.2% of PC cases (2,600 cases), from 2003 to 2009. If we assume the UK population of men aged ≥40 equaled ~14,000,000 in 2007, the prevalence would be ~18.6 per 100,000 men. The UK prevalence reported by Morgan et al 2010 was based on an extrapolation and is higher than the other estimates identified in this review. As this study was only presented as an abstract, limited details on methodology or context for the extrapolation are available, although the abstract concludes that the study findings are consistent with other UK studies.

Two UK based studies (Hirst et al 2012, Morgan et al 2010) reported the proportion of mCRPC in the CRPC population from 8.8% to 15.7% (1,821-2,600 PC cases), between 1998 and 2009 using THIN and General Practice Research Database (GPRD).

In the US, the estimated prevalence of mCRPC was 2.1% of PC cases (13,818 cases) from 2007 to 2017 (Fuld et al 2018). Based on a dynamic transition model, Scher et al 2015 estimated the prevalence of mCRPC in the US. It was 62,110 in 2009 and estimated to be 76,690 in 2020. Assuming the USA population of men aged ≥40 years equals ~67,000,000 in 2009 and ~160,000,000 in 2020, corresponding annual incidence rate per 100,000 men would be ~92.7 and ~47.9, respectively. Scher et al 2015 estimated that improved progression-free survival by 25% in nmCRPC in 2015 would decrease the mCRPC prevalence by 12% in 2020 (from 72,677 to 68,837).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Multivariate analyses showed that high occupational physical activity (AOR 6.7, 95% CI 1.3-35. 1), history of prostatitis (AOR 31.5, 95% CI 9.2-170.5), and old age (over 80 years vs 70 or young, AOR 299.1, 95% CI 5.3-16985.9) were associated with higher risk of PC (Hosseini et al 2010).

Obesity in general was found to be associated with more aggressive PC with higher risk of biochemical recurrence (HR = 1.20, p = 0.026), risk of CRPC (HR = 2.12, p = 0.026) and risk of mortality (HR 3.38, p = 0.0170) (Vidal et al 2017). Another study showed similar results where high BMI was associated with a trend for greater risk of progression to CRPC (HR: 3.36, 95% CI: 0.96-11.71, p=0.063), risk of developing metastases (HR: 3.58, 95% CI: 0.77-16.65, p=0.027) and a trend toward worse PCSM (HR: 8.21 95% CI: 0.97-69.72, p=0.119). (Keto et al 2012).

The main existing treatment options:

There is an urgent need for more effective treatments to improve outcomes for patients with mCRPC.

As per the ESMO practice guidelines (Parker et al 2020), docetaxel is recommended for men with mCRPC. In patients with mCRPC in the post-docetaxel setting, abiraterone, enzalutamide and cabazitaxel are recommended. In patients with bone metastases from CRPC at risk for clinically significant skeletal-related events (SREs), a bisphosphonate or denosumab is

recommended. ^{223}Ra is recommended for men with bone-predominant, symptomatic mCRPC without visceral metastases.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality data in prostate cancer is limited across EU. Morgan et al 2010 reported mortality of CRPC in the UK. Following the onset of CRPC, the mortality rate was 201.2 per 1,000 patient years compared with 86.7 per 1,000 for non-CRPC (Morgan et al 2010).

Helgstrand and colleagues reported five-year mortality in men with newly diagnosed mPC. The 5-year overall mortality in the Danish Prostate Cancer Registry cohort after diagnosis of de-novo metastatic PCa was 78.5% (95% CI, 77.4%-79.5%). In the DaPCaR cohort, 5-year PCa-specific mortality significantly decreased from 73.4% (95% CI, 71.2%-75.6%) for patients who were diagnosed during 1995 through 1999 to 56.8% (95% CI, 54.8%-58.8%; p<.0001) for the patients diagnosed during 2005 and 2009 (Figure 28) (Helgstrand et al 2018).

Five-year PCa mortality was stable in the US for men diagnosed with de novo mPC from 1980-1994 and increased slightly for the 2005-2008 period; whereas, it decreased significantly by 16.6% (p<.0001) in the DaPCaR cohort from diagnosis period 1995-1999 to 2005-2009 (Helgstrand et al 2018)

The majority of men with localized PC died from other reasons (n=11,228, 23.9%) than PC (n=4058, 8.6%) during 1985-1994, while the majority of men with metastatic disease (48%) died from PC during the same period (Seikkula et al 2017)

Palliative radiation was the most common symptomatic skeletal event (83%), followed by spinal cord compression (10%), pathological fracture (6%), and surgery to bone (1%) with majority of the patients having ≥2 symptomatic skeletal-related events (Saad et al 2018).

Important co-morbidities:

In the UK, the retrospective cohort study by Hirst and colleagues used data from General Practice Research database to identify patients who were diagnosed with CRPC from July 1999 until June 2009. Prevalence of comorbidities was evaluated from any qualifying event in the 36 months pre-CRPC time frame and after CRPC. Hypertension (24.4% and 3.19 per 100 PY), dyspnea (19.9% and 7.75 per 100 PY), and anemia (11.2% and 7.66 per 100 PY) were most common comorbidities with higher prevalence and incidence rates before and after CRPC respectively. Cardiovascular events and diabetes were also relatively common, in line with expectations of an older male population; in this population almost 7% had pre-existing diabetes. The other most commonly reported comorbidities in this population are urinary complaints (hematuria, urinary tract infection, dysuria, retention of urine, and nocturia), digestive problems (constipation, diarrhea, abdominal pain, dyspepsia, nausea and vomiting), respiratory infections (cough and chest infection), back pain, leg pain, joint pain (hip, shoulder, and knee), chest pain, and cervicalgia (Hirst et al 2012).

In the United States, using Surveillance, Epidemiology, and End Results (SEER) database, of the 2,234 patients with CRPC diagnosed between 2000 to 2011, most of the patients had a history of other serious medical conditions on or before the cohort entry date. The most common

comorbidities (present in >20% of patients) were chronic pulmonary disease (42.4%), diabetes without chronic complications (41.2%), peripheral vascular disease (37.2%), cerebrovascular disease (30.5%), congestive heart failure (28.5%), mild liver disease (22.9%), and renal disease (21.8%) (Saltus et al 2019).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Single and repeat-dose toxicity: Single-dose GLP toxicity studies with unlabeled PSMA-617 and ^{175}Lu-PSMA-617 in rats and mini-pigs provided a systemic no-observed-adverse-effect-level (NOAEL) at the highest doses tested (4.0 mg/kg rat and 1.8 mg/kg mini-pig). These exposures provide a safety margin of between 150 and 400-fold relative to the potential maximum human dose (0.275 mg) in the average patient with a body surface area of 1.7 m^2. In the repeat-dose GLP toxicity study with unlabeled PSMA-617 in rats, the NOAEL was ≥400 µg, the highest dose tested. This provides a safety margin of approximately 15-fold relative to the potential maximum human dose (0.275 mg) in the average patient with a body surface area of 1.7 m^2.	Based on the current available non-clinical data, there is no concern relevant to human usage.
Reproductive/Developmental toxicity Fertility and embryo-fetal development studies have not been conducted with lutetium (^{177}Lu) vipivotide tetraxetan as they are not required as per ICH S9 guidance and the CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018).	Beta, and gamma radiation cause deoxyribonucleic acid damage and damage male and female germ cells and a developing fetus. The risks of potential of fetal harm and infertility are appropriately communicated in product labeling.
Carcinogenicity Carcinogenicity studies have not been conducted with lutetium (^{177}Lu) vipivotide tetraxetan as they are not required as per ICH S9 guidance and the CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018).	Beta, and gamma radiation cause deoxyribonucleic acid damage and are inherently carcinogenic. The risk of radiation being a carcinogen is appropriately communicated in product labeling.
Genotoxicity Genotoxicity/mutagenicity studies have not been conducted with lutetium (^{177}Lu) vipivotide tetraxetan as they are not required as per ICH S9 and the CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018). PSMA-617, the unlabeled precursor, was not mutagenic in the in vitro bacterial reverse mutation assay (AMES test). Genotoxicity/mutagenicity studies have not been conducted with lutetium (^{177}Lu) vipivotide tetraxetan as they are not required as per ICH S9.	Beta, and gamma radiation cause deoxyribonucleic acid damage and are inherently genotoxic. The risk of radiation being a mutagen is appropriately communicated in product labeling.
Safety Pharmacology:	

