Regulatory Affairs

Pluvicto® / Pluvicto® CA

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Lutetium (^{177}Lu) vipivotide tetraxetan*
Product(s) concerned (brand name(s)):	*Pluvicto / Pluvicto CA*
Document status:	*Final*
Version number of the RMP Public Summary:	*1.2*
Date of final sign off of the RMP Public Summary:	*11-Oct-2022*

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Pluvicto/-CA” is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Pluvicto/-CA” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Advanced Accelerator Applications International SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Pluvicto/-CA”.

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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.

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 castrationresistant 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.

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.

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 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

II B: Summary of important risks

Table 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 3 Important identified risk - Renal toxicity

Evidence for linking the risk to the medicine	Kidneys are a primary site of PSMA uptake, and lutetium (^{177}Lu) 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 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 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 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 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

II C: Post-authorization development plan

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.*

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

Table 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.