EU RISK MANAGEMENT PLAN FOR ILUMIRA 37 GBQ/ML RADIOPHARMACEUTICAL PRECURSOR, SOLUTION

RMP version to be assessed as part of this application:

RMP Version number: 0.3

Data lock point for this RMP: 31 May 2024

Date of final sign off: 05 August 2025

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission

Summary of significant changes in this RMP: Not applicable.

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Abbreviations

AML	Acute Myeloid Leukemia
ART	Activity Reference Time
ATC	Anatomical Therapeutic Chemical
DTPA	Diethylenetriamine Pentaacetate
EEA	European Economic Area
EPAR	European Public Assessment Report
EBRT	External Beam Radiation Therapy
EU	European Union
GBq	Gigabecquerels
GFR	Glomerular filtration rate
GVP	Good Pharmacovigilance Practices
INN	International Nonproprietary Name
IRCP	International Commission on Radiological Protection
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic Syndrome
NET	Neuroendocrine Tumour
PL	Package Leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Pharmacovigilance Qualified Person
RLT	Radioligand Therapy
RMP	Risk Management Plan
SmPC	Summary of Products Characteristics
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Lutetium (^{177}Lu) chloride
Pharmacotherapeutic group(s) (ATC Code)	V10X
Marketing Authorisation Applicant	SHINE Europe B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ilumira
Marketing authorisation procedure	Centralised procedure
Brief description of the product	*Chemical class* Radiopharmaceutical precursor. Lutetium belongs to the group of lanthanides and is a rare earth metal.
	Summary of mode of action Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor for *in vitro* labelling of appropriate carrier molecules that have been specifically developed for radiolabelling with lutetium (^{177}Lu) chloride to produce Radioligand Therapy drug product. Upon administration, the radiolabelled molecule binds with the specific target expressed on the tumoral cells, while lutetium (^{177}Lu) emits cytotoxic β radiation inducing tumoral cell death.
	Important information about its composition Lutetium (^{177}Lu) chloride is produced by neutron irradiation of enriched Ytterbium (^{176}Yb).
Hyperlink to the Product Information	See product information in Module 1.3.1.
Indication(s) in the EEA	Current: Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.

	Proposed: Not applicable
Dosage in the EEA	Current: The quantity of Lutetium (^{177}Lu) chloride required for radiolabelling and the quantity of lutetium (^{177}Lu)-labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Radiopharmaceutical precursor, solution. 1 mL solution contains 37 GBq ^{177}Lu chloride at calibration time(CAL) corresponding to maximum 9 micrograms of lutetium (177Lu) (as chloride). Each 2 mL vial contains a volume varying from 0.05 mL to 1.3 mL corresponding to an activity ranging from 1.8 to 48.1 GBq at CAL. Each 10 mL vial contains a volume varying from 0.05 mL to 6.6 mL corresponding to an activity ranging from 1.8 to 244.2 GBq at CAL.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Ilumira is intended to be authorized as 'well established medicinal use product' according to Article 10a of Directive 2001/83/EC, as amended. Following Module V – Risk management systems, rev 2 (EMA/838713/2011 Rev 2*) of the current Guideline on Good Pharmacovigilance Practices (GVPs), modules Part II SI-SVI can be omitted for products under Article 10a of Directive 2001/83/EC.

Part II: Module SI - Epidemiology of the indication(s) and target population

Based on the GVP Module V – Risk management system this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10a of Directive 2001/83/EC, as amended.

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

Based on the GVP Module V – Risk management system this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10a of Directive 2001/83/EC, as amended.

Part II: Module SIII - Clinical trial exposure

Based on the GVP Module V – Risk management system this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10a of Directive 2001/83/EC, as amended.

Part II: Module SIV - Populations not studied in clinical trials

Based on the GVP Module V – Risk management system this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10a of Directive 2001/83/EC, as amended.

Part II: Module SV - Post-Authorisation Experience

Based on the GVP Module V – Risk management system this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10a of Directive 2001/83/EC, as amended.

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

Based on the GVP Module V – Risk management system this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10a of Directive 2001/83/EC, as amended.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Lutetium chloride ($LuCl_3$) has been used clinically for more than a decade, so its safety profile is recognized and well established. Lutetium (^{177}Lu) chloride is to be used only for radiolabelling of carrier molecules that have been specifically developed and authorised for therapeutic purposes, and not intended for direct use in patients. Therefore, the specific safety profile of Lutetium (^{177}Lu)-labelled radiopharmaceutical will depend on the carrier molecule that is labelled.

An additional aspect to consider when identifying safety concerns is the impact of the invented name on the safety profile of the medicinal product. This assessment has been conducted according to the criteria specified in the *Guideline on the acceptability of names for human medicinal products processed through the centralised procedure* (EMA/CHMP/287710/2014 – Rev. 6, 2014).

For this purpose, the intended name (Ilumira) has been compared against the Article 57 Public product data (EMA/518502/2018, 2024) to detect any similarity in the name with another already authorised medicinal product that could lead to confusion in print, speech or handwriting with the invented name of another medicinal product. A potential similarity was identified with an already authorised product identified in the Article 57 Public product data, Humira®. However, this similarity that may exist between products does not significantly affect the safety profile of Ilumira.