Cardiovascular findings Unlabeled PSMA-617 and ^{175}Lu-PSMA-617 were negative in the *in vitro* hERG and the in vivo cardiovascular safety pharmacology study in minipigs after single dose administration up to 1.0 mg/kg.	Based on the current available non-clinical data, there is no concern relevant to human usage.
Nervous system No effects of unlabeled PSMA-617 or ^{175}Lu-PSMA-617 on behavioural, neurologic or autonomic parameters in male Sprague Dawley (SD) rats after single-dose administration up to 1.8 mg/kg.	Based on the current available non-clinical data, there is no concern relevant to human usage.
Respiratory system No effects of unlabeled PSMA-617 or ^{175}Lu-PSMA-617 on respiratory parameters in male SD rats after single-dose administration up to 1.8 mg/kg.	Based on the current available non-clinical data, there is no concern relevant to human usage.
Drug-drug interactions	
In vitro assessments have been carried out with a test solution containing unlabeled PSMA-617 and ^{175}Lu-PSMA-617, in lieu of lutetium (^{177}Lu) vipivotide tetraxetan. **CYP450 enzymes** Lutetium (^{177}Lu) 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** Lutetium (^{177}Lu) vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, and OCT2, and it is not an inhibitor of BCRP, P-gp, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 in vitro.	Based on the results from the in vitro assessments, the low dose and infrequent administration of lutetium (^{177}Lu) vipivotide tetraxetan, and its passive renal clearance, lutetium (^{177}Lu) vipivotide tetraxetan is unlikely to be the cause or subject of a clinical drug-drug interaction.

Conclusions:

The nonclinical studies carried out on unlabeled PSMA-617 and ^{175}Lu-PSMA-617 (cold compound) did not identify any safety concerns. There are risks which are known to be inherent with radiation (lutetium (^{177}Lu) vipivotide tetraxetan) such as genotoxicity/mutagenicity, reproductive/developmental toxicity, and carcinogenicity.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Table 4-1 Duration of exposure (FAS Safety Analysis Set)

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC (N=529)	BSC/BSoC only (N=205)	Overall (N=734)
Duration of exposure (months)			
n	529	205	734
Mean	7.89	3.46	6.66
SD	4.302	3.878	4.634
Median	7.82	2.07	5.55
Min-Max	0.3-24.9	0.0-26.0	0.0-26.0
Number of cycles started by patient			
n	529	205	734
Mean	5.6	2.7	4.8
SD	3.00	2.16	3.09
Median	5.0	2.0	4.0
Min-Max	1-16	1-14	1-16
Average duration of treatment cycles (months)			
n	529	205	734
Mean	1.42	1.09	1.33
SD	0.242	0.342	0.311
Median	1.38	1.12	1.37
Min-Max	0.2-2.4	0.0-2.0	0.0-2.4

Cycle visits are scheduled every 6 weeks for the first 6 cycles and then every 12 weeks after cycle 6.
Data Cutoff Date: 27-Jan-2021
[Attachment to Annex 7 of RMP v 1.0. Table 7-1]

Table 4-2 Exposure by age group (FAS Safety Analysis Set)

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC		BSC/BSoC only		Overall	
	Age < 65 (N=142)	Age >= 65 (N=387)	Age < 65 (N=42)	Age >= 65 (N=163)	Age < 65 (N=184)	Age >= 65 (N=550)
Duration of exposure (months)						
n	142	387	42	163	184	550
Mean	7.99	7.86	2.77	3.64	6.80	6.61
SD	4.287	4.313	4.164	3.793	4.783	4.587
Median	7.87	7.75	1.87	2.17	5.62	5.55

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC		BSC/BSoC only		Overall	
	Age < 65 (N=142)	**Age >= 65 (N=387)**	**Age < 65 (N=42)**	**Age >= 65 (N=163)**	**Age < 65 (N=184)**	**Age >= 65 (N=550)**
Min-Max	0.3-22.3	0.4-24.9	0.0-26.0	0.1-21.0	0.0-26.0	0.1-24.9
Number of cycles started by patient						
n	142	387	42	163	184	550
Mean	5.8	5.6	2.3	2.8	5.0	4.7
SD	3.22	2.92	2.30	2.11	3.37	2.99
Median	5.0	5.0	2.0	2.0	4.0	4.0
Min-Max	1-16	1-14	1-14	1-11	1-16	1-14
Average duration of treatment cycles (months)						
n	142	387	42	163	184	550
Mean	1.42	1.42	1.00	1.12	1.32	1.33
SD	0.238	0.244	0.375	0.329	0.326	0.306
Median	1.38	1.38	0.99	1.15	1.38	1.37
Min-Max	0.3-2.0	0.2-2.4	0.0-1.9	0.1-2.0	0.0-2.0	0.1-2.4

A patient may be counted in more than one row for reason for delay of cycle.
Cycle visits are scheduled every 6 weeks for the first 6 cycles and then every 12 weeks after cycle 6.
Data Cutoff Date: 27-Jan-2021

[Attachment to Annex 7 of RMP v 1.0. Table 7-2]

Table 4-3 Exposure by Region (FAS Safety Analysis Set)

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC		BSC/BSoC only		Overall	
	North America (N=381)	**Europe[1] (N=148)**	**North America (N=144)**	**Europe[1] (N=61)**	**North America (N=525)**	**Europe[1] (N=209)**
Duration of exposure (months)						
n	381	148	144	61	525	209
Mean	7.95	7.74	3.62	3.10	6.77	6.38
SD	4.295	4.332	4.175	3.064	4.678	4.521
Median	7.79	7.85	2.02	2.10	5.75	5.32
Min-Max	0.3-24.9	0.6-19.8	0.0-26.0	0.1-16.6	0.0-26.0	0.1-19.8
Number of cycles started by patient						
n	381	148	144	61	525	209
Mean	5.6	5.6	2.8	2.5	4.9	4.7
SD	2.97	3.10	2.27	1.85	3.07	3.13
Median	5.0	5.0	2.0	2.0	4.0	4.0
Min-Max	1-16	1-14	1-14	1-9	1-16	1-14
Average duration of treatment cycles (months)						

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC		BSC/BSoC only		Overall	
	North America (N=381)	Europe[1] (N=148)	North America (N=144)	Europe[1] (N=61)	North America (N=525)	Europe[1] (N=209)
n	381	148	144	61	525	209
Mean	1.43	1.41	1.08	1.12	1.33	1.32
SD	0.248	0.228	0.359	0.297	0.321	0.283
Median	1.38	1.38	1.11	1.12	1.37	1.37
Min-Max	0.2-2.4	0.6-2.0	0.0-2.0	0.1-1.8	0.0-2.4	0.1-2.0

A patient may be counted in more than one row for reason for delay of cycle.
Cycle visits are scheduled every 6 weeks for the first 6 cycles and then every 12 weeks after cycle 6.
Data Cutoff Date: 27-Jan-2021

[Attachment to Annex 7 of RMP v 1.0. Table 7-4]

[1] Europe includes sites from Belgium, France, United Kingdom, Denmark, Sweden and Netherlands.

