Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for Lumark. The RMP details important risks of Lumark.

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

This summary of RMP for Lumark 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 EPAR.

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

I The Medicine and what it is used for

Lumark is a radiolabelling precursor and as no direct indication. Once link to the appropriate ligand/carrier, Lumark can be used in several oncologic indications depending on the carrier to which Lumark is linked.

Further information about the evaluation of Lumark's benefits can be found in Lumark's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/lumark#product-information-section.

II Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 minimise its risks.

Together, these measures constitute routine risk minimisation 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.

II.A List of important risks and missing information

Important risks of Lumark are risks that need special risk management activities to further investigate or minimise 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 Lumark. 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);

List of important risks and missing information	
Important identified risks	- Radiotoxicity including occupational exposure and inadvertent exposure - Developmental Toxicity including reproductive toxicity - Myelosuppression - Myelodysplastic syndrome/Acute myeloid leukaemia
Important potential risks	- Medication Errors associated with preparation and procedures - Osteosarcoma - Radiation nephropathy - Hepatotoxicity
Missing information	None

II.B Summary of important risks

Important identified risk: Radiotoxicity, including occupational exposure and inadvertent exposure	
Evidence for linking the risk to the medicine	No data available
Risk factors and risk groups	Health Professionals, patients, patients' relative
Risk minimisation measures	**Sections in SmPC** **4.4 Special warnings and precautions for use** In this section of the SmPC General warnings and Radiation protection information are provided. In summary, Lutetium(^{177}Lu)-labelled medicinal product should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements and their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official authorities. Administration of a high activity (7.400 MBq) of the Lutetium(^{177}Lu)-labelled medicinal product results in an average radiation dose rate at 1 m distance from the patient of 4-11 µSv/h after 24 hours. This is below the threshold considered acceptable for discharge from the clinic (20 µSv/h). For a person in the vicinity of the patient, assuming continuous exposure at 2 m and infinite biological half-life (no disposal by the patient after discharge from the hospital), this dose rate will result in an overall dose of approximately 0.6 mSv, which is approximately one half of the dose limit set for general public (1 mSv/year). **6.6 Special precautions for disposal and other handling** Within this section additional general warning are provided including instruction to: - Not use product when the integrity of the container is compromised - Put in place administration procedures with the aim to minimise the risk of contamination - Follow local requirements for unused product or waste material **12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** Within this section of the SmPC, it is recommended to measure activity using an ionisation chamber under geometric conditions which have been appropriately validated. Usual precautions regarding sterility (throughout the labelling procedures) and radioactivity should be respected. The vial should never be opened and must be kept inside its lead shielding. The product should be aseptically withdrawn through the stopper using sterilized single use needle and syringe after disinfection of the stopper.

Important identified risk: Developmental Toxicity including reproductive toxicity	
Evidence for linking the risk to the medicine	No data available
Risk factors and risk groups	Childbearing age patients and breast-feeding patients.
Risk minimisation measures	Sections in SmPC: **4.3 Contraindications** - Pregnancy (see section 4.6). **4.6 Fertility, pregnancy and lactation** Women of childbearing potential […] Before the use of ^{177}Lu -labelled medicinal products, pregnancy should be excluded using an adequate/validated test. Pregnancy: The use of ^{177}Lu -labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3). Breast-feeding: […] If the administration is considered necessary, breastfeeding should be interrupted and the expressed feeds discarded. Fertility: According to literature reports and taking a conservative approach (maximum patient dose of 10 GBq, average labeling yield and no additional measures), it may be considered that ^{177}Lu-labelled medicinal products do not lead to reproductive toxicity including spermatogenetic damage in male testes or genetic damage in male testes or female ovaries. Further information concerning the use of 177Lu-labelled medicinal products is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

Important identified risk: Myelosuppression / cytopenias (immediate hematotoxicity)	
Evidence for linking the risk to the medicine	Scientific literature dealing with safety of ^{177}Lu radiolabelled compound
Risk factors and risk groups	***<u>LU-DOTATATE literature data</u>*** Identified risk factors of myelosuppression/cytopenias after PRRT: Baseline (pre-existent) cytopenias; Baseline renal dysfunction (eGFR ≤ 60 ml/min) Uncertain risk factors of myelosuppression / cytopenias after PRRT (positive correlation detected in most studies, but none in others): Age > 70 years at PRRT onset; Previous chemotherapy; Presence of bone metastases Identified co-dependent associative factor of myelosuppression / cytopenias after PRRT: Higher whole-body 177Lu-DOTA-TATE residence time Uncertain co-dependent associative factor of myelosuppression / cytopenias after PRRT: A cumulative injected activity of > 29.6 GBq emerged as a statistically significant co-dependent associative factor and the correlation between myelosuppression and cumulative activity had also been reported. ***<u>LU-PSMA PRLT literature data</u>*** Pre-PRLT baseline myelosuppression; Injected activity; Prior radiotherapy or chemotherapy treatment; Pre-treatment bone marrow involvement by PrCa metastases.
Risk minimisation measures	Sections in SmPC: **4.4 Special warnings and precautions for use** Within this section of the SmPC it is instructed to perform blood count test at baseline and then monitored regularly blood count during treatment. **4.8 Undesirable effects** Under the SOC Blood and lymphatic system disorders Very common: Anaemia, thrombocytopenia, leukopenia and lymphopenia
Additional pharmacovigilance activities	Review of data coming from Post-Authorization Safety registry and NETTER-1 long term.