Ilumira is a radiopharmaceutical precursor for *in vitro* labelling of appropriate carrier molecules, so it is not indicated for direct use in patients. This product can only be ordered and received by licensed radiopharmacies or nuclear medicine departments with specialised training and equipment. It is supplied in a vial within a lead container in a protected, radioactive-labelled box, and it must be conjugated with components or radiolabelled with carrier molecules prior to administration. Any administration must be carried out by a professional with specialized training in a licensed facility after such conjugation or radiolabelling.

Humira® (adalimumab), on the other hand, is a recombinant human monoclonal antibody indicated for the treatment of various conditions such as plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, ulcerative colitis etc. (Humira® - Product Information EMA, 2024). Humira® is placed on the market as a pre-packaged "pen" that can be prescribed by most health care professionals, obtained in most pharmacies, and administered by patient self-injection.

In addition to the indicated above, the following aspects of the guideline were also considered in order to assess the impact on the safety profile of the intended medicinal product:

- The invented name of Ilumira does not include the full invented name of another medicinal product.
- The invented name does not convey misleading therapeutic connotations.
- The invented name does not convey a promotional message.
- The invented name is not misleading with respect to the pharmaceutical connotations such as the qualitative or quantitative composition, the pharmaceutical form or the route of administration.
- The invented name does not contain common umbrella segment (e.g. part of the name of the sponsor) that can create a link which may lead to confusion and medication errors with other medicinal products.

Therefore, no additional risks associated with the invented name have been identified. As mentioned above, the likelihood of name-related medication error is very low due to the distinctive features of each product.

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 with minimal clinical impact on patients (in relation to the severity of the indication treated):
    - Dry mouth
    - Nausea
    - Vomiting
    - Alopecia
- Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
    - Carcinoid crisis
    - Tumour lysis syndrome
- Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):
    - Developmental toxicity including reproductive toxicity
    - Hypersensitivity
    - Extravasation

- Hormone release syndromes

➢ Other reasons for considering the risks not important:

- Name-related medication error with Humira®.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risk: Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient

The radioactive isotope ^{177}Lu emits β particles with a peak energy of 497 keV and 6.65 days half-life (161 h) (Dash et al., 2015). Exposure to ionizing radiation has the potential to cause cancer and genetic mutations (Khazaei Monfared et al., 2023). Therefore, concurrent release of low-energy gamma rays can be considered as a point of concern regarding the exposure for third parties who may come into close contact with patients treated with ^{177}Lu-labelled radiopharmaceuticals.

Risk-Benefit impact: Despite of the seriousness of the consequences, the impact on the risk-benefit balance is deemed to be low if appropriate measures are in place.

Exposure levels for workers in the field of nuclear medicine and for the relatives of patients who have received ^{177}Lu-labelled molecules as part of targeted radiotherapy treatments for tumours have been assessed in different studies (Bakker *et al.*, 2006; Sghedoni *et al.*, 2011; Calais *et al.*, 2014; Abuqbeitah *et al.*, 2018; Sulieman *et al.*, 2020; Riveira-Martin *et al.*, 2023). Overall, the radiation levels experienced by staff during the preparation of radiopharmaceuticals, by medical personnel during treatment sessions, and by the general public have been deemed acceptable and within the guidelines set by the International Commission on Radiological Protection (IRCP).

Guidelines for managing radiotherapy, which include patient discharge regulations, have been established and must be adhered to rigorously to minimize unnecessary radiation exposure (Commission et al., 2015). Moreover, to ensure proper and safe handling of the proposed medicinal product, instructions for preparation of the radiopharmaceutical are provided in section 12 of the proposed SmPC. Therefore, occupational exposure to radiotoxicity is not considered to constitute a safety concern as radiopharmaceuticals are administered in a highly controlled environment.

However, the main concern regarding the risk of radiation primarily relates to inadvertent exposure, particularly for individuals who are unaware they are being exposed. Although the risk of hazard exposure has been considered as low, the relationship between ionizing radiation and severe adverse reactions like mutations and cancer has been reported. Therefore, this risk will be explicitly stated in section 4.4 of the SmPC. However, with appropriate measures in place to reduce the radiation exposure, the risk-benefit balance of the product is acceptable within the therapeutic context.

Important identified risk: Decrease blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)

Myelosuppression, commonly known as bone marrow suppression, is a decline in the activity of the bone marrow, leading to a decrease in the production of blood cells. Severe myelosuppression, also known as myeloablation, can be life-threatening. Clinical signs of

myelosuppression manifest as reduced blood cell counts, including anemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, and pancytopenia. Pancytopenia is particularly dangerous as it can result in a deficiency of oxygen and compromise the immune system.

Various studies indicate that myelosuppression is a possible side effect of radioligand therapy with ^{177}Lu. Haematological toxicity, including anaemia, leukopenia, and thrombocytopenia, with varying grades have been observed across different studies with various ^{177}Lu-labelled molecules, such as ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC or ^{177}Lu-PSMA-617 (Bodei *et al.*, 2011; Horsch *et al.*, 2016; Khreish *et al.*, 2022; Sundlov *et al.*, 2022; Zidan *et al.*, 2022; Patell *et al.*, 2023)

Haematological disorders have also been noted after administration of ^{177}Lu-PSMA-targeted treatments for metastatic Castrate-Resistant Prostate Cancer (mCRPC) (Groener *et al.*, 2021). The link between radioligand therapy and hematotoxicity is biologically plausible, given the established myelosuppressive properties of radiation.

Risk-Benefit impact: While cases are usually mild and temporary, severe hematotoxicity has been reported, sometimes leading to treatment discontinuation and/or requiring