Table 4-4 Exposure by race (FAS Safety Analysis Set)

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC				BSC/BSoC only				Overall			
	White (N=465)	Black or African American (N=34)	Asian (N=9)	Other (N=2)	White (N=173)	Black or African American (N=19)	Asian (N=8)	Other (N=0)	White (N=638)	Black or African American (N=53)	Asian (N=17)	Other (N=2)
Duration of exposure (months)												
n	465	34	9	2	173	19	8	0	638	53	17	2
Mean	7.92	8.80	4.85	4.50	3.28	4.68	4.74		6.66	7.32	4.80	4.50
SD	4.267	4.152	2.681	0.511	3.601	5.311	6.132		4.585	4.967	4.477	0.511
Median	7.85	8.28	4.14	4.50	2.07	2.07	2.61		5.55	6.74	3.52	4.50
Min-Max	0.3-24.4	2.8-19.2	1.4-9.0	4.1-4.9	0.0-26.0	0.3-18.4	1.0-19.6		0.0-26.0	0.3-19.2	1.0-19.6	4.1-4.9
Number of cycles started by patient												
n	465	34	9	2	173	19	8	0	638	53	17	2
Mean	5.7	6.0	3.6	3.0	2.6	3.3	3.3		4.8	5.0	3.4	3.0
SD	3.03	2.66	2.13	0.00	2.06	2.75	2.92		3.12	2.98	2.45	0.00
Median	5.0	6.0	3.0	3.0	2.0	2.0	2.5		4.0	5.0	3.0	3.0
Min-Max	1-16	2-12	1-7	3-3	1-14	1-9	1-10		1-16	1-12	1-10	3-3
Average duration of treatment cycles (months)												
n	465	34	9	2	173	19	8	0	638	53	17	2
Mean	1.42	1.49	1.33	1.30	1.08	1.18	1.19		1.33	1.38	1.26	1.30

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC				BSC/BSoC only				Overall			
	White (N=465)	Black or African American (N=34)	Asian (N=9)	Other (N=2)	White (N=173)	Black or African American (N=19)	Asian (N=8)	Other (N=0)	White (N=638)	Black or African American (N=53)	Asian (N=17)	Other (N=2)
SD	0.244	0.217	0.084	0.108	0.343	0.374	0.296		0.314	0.316	0.217	0.108
Median	1.38	1.43	1.33	1.30	1.11	1.16	1.13		1.38	1.38	1.28	1.30
Min-Max	0.2-2.4	1.1-1.9	1.2-1.5	1.2-1.4	0.0-1.9	0.3-2.0	0.9-1.8		0.0-2.4	0.3-2.0	0.9-1.8	1.2-1.4

A patient may be counted in more than one row for reason for delay of cycle.
Cycle visits are scheduled every 6 weeks for the first 6 cycles and then every 12 weeks after cycle 6.
Data Cutoff Date: 27-Jan-2021
[Attachment to Annex 7 of RMP v 1.0. Table 7-3]

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Any radioligand treatment, or hemi-body irradiation within previous 6 months	Prevention of cumulative radiotoxicity, confounder for efficacy and safety	No	Other radioligand treatments are uncommon; hemi-body irradiation is becoming infrequent. These pre-treatments were excluded for efficacy reasons
Systemic anti-cancer therapy (including chemo-, immuno- and biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization	Prevention of cumulative toxicity, confounder for efficacy and safety	No	This one-month wash-out period is established and makes medical sense. It is not foreseen that physicians will want to shorten it in clinical practice.
Patients with a history of CNS metastases who have received prior therapy (surgery, radiotherapy, gamma knife)	Compromise of the blood-brain barrier, confounder for efficacy and safety	No	Patients with symptomatic central nervous system (CNS) metastases are not expected to have a different safety profile, and hence were excluded for efficacy reasons
Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression	Confounder for efficacy and safety	No	Patients with spinal cord compression are not expected to have a different safety profile, and hence were excluded for efficacy reasons
Patients with severe renal impairment (serum/plasma creatinine ≤ 1.5 times	Estimated extended time of lutetium (^{177}Lu) vipivotide tetraxetan of renal uptake and renal	Yes	Included as missing information

ULN or creatinine clearance ≥ 50 ml/min)	excretion, possible systemic effect of delayed excretion		
Patients with negative PSMA-expressing lesions receiving treatment in the absence of screening	In patients receiving lutetium (^{177}Lu) vipivotide tetraxetan treatment despite negative PSMA-expressing lesions (e.g. because of a false positive result of the gallium (^{68}Ga) gozetotide PET/CT scan) it is possible that the therapeutic benefit would be lower, though it also remains a possibility that the patient would still derive benefit due to small PSMA-expressing lesions that escape imaging resolution.	No	Literature evidence suggests that the use of lutetium (^{177}Lu) vipivotide tetraxetan is safe irrespective of PSMA status, and does not confer an added risk of harm in those who have negative lesions. One erroneously randomised patient in the VISION study who received 6 cycles of lutetium (^{177}Lu) vipivotide tetraxetan after a negative PSMA scan did not experience severe/serious AEs.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Treatment is intended to be administered to adult (often elderly) males with mPC. Therefore, as lutetium (^{177}Lu) vipivotide tetraxetan is not indicated in females, the safety and efficacy of lutetium (^{177}Lu) vipivotide tetraxetan in pregnant/breastfeeding women has not been assessed in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	• Patients with severe hepatic impairment were not included in the clinical development program. Limited exposure was observed in

	patients with mild and moderate hepatic impairment. • Limited number of subjects with mild and partly moderate renal impairment were exposed
Population with relevant different ethnic origin	Refer to Table 4-4 for additional details
Subpopulations carrying relevant genetic polymorphisms	Not prospectively identified in the clinical development program"

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

This section is not applicable as this drug is not yet marketed anywhere in the world.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

There is no abuse or recreational use potential for this product.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks not considered important for inclusion in the list of safety concerns