Important identifed risk: Myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)	
Evidence for linking the risk to the medicine	Scientific literature dealing with safety of ^{177}Lu radiolabelled compound.
Risk factors and risk groups	Identified risk factors of MDS: Prior acute leukemia Identified co-dependent associative factors of MDS development: Higher thrombocytopenia CTCAE grade; Longer duration of PRRT Uncertain risk factors of MDS development (positive correlation in some analyses, none in others): Thrombocytopenia > CTCAE grade 1.
Risk minimisation measures	Sections in SmPC: **4.4 Special warnings and precautions for use** Within this section of the SmPC information a warning in regard to these reactions occurrence had been added. **4.8 Undesirable effects** Under the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps): common: Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) uncommon : Acute myeloid leukaemia
Additional pharmacovigilance activities	Review of data coming from Post-Authorization Safety registry and NETTER-1 long term Completion of the “Myelodysplastic syndrome/Acute Myeloid Leukaemia safety questionnaire follow up form” for all ICSRs reported to the company.

Important potential risk: Medication Errors associated with preparation and procedures	
Evidence for linking the risk to the medicine	Not Applicable
Risk factors and risk groups	Healthcare Professionals and patients
Risk minimisation measures	Sections in SmPC: **4.1 Therapeutic indications** Lumark is a radiopharmaceutical precursor. It is not intended for direct use in patients. This medicinal product must be used only for the radiolabelling of carrier molecules, which have been specifically developed for radiolabelling with this radionuclide. **4.2 Posology and method of administration** Lumark is only to be used by specialists experienced with *in vitro* radiolabelling. … Method of administration Lumark is intended for *in vitro* radiolabelling of medicinal products, which are subsequently administered by the approved route. Lumark should not be administered directly to the patient. For instructions on extemporary preparation of the medicinal product before administration, see section 12. **4.4 Special warnings and precautions for use** … Individual benefit/risk justification Lumark is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates. … Specific warnings … Radioactive medicinal products should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. **6.2 Incompatibilities** Radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates, with Lutetium (177Lu) chloride is very sensitive to the presence of trace metal impurities. It is important that all glassware, syringe needles etc, used for the preparation of the radiolabelled medicinal product are thoroughly cleaned to ensure freedom from such trace metal impurities. Only syringe needles (for example nonmetallic) with proven resistance to dilute acid should be used to minimize trace metal impurity levels. In the absence of compatibility studies, this medicinal product must not be mixed with medicinal products other than the medicinal products to be radiolabelled. **6.6 Special precautions for disposal and other handling** Lumark is not intended for direct use in patients. … Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. For instruction on extemporary preparation of the medicinal product before administration, see section 12. **12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** Appropriate aseptic precautions should be taken, in order to maintain the sterility of Lumark and to maintain sterility throughout the labelling procedures. The complexing agent and other reagents should be added to the vial with ^{177}LuCl3. Free ^{177}LuCl3 is taken up and accumulates in the bones. This could potentially result in osteosarcomas. It is recommended to add a binding agent such as DTPA prior to intravenous administration of ^{177}Lu-labeled conjugates in order to form a complex with free ^{177}Lu, if present, leading to a rapid renal clearance of ^{177}Lu.

Important potential risk: Osteosarcoma	
Evidence for linking the risk to the medicine	Not Available
Risk factors and risk groups	Not Available
Risk minimisation measures	Section in SmPC: **12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** Free ^{177}LuCl3 is taken up and accumulates in the bones. This could potentially result in osteosarcomas. It is recommended to add a binding agent such as DTPA prior to intravenous administration of ^{177}Lu -labeled conjugates in order to form a complex with free ^{177}Lu, if present, leading to a rapid renal clearance of ^{177}Lu.
Additional pharmacovigilance activities	Review of data coming from Post-Authorization Safety registry and NETTER-1 long term.

Important potential risk: Renal dysfunction (radiation nephropathy, chronic kidney disease, minor renal function deterioration, etc.)	
Evidence for linking the risk to the medicine	Scientific literature dealing with safety of ^{177}Lu radiolabelled compound.
Risk factors and risk groups	Identified risk factors of kidney injury following ^{177}Lu radiolabeled compound therapy: Hypertension; Older age (> 60 yrs); Diabetes mellitus; Renal morphological abnormalities; Low baseline GFR; Previous nephrotoxic chemotherapy or trans-arterial chemoembolization; Male gender.
Risk minimisation measures	Section in SmPC: **4.4 Special warnings and precautions for use** Within this section of the SmPC it is mentioned that - Renal function should be assessed at baseline and during treatment - Renal protection should be considered, in accordance with clinical guidance.
Additional pharmacovigilance activities	Review of data coming from Post-Authorization Safety registry and NETTER-1 long term Completion of the “Radiation Nephropathy safety questionnaire follow up form” for all ICSRs reported to the company.

Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Scientific literature dealing with safety of ^{177}Lu radiolabelled compound.
Risk factors and risk groups	The presence of liver metastases transpires as the sole risk factor.
Risk minimisation measures	Section in SmPC: **4.4 Special warnings and precautions for use** Within this section of the SmPC it is mentioned that: - Liver function should be monitored regularly during treatment - Dose reduction may be necessary in affected patients.
Additional pharmacovigilance activities	Review of data coming from Post-Authorization Safety registry and NETTER-1 long term Completion of the "Hepatotoxicity questionnaire follow up form" for all ICSRs reported to the company.

II.C Post Authorisation development plan

II.C.1 Studies wich are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lumark.

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

There are no studies required for Lumark.