Risk	Reason for non-inclusion as an RMP safety concern
Hepatic safety	There are no pre-clinical or mechanistic data suggesting risk to the liver. Preclinical and clinical experience with lutetium (^{177}Lu) vipivotide tetraxetan showed that liver metabolism of the compound is negligible. Hepatotoxicity events in the pivotal VISION study were reported with similar incidence in both treatment arms, including high grade events (≥ grade 3 events in 2.8% of patients in the lutetium (^{177}Lu) vipivotide tetraxetan +BSoC arm and 2.4% in the BSoC-only arm). There were no cases suggestive of drug-induced liver injury. Therefore, there is no cause to further investigate this safety topic beyond routine pharmacovigilance or to implement risk minimization activities.
Patients with negative PSMA-expressing lesions receiving treatment in the absence of screening	In patients receiving lutetium (^{177}Lu) vipivotide tetraxetan treatment despite being PSMA-negative (e.g. because of a false positive result of the gallium (^{68}Ga) gozetotide PET/CT scan) it is possible that the therapeutic benefit would be lower, though it also remains a possibility that the patient would still derive benefit due to small PSMA-expressing lesions that escape imaging resolution. Clinical data indicate that the safety and tolerability of lutetium (^{177}Lu) vipivotide tetraxetan is favourable enough not to confer additional risk of harm from severe and irreversible effects should it be administered to patients who have negative PSMA-expressing lesions, especially as the radionuclide would not be bound in such cases and excreted promptly.
Salivary gland toxicity	Salivary glands have been shown as a site of PSMA uptake. Dry mouth is a very common AE as reported in the pivotal VISION study, but appears to be more of a tolerability/ inconvenience issue to patients with mostly mild events (majority grade 1, no grade ≥3) rather than a safety risk. Data do not suggest an increase in infections or other complications. Risk is adequately covered by routine labeling. Further data is not expected to change knowledge or actions that would impact patient safety.
Lacrimal glands	Lacrimal glands express PSMA receptors and are a site of PSMA uptake. Dry eye is a common AE as reported in the pivotal VISION study, but these events were mostly of mild severity (grade 1-2), reversible and there was no suggestion of enduring impact to patient safety.

	Risk is adequately covered by routine labeling. Further data is not expected to change knowledge or actions that would impact patient safety.
Gastrointestinal toxicity	Nausea, diarrhea, vomiting, constipation and decreased appetite / weight are very common AEs in the pivotal VISION study, but have not been shown to be of significant impact on patient safety. Risk is adequately covered by routine labeling. Further data not expected to change knowledge or actions that would impact patient safety.
Misuse and abuse	No addictive or misuse has been seen. This therapeutic product will only be administered by trained/qualified health-care professionals authorised to handle radiopharmaceuticals in designated clinical settings. Risk is adequately covered by routine labeling. Further data not expected to change knowledge or actions that would impact patient safety. The risk of misuse and abuse is therefore considered to be of little or no impact to the risk-benefit balance of the product and does not warrant further investigation or mitigation.
Long-term toxicity	The proposed indication is for late stage prostate cancer patients with a short life-expectancy. Long-term toxicity of lutetium (^{177}Lu) vipivotide tetraxetan can be considered to be beyond the horizon of relevance. Any long-term toxicity of the product, based on the mechanism of action and known risk profile is most likely to be related to renal toxicity and second primary malignancies. These are safety concerns in their own right with a category 3 study to further characterise them. Therefore, “long-term toxicity” as a separate risk is considered to be of little to no further impact to the benefit-risk balance of the product in the current indication and does not warrant further investigation or mitigation beyond routine pharmacovigilance.
Extravasation tissue damage	Extravasation is always possible with the administration of intravenous agents. There were two reports of infusion site extravasation in the lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC arm of the PSMA-617-01 study (0.4%): two grade 1 episodes in two patients with no report of clinical consequences. There are two literature reports of extravasation of lutetium (^{177}Lu) vipivotide in the forearm in which the events were managed without tissue damage. Extravasation can be managed by routine medical practice, and the risk is adequately covered by routine labeling. Further data is not expected to change knowledge or actions that would impact patient safety. Extravasation tissue damage is therefore considered to be of little to no impact to the benefit-risk balance of the product and does not warrant further investigation or mitigation.
Elderly patients	Target patients are often elderly and constitute a large part of the population studied (~75%). The safety profile and risks of lutetium (^{177}Lu) vipivotide tetraxetan have been evaluated including the elderly, and data do not show that this age group constitutes a risk, per se, or missing information whose collection would impact the benefit-risk balance.
Medication errors	Medication errors may include wrong dosing to the patient. The product is an intravenous administration of a single-dose vial by a healthcare professional in a specialist center. Current manufacturing foresees a radioactivity of 1000 MBq/ml at the date and time of production

	/calibration that will progressively diminish over time. The total amount of radioactivity per single-dose vial is 7400 MBq +/-10% at the date and time of administration. Inadvertent overdosing is unlikely. Administration by an HCP limits the likelihood of confusing products, under-dosing, wrong scheduling etc. Inadvertent exposure which may be considered a form of medication error is categorised separately as a potential risk. Medication errors are therefore considered not to be an important safety concern.
Reproductive toxicity	Lutetium (^{177}Lu) vipivotide tetraxetan is a genotoxic drug by virtue of its radioactivity. However, being used in prostate cancer, it will not be given to women. Furthermore, the male patients receiving the product are predominantly > 60 years old and have been subject to chemical or surgical castration. Routine risk minimisation measures addressing the use of condoms for sexually active patients are proposed in section 4.6 of the SmPC. Therefore, this risk is considered not important and does not require further characterisation or risk minimisation measures.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 8-1 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Myelosuppression	Acute disruption of the production of blood cells in the bone marrow as a toxic result of the administration of the product may have severe consequences for the patient, including severe infections, anemia and bleeding.
Renal toxicity	Kidneys are a primary site of PSMA uptake, and lutetium (^{177}Lu) vipivotide tetraxetan is rapidly excreted through the kidneys. Study documents recommend good hydration to promote drug wash-out. Acute kidney injury and increased serum/blood creatinine are common AEs in the pivotal VISION study. Given that the kidneys are exposed to PSMA, the long-term toxicity of repeated administrations of lutetium (^{177}Lu) vipivotide tetraxetan cannot be ruled out.

Table 8-2 Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Intracranial haemorrhage	It is not known that lutetium (^{177}Lu) vipivotide tetraxetan presents a direct risk to intracranial vessels or to brain integrity, though PSMA may be expressed in tumor vasculature. Intracranial haemorrhages are medically impactful in terms of symptoms and care required.
Inadvertent radiation exposure	Precautionary measures for HCPs, patients, care givers and their environment during and after RLT administration are included in

	national/local guidelines on radioprotection, though these can vary locally between countries and states. Occupational exposure of HCPs, due either to mishaps or during routine use, cannot be ruled out. While there is currently no data identifying occupational and inadvertent exposure as a risk, there is potential for this risk to impact the benefit-risk balance in real world use, due to its nature as an invisible risk factor to the healthy people in the patient's environment.
Second primary malignancies	Radiation tissue damage is known to predispose to the formation of malignancies. This would impact benefit-risk balance because of its potential for severe disease in the short term or long term.

Table 8-3 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Patients with severe renal impairment	Current data do not include patients with severe renal impairment. Only patients with adequate renal function, and also a limited number of patients with mild and partly moderate renal impairment were included in clinical trials so far (Serum creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min) Safety profile in severe renal impaired patients is expected to be different from general target population due to estimated extended time of lutetium (^{177}Lu) vipivotide tetraxetan of renal uptake and renal excretion. This could induce more severe renal damage and a possible systemic effect of delayed excretion and increase the risk of adverse drug reactions with existing co-treatments. Slower elimination of renally excreted drugs would be causing their accumulation to high plasma levels, potentially leading to toxicity or further exacerbating negative effects on the kidneys. Risk anticipated in severe renal impairment population include further deterioration and sudden drop of renal function, occurrence of acute kidney injury and/or hospital admissions and as consequence the need of renal transplant or renal replacement therapy.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

This is the first version of the RMP and therefore this section is not applicable.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Identified Risk: Myelosuppression

Table 8-4 Clinical trial data of Important Identified Risk: Myelosuppression

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC (N=529) n (%)	**BSC/BSoC only (N=205) n (%)**	**Overall (N=734) n (%)**
Number of subjects with at least one event	251 (47.4)	36 (17.6)	287 (39.1)
Maximum severity / grade			
• Grade 3 AEs	104 (19.7)	14 (6.8)	118 (16.1)
• Grade 4 AEs	17 (3.2)	0	17 (2.3)
• Grade 5 AEs	3 (0.6)	0	3 (0.4)
SAEs	27 (5.1)	1 (0.5)	28 (3.8)
AE outcome			
• Recovered/resolved	123 (23.3)	16 (7.8)	139 (18.9)
• Recovering/resolving	4 (0.8)	1 (0.5)	5 (0.7)
• Not recovered/not resolved	188 (35.5)	26 (12.7)	214 (29.2)
• Recovered/resolved with sequelae	3 (0.6)	0	3 (0.4)
• Fatal	3 (0.6)	0	3 (0.4)
• Unknown	3 (0.6)	0	3 (0.4)

A patient may be counted in several rows for action taken and outcome.
Numbers (n) represent counts of subjects.
MedDRA version 24.0, CTCAE version 5.0, Case Retrieval Strategy version 14-Jun-2021.
Source: [Attachment to Annex 7 of RMP v 1.0. Table T-7-6]
Data Cutoff Date: 27-Jan-2021

Table 8-5 Important identified risk - Myelosuppression: Other details

Name of the risk	**Details**
Potential mechanisms	Biodistribution of lutetium (^{177}Lu) vipivotide tetraxetan in pre-clinical models has shown activity in the blood in the hours following administration, consistent with the i.v. mode of administration. Pre-clinical evidence for myelosuppression is not significant, however, ionising radiation from ^{177}Lu may have a direct, brief effect on circulating blood cells in patients. Dosimetry studies show radiation absorption in the red marrow to varying degrees, with the highest in patients with extensive skeletal metastases

Name of the risk	Details
Evidence source(s) and strength of evidence	The clinical evidence is strong that treatment of patients with lutetium (^{177}Lu) vipivotide tetraxetan can cause reversible reductions in blood cell counts. Prostate cancer metastases preferentially to the bone, which may put the marrow at risk of the effects of radioactivity during the short time of exposure.
Characterization of the risk:	Myelosuppression-related events are very common in patients treated with lutetium (^{177}Lu) vipivotide tetraxetan. These events are also common in patients receiving best standard of care, though less so, suggesting that the patient population as a whole is prone to low and fluctuating blood counts due to the underlying malignancy, comorbidities and concomitant medications. • In the lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC treatment group a total of 251 (47.4%) patients had myelosuppression-related AEs, of which 27 (5.1%) patients had SAEs, and 3 of them were fatal. • In the BSC/BSoC only group, a total of 36 (17.6%) patient had myelosuppression-related AEs, of which one had a serious event, and no fatal AEs were reported.
Risk factors and risk groups	Patients may be at increased risk if they have: • Recent or concomitant exposure to anti-cancer drugs with myelosuppressive actions • Low pre-treatment blood cell counts for any reason • High tumor load, particular with bone metastases
Preventability	Risk of adverse effects of low blood cell counts may be reduced by delaying administration of lutetium (^{177}Lu) vipivotide tetraxetan when blood cell counts are low until a time when counts have recovered. Blood count monitoring after treatment can identify low blood counts and allow corrective measures to prevent clinical complications.
Impact on the benefit-risk balance of the product	Moderate
Public health impact	Low

8.3.1.2 Important Identified Risk: Renal toxicity

Table 8-6 Clinical trial data of Important Identified Risk: Renal toxicity

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC (N=529) n (%)	**BSC/BSoC only (N=205) n (%)**	**Overall (N=734) n (%)**
Number of subjects with at least one event	46 (8.7)	12 (5.9)	58 (7.9)
Maximum severity / grade			
• Grade 3 AEs	18 (3.4)	6 (2.9)	24 (3.3)

• Grade 4 AEs	0	0	0
• Grade 5 AEs	0	0	0
SAEs	9 (1.7)	7 (3.4)	16 (2.2)
AE outcome			
• Recovered/resolved	29 (5.5)	8 (3.9)	37 (5.0)
• Recovering/resolving	1 (0.2)	1 (0.5)	2 (0.3)
• Not recovered/not resolved	18 (3.4)	3 (1.5)	21 (2.9)
• Recovered/resolved with sequelae	0	0	0
• Fatal	0	0	0
• Unknown	1 (0.2)	1 (0.5)	2 (0.3)

A patient may be counted in several rows for action taken and outcome.
Numbers (n) represent counts of subjects.
MedDRA version 24.0, CTCAE version 5.0, Case Retrieval Strategy version 14-Jun-2021.
Source: [Attachment to Annex 7 of RMP v 1.0. Table T-7-6]
Data Cutoff Date: 27-Jan-2021

Table 8-7 Important Identified risk - Renal toxicity: Other details

Renal toxicity	Details
Potential mechanisms	Kidney is the primary route of lutetium (^{177}Lu) vipivotide tetraxetan excretion and a PSMA-expressing tissue. Renal toxicities in this frail, elderly patient population can be expected as a consequence of prior anti-cancer treatments and the advanced, metastatic disease state.
Evidence source(s) and strength of evidence	Nephrotoxicity (i.e. serious acute kidney injury) was reported in literature, as well in company sponsored clinical trials.
Characterization of the risk:	Data from VISION show that about 5-10% experienced renal AEs during treatment in either arm. Patients receiving lutetium (^{177}Lu) vipivotide tetraxetan were more likely to have renal events overall, though there appeared no difference in the likelihood to experience serious or high grade events. No grade 4 or 5 events were reported in VISION. • In the lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC treatment group a total of 46 (8.7%) subjects had at least one event of renal toxicity, of which 9 (1.7%) patients reported SAEs, of which none of them were fatal. • In the BSC/BSoC only group, 12 (5.9%) subjects had at least one event of renal toxicity, of which of which 7 (3.4%) patients reported were SAEs, of which none of them were fatal.
Risk factors and risk groups	Pre-existing and concomitant conditions: kidney function impairment, urinary tract disorders, previous or concomitant nephrotoxic treatments Physiological changes associated with aging: diminished renal mass, reduction in renal blood flow, loss of nephron function
Preventability	As per the SmPC, patients are encouraged to remain hydrated, increasing oral fluids and urinating as often as possible.

Renal toxicity	Details
Impact on the benefit-risk balance of the product	The impact on the benefit-risk balance of the product is considered moderate
Public health impact	The public health impact is low to moderate (50% pts with solid tumors have abnormal renal function)

8.3.1.3 Important Potential Risk: Intracranial hemorrhage

Table 8-8 Clinical trial data of Important Potential Risk: Intracranial hemorrhage

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC (N=529) n (%)	BSC/BSoC only (N=205) n (%)	Overall (N=734) n (%)
Number of subjects with at least one event	7 (1.3)	3 (1.5)	10 (1.4)
Maximum severity / grade			
• Grade 3 AEs	3 (0.6)	1 (0.5)	4 (0.5)
• Grade 4 AEs	0	0	0
• Grade 5 AEs	2 (0.4)	1 (0.5)	3 (0.4)
SAEs	7 (1.3)	2 (1.0)	9 (1.2)
AE outcome			
• Recovered/resolved	2 (0.4)	1 (0.5)	3 (0.4)
• Recovering/resolving	0	0	0
• Not recovered/not resolved	3 (0.6)	1 (0.5)	4 (0.5)
• Recovered/resolved with sequelae	0	0	0
• Fatal	2 (0.4)	1 (0.5)	3 (0.4)
• Unknown	0	0	0

A patient may be counted in several rows for action taken and outcome.
Numbers (n) represent counts of subjects.
MedDRA version 24.0, CTCAE version 5.0, Case Retrieval Strategy version 14-Jun-2021.
Source: [Attachment to Annex 7 of RMP v 1.0. Table T-7-6]
Data Cutoff Date: 27-Jan-2021

Table 8-9 Important Potential risk - Intracranial hemorrhage: Other details

Intracranial hemorrhage	Details
Potential mechanisms	It is not currently known if lutetium (^{177}Lu) vipivotide tetraxetan presents a direct risk to intracranial vessels or to brain integrity. PSMA is a unique membrane bound glycoprotein which is overexpressed manifold on prostate cancer as well as neovasculature of most of the solid tumors, but not in the vasculature of the normal tissues (Ghosh and Heston 2004).

Intracranial hemorrhage	Details
	Thrombocytopenia may contribute to the risk indirectly by reducing the patient's inherent clotting ability.
Evidence source(s) and strength of evidence	Some events of intracranial hemorrhage occurred in the pivotal VISION clinical trial, but also in the comparator group, and no conclusive association with lutetium (^{177}Lu) vipivotide tetraxetan was made.
Characterization of the risk:	• In the lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC treatment group a total of 7 (1.3%) subjects reported at least one event of intracranial hemorrhage. Two subjects (0.4%) had fatal outcomes (intracranial hemorrhage, subdural hematoma) • In the BSC/BSoC only group, 3 subjects (1.5%) reported at least one event of intracranial hemorrhage, of which one patient (0.5%) had a fatal outcome (subdural hematoma).
Risk factors and risk groups	• Underlying: vascular disease; concomitant blood thinners • Concomitant risks/events: thrombocytopenia; anemia; weakness leading to fall • Presence of brain metastases may increase the risk.
Preventability	None
Impact on the benefit-risk balance of the product	Moderate
Public health impact	Low

8.3.1.4 Important Potential Risk: Inadvertent radiation exposure

No events corresponding to inadvertent radiation exposure were reported as of the data cut-off for this submission [Attachment to Annex 7 of RMP v 1.0. Table T-7-6]

Table 8-10 Important Potential risk - Inadvertent radiation exposure

Medication errors	Details
Potential mechanisms	Any deviation in institutional good radiation safety practices may lead to exposure to ionising radiation in patients, medical personnel, and household contacts during and after treatment with lutetium (^{177}Lu) vipivotide tetraxetan.
Evidence source(s) and strength of evidence	Theoretical risk, currently low strength of evidence
Characterization of the risk:	Currently there are no events informing the character of this risk. No AEs were reported in the VISION study.
Risk factors and risk groups	The administration of lutetium (^{177}Lu) vipivotide tetraxetan may result in significant hazard to people close to the patient (caregivers, family members, etc.). This may be of concern to the immediate family of those patients undergoing treatment or the general public depending on the level of radioactivity administered.
Preventability	Radiation exposure should be minimized to patients, medical personnel, and household contacts during and after treatment with lutetium (^{177}Lu) vipivotide tetraxetan consistent with institutional good radiation safety

Medication errors	Details
	practices, patient management procedures, and instructions to the patient for follow-up radiation protection at home.
Impact on the benefit-risk balance of the product	Moderate
Public health impact	Low

8.3.1.5 Important Potential Risk: Second primary malignancies

Table 8-11 Clinical trial data of Important Potential Risk: Second primary malignancies

	Lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC (N=529) n (%)	BSC/BSoC only (N=205) n (%)	Overall (N=734) n (%)
Number of subjects with at least one event	11 (2.1)	2 (1.0)	13 (1.8)
Maximum <severity / grade>			
• Grade 3 AEs	3 (0.6)	1 (0.5)	4 (0.5)
• Grade 4 AEs	0	0	0
• Grade 5 AEs	1 (0.2)	0	1 (0.1)
SAEs	3 (0.6)	0	3 (0.4)
AE outcome			
• Recovered/resolved	4 (0.8)	2 (1.0)	6 (0.8)
• Recovering/resolving	0	0	0
• Not recovered/not resolved	4 (0.8)	0	4 (0.5)
• Recovered/resolved with sequelae	1 (0.2)	0	1 (0.1)
• Fatal	1 (0.2)	0	1 (0.1)
• Unknown	1 (0.2)	0	1 (0.1)

A patient may be counted in several rows for action taken and outcome.
Numbers (n) represent counts of subjects.
MedDRA version 23.1, CTCAE version 5.0, Case Retrieval Strategy version 03-Nov-2020.
Source: [Attachment to Annex 7 of RMP v 1.0. Table T-7-6]
Data Cutoff Date: 27-Jan-2021

Table 8-12 Important potential risk - Second primary malignancies: Other details

Second primary malignancies	Details
Potential mechanisms	Treatment of cancer with conventional radiotherapy may contribute to second primary malignancies. Radiation-induced second

Second primary malignancies	Details
	malignancies (RISM) is one of the important late adverse effects of conventional radiation therapy. Radiation damage to blood precursor cells may potentially cause later malignant transformation.
Evidence source(s) and strength of evidence	Reports of second primary malignancies were reported from VISION (as of 27-Jan-2021), and are discussed below Additional evidence from literature suggests that around 17%–19% of patients who survive a primary malignancy, ultimately develop a second primary malignancy. At present radiotherapy contributes to only about 5% of the total treatment-related second primary malignancies.
Characterization of the risk:	• In the lutetium (^{177}Lu) vipivotide tetraxetan +BSC/BSoC treatment group a total of 11 (2.1%) subjects reported at least one event. One event of CNS metastases had a fatal outcome. • In the BSC/BSoC only group, 2 (1.0%) subjects with AEs were reported. The reported malignancies were metastases and skin malignancies (melanoma and squamous cell carcinoma). There were no TEAEs of hematological malignancies, the relatively short time to onset seen in this trial does not suggest causal relationship.
Risk factors and risk groups	The risk of developing a second malignancy may increase with exposure to chemotherapy, other radiotherapeutic modalities, with age and family history of cancer.
Preventability	As per the SmPC, patients are encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation.
Impact on the benefit-risk balance of the product	Low to Moderate
Public health impact	Low

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-13 Missing information: Patients with severe renal impairment

Patients with severe renal impairment	Details
Evidence source	Current data do not include patients with severe renal impairment. Only patients with adequate renal function were included in clinical trials (Serum creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min). Preclinical work, dosimetry studies, and clinical experience with lutetium (^{177}Lu) vipivotide tetraxetan confirmed the kidney expresses PSMA and are highly exposed to radiation. **Anticipated risk/consequence of the missing information:** Risks anticipated in the severe renal impairment population include further deterioration and sudden drop of renal function, occurrence of acute kidney injury and/or hospital admissions and as consequence the need of renal transplant or renal replacement therapy.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	• Myelosuppression • Renal toxicity
Important potential risks	• Intracranial hemorrhage • Inadvertent radiation exposure • Second primary malignancies
Missing information	• Patients with severe renal impairment

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists will be used to collect further data to help characterize and/or closely monitor the respective risks. The following adverse event follow-up checklist is used to collect additional data for lutetium (^{177}Lu) vipivotide tetraxetan.

Intracranial hemorrhage:

This checklist is provided in Annex 4 of the RMP

Other forms of routine pharmacovigilance activities for risks

None.

10.2 Part III.2. Additional pharmacovigilance activities

PSMA-617-01 (VISION): An international, prospective, open-label, multicenter, randomized phase 3 study of lutetium (^{177}Lu) vipivotide tetraxetan in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

Rationale and study objectives:

An extension of this pivotal phase 3 study is planned to conduct long-term follow-up for a 12-month period in subjects still alive and consented for follow up in this study. This long-term follow-up period will include the collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be seen or contacted by a clinician every 3 months (±1 month) via phone, in person or via telemedicine visit, email or letter for up to 12 months, until death or until withdrawal of consent, whichever occurs first.

Study design:

This is a Phase III, open-label, international, randomized study to evaluate the efficacy and safety of lutetium (^{177}Lu) vipivotide tetraxetan in patients with progressive PSMA-positive mCRPC, when administered in addition to BSC/BSoC as compared to BSC/BSoC alone and is a Category 3 study commitment.

Study population:

Patients with progressive mCRPC, who had received at least one NAAD and who were previously treated with at least one, but no more than 2 prior taxane-based chemotherapy regimens.

Milestones:

Final CSR: 31-Mar-2025

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PSMA-617-01 (VISION) (Ongoing) An international, prospective, open-label, multicenter, randomized phase 3 study of lutetium (^{177}Lu) vipivotide tetraxetan in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) Category 3	The extended 12-month long-term follow-up period will include the collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of hematology and chemistry testing.	Renal toxicity Second primary malignancies	Final CSR	31-Mar-2025

11 Part IV: Plans for post-authorization efficacy studies

None.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern:	Routine risk minimization activities
Myelosuppression	**Routine risk communication** Sections 4.2, 4.4, 4.8 of SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk**: Monitoring of hematology (hemoglobin, white blood cell count, absolute neutrophil count, platelet count) by laboratory tests before and during treatment. Specific dosage modification instructions are provided for management of anemia, leukopenia, neutropenia, thrombocytopenia, and other hematological toxicity. **Other routine risk minimization measures beyond the Product Information**: None
Renal toxicity	**Routine risk communication** Sections 4.2, 4.4, 4.8 of SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk**: As per the SmPC, kidney function laboratory tests, including serum creatinine and calculated creatinine clearance, should be performed. Pluvicto should be withheld, dose reduced, or permanently discontinued based on the severity of renal toxicity. Patients should also be encouraged to remain hydrated. **Other routine risk minimization measures beyond the Product Information**: None
Intracranial hemorrhage	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**:

	None
Inadvertent radiation exposure	**Routine risk communication** Sections 4.2, 4.4, 4.9, 6.6 of SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Institutional guidelines will stipulate routine practice for radiation protection.
Second primary malignancies	**Routine risk communication** Section 4.8 of SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None
Patients with severe renal impairment	**Routine risk communication** Sections 4.2, 5.2 of SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None

12.2 Part V.2. Additional Risk minimization measures

Additional Risk minimization measures: Patient guide

Objective: The objective of this educational program is to minimize the important potential risk of inadvertent radiation exposure while on lutetium (^{177}Lu) vipivotide tetraxetan therapy for PSMA- positive mCRPC. Additional guidance/measures, after treatment for the management of inadvertent radiation exposure are included in the patient guide.

Rationale for the additional risk minimization activity: Although inadvertent radiation exposure is mentioned in the Package Leaflet (PL) and clear instructions are provided in the PL, a patient guide has been developed to increase the awareness of the patient.

Target audience and planned distribution path:

- **Target audience**: Patients treated with lutetium (^{177}Lu) vipivotide tetraxetan

- **Planned distribution path**: A patient guide will be prepared nationally in line with the key safety messages defined in the RMP and with each EU member state's national regulations and legislations. The patient guide will be distributed to institutions where lutetium (^{177}Lu) vipivotide tetraxetan is expected to be administered in patients. The treating physician is expected to provide the patient guide to all patients receiving treatment with lutetium (^{177}Lu) vipivotide tetraxetan.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the proposed risk minimization measure will be assessed by monitoring in the PSUR the reported frequency of the important potential risk of inadvertent radiation exposure.

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Myelosuppression	**Routine risk minimization measures:** Sections 4.2, 4,4, 4.8 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Renal toxicity	**Routine risk minimization measures:** Sections 4.2, 4.4, 4.8 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** **Additional pharmacovigilance activities**: PSMA-617-01 (VISION)
Intracranial hemorrhage	**Routine risk minimization measures:** **None**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist **Additional pharmacovigilance activities:** None
Inadvertent radiation exposure	**Routine risk minimization measures:** Sections 4.2, 4.4, 4.9, 6.6 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Patient guide

Second primary malignancies	**Routine risk minimization measures**: Section 4.8 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities**: PSMA-617-01 (VISION)
Patients with severe renal impairment	**Routine risk minimization measures:** Sections 4.2, 5.2 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

13 Part VI: Summary of the risk management plan for Pluvicto (lutetium (^{177}Lu) vipivotide tetraxetan)

This is a summary of the risk management plan (RMP) for Pluvicto. The RMP details important risks of Pluvicto, how these risks can be minimized, and how more information will be obtained about Pluvicto's risks and uncertainties (missing information).

Pluvicto's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Pluvicto should be used.

This summary of the RMP for Pluvicto should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Pluvicto's RMP.

13.1 Part VI: I. The medicine and what it is used for

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.

Pluvicto 1000 MBq/ml is a solution for injection/infusion. One ml of solution contains 1000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.

Further information about the evaluation of Pluvicto's benefits can be found in Pluvicto's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Pluvicto, together with measures to minimize such risks and the proposed studies for learning more about Pluvicto's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Pluvicto is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Pluvicto are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pluvicto. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Myelosuppression • Renal toxicity
Important potential risks	• Intracranial hemorrhage • Inadvertent radiation exposure • Second primary malignancies
Missing information	• Patients with severe renal impairment

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 Important identified risk - Myelosuppression

Evidence for linking the risk to the medicine	The clinical evidence is strong that treatment of patients with lutetium (^{177}Lu) vipivotide tetraxetan can cause reversible reductions in blood cell counts. Prostate cancer metastases preferentially to the bone, which may put the marrow at risk of the effects of radioactivity during the short time of exposure.
Risk factors and risk groups	Patients may be at increased risk if they have: • Recent or concomitant exposure to anti-cancer drugs with myelosuppressive actions • Low pre-treatment blood counts for any reason • High tumor load, particular with bone metastases
Risk minimization measures	**Routine risk minimization measures** Sections 4.2, 4.4, 4.8 of SmPC **Additional risk minimization measures** None

Table 13-3 Important identified risk - Renal toxicity

Evidence for linking the risk to the medicine	Kidneys are a primary site of PSMA uptake, and lutetium (177Lu) vipivotide tetraxetan is rapidly excreted through the kidneys. Nephrotoxicity (i.e., serious acute kidney injury) was reported in company sponsored clinical trials. Given that the kidneys are exposed to PSMA, long-term toxicity of repeated administrations of lutetium (^{177}Lu) vipivotide tetraxetan cannot be ruled out.
Risk factors and risk groups	Pre-existing and concomitant conditions: kidney function impairment, urinary track disorders, previous or concomitant nephrotoxic treatments Physiological changes associated with aging: diminished renal mass, reduction in renal blood flow, loss of nephron function
Risk minimization measures	**Routine risk minimization measures** Sections 4.2, 4.4, 4.8 of SmPC **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PSMA-617-01 (VISION): An international, prospective, open-label, multicenter, randomized phase 3 study of lutetium (^{177}Lu) vipivotide tetraxetan in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

Table 13-4 Important potential risk - Intracranial hemorrhage

Evidence for linking the risk to the medicine	It is not known that lutetium (^{177}Lu) vipivotide tetraxetan presents a direct risk to intracranial vessels or to brain integrity, though PSMA may be expressed in tumour vasculature.

	Intracranial haemorrhages are medically impactful in terms of symptoms and care required.
Risk factors and risk groups	• Underlying: vascular disease; concomitant blood thinners • Concomitant risks/events: thrombocytopenia; anemia; weakness leading to fall • Presence of brain metastases may increase the risk.
Risk minimization measures	**Routine risk minimization measures** None **Additional risk minimization measures** None

Table 13-5 Important potential risk - Inadvertent radiation exposure

Evidence for linking the risk to the medicine	Theoretical risk, currently low strength of evidence
Risk factors and risk groups	No particular risk groups for patients. Close contact between patient and caregivers in the hours and days following product administration may increase the risk of inadvertent radiation exposure from directly from the patient's body or from excretions.
Risk minimization measures	**Routine risk minimization measures** Sections 4.2, 4.4, 4.9, 6.6 of SmPC **Additional risk minimization measures** Patient guide.

Table 13-6 Important potential risk - Second primary malignancies

Evidence for linking the risk to the medicine	Data from a published randomized clinical trial showed that after surviving from a primary malignancy, 17%–19% patients develop second malignancy. Radiotherapy contributes to only about 5% of the total treatment related second malignancies.
Risk factors and risk groups	Aged patients, individual and family history of cancer
Risk minimization measures	**Routine risk minimization measures** Section 4.8 of SmPC **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PSMA-617-01 (VISION): An international, prospective, open-label, multicenter, randomized phase 3 study of lutetium (^{177}Lu) vipivotide tetraxetan in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

Table 13-7 Important Missing information - Patients with severe renal impairment

Risk minimization measures	**Routine risk minimization measures** Sections 4.2, 5.2 of SmPC **Additional risk minimization measures** None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Pluvicto.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-8 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
PSMA-617-01 (VISION): An international, prospective, open-label, multicenter, randomized phase 3 study of lutetium (^{177}Lu) vipivotide tetraxetan in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) Category 3	Rationale: An extension of this pivotal phase 3 study is planned to conduct long-term follow-up for a 12-month period in subjects still alive and consented for follow up in this study. Objective: This long-term follow-up period will include the collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be seen or contacted by a clinician every 3 months (±1 month) via phone, in person or via telemedicine visit, email or letter for up to 12 months, until death or until withdrawal of consent, whichever occurs first.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Safety concern 1: Intracranial haemorrhage

A generic checklist for cerebral haemorrhage is being used as a Specific adverse drug reaction follow-up form for this safety concern

Name of checklist 1 (Version 3.0, Jun-2017)

Targeted Follow-up Checklist
Cerebral Hemorrhage

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide detailed information regarding the following:

- History of the event(s)_____
- Location of hemorrhage (e.g. specify if subdural hematoma; if cerebral hemorrhage, state location:_____
- Diagnostic procedures_____
- Interventions *(i.e., surgical drainage)*_____
- Treatments_____
- Outcome of the event(s)_____
- Did the patient have any residual neurological deficits? *(If yes, please specify)*_____

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Did the patient have any of the following current or past medical conditions? **Check all that apply and specify date(s)**

☐**Injuries or previous operations** *(e.g., head trauma/skull fractures, previous brain surgery/craniotomy, splenectomy, and fall)*
☐**Central nervous system** *(e.g., cerebral hemorrhage / intracranial hemorrhage, cerebrovascular accident (stroke), cerebral aneurysms, seizure disorder, brain tumors, arteriovenous malformations (AVM), syncope)*
☐**Cardiovascular / metabolic disorders** *(e.g., hypertension, diabetes mellitus)*
☐ **Renal disorders** *(e.g., renal disease, history of polycystic kidney disease)*
Hematological / bleeding conditions
☐ Family history of bleeding disorders *(e.g., von Willebrand disease and hemophilia)*
☐ History of platelet disorders *(e.g., thrombocytopenia, idiopathic thrombocytopenic purpura)*
☐ Clotting factor deficiency
☐ Sickle cell anemia / sickle cell trait
☐ Disseminated intravascular coagulation
☐ History of gastrointestinal bleeding, hemoptysis, hematuria, or epistaxis
Social history
☐ Alcohol use *(please specify: mild, moderate, or heavy)*
☐Tobacco use *(please specify number of pack years)*

Concomitant medications

Did the patient take any of the following concomitant medications within the last 12 months *(please provide date, route, dose, duration, and indication)*?

☐ **Anticoagulants** (coumadin, heparin, other)
☐ **Prostacyclins**
☐ **Acetylsalicylic acid** (aspirin)
☐ **Non-steroidal anti-inflammatory agents** (NSAIDs)
☐ **Antibiotics**
☐ **Herbal medications** *(e.g., gingko biloba, ginseng, alfalfa, angelica, aniseed, asafoetida, boldo, buchu, capsicum, cassia, celery, chamomille, clove, dong quai, echinacea, evening primrose oil, fenugreek, fever few, ginger, panax, goldenseal, horse chestnut, horseradish, kava, licorice, meadowsweet, passion flower, prickly ash, poplar, quassia, red clover, white willow, and willow bark)*
☐ **Chemotherapy agents**
☐ **Recreational / illicit drug usage**

Laboratory / Diagnostic studies:

Were any of the following laboratory and/or diagnostic tests performed? **Check all that apply**

►If **yes**, please specify which test(s) and include reference range and pre- and post- treatment values and dates:

Laboratory studies:

☐ Complete blood count (CBC) with differential	☐ Serum creatinine	☐ Bleeding time
☐ Platelet count	☐ Platelet function analyzer	☐ Vitamin K level
☐ Glucose	☐ Platelet aggregometry	☐ Sedimentation rate
☐ Blood urea nitrogen	☐ Hemoglobin electrophoresis	☐ Creatinine clearance
☐ Liver function tests	☐ Prothrombin time (PT)	☐ Urinalysis
☐ Partial thromboplastin time (PTT)	☐ Iinternational normalized ratio (INR)	☐ C-reactive protein
☐ Electrolytes	☐ Lipid levels	☐ Anti-nuclear antibodies

Diagnostic studies:

☐ CT-scan	☐ Ultrasound	☐ Angiography
☐ Neurological examination with 24 hours of event	☐ Magnetic resonance imaging	☐ EEG
☐ Echocardiogram	☐ Cardiac catheterization	☐ None of the above

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Additional risk minimization measures

Prior to the 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 (MS) where Pluvicto is marketed, patients have access to the patient guide.

The Pluvicto patient guide will contain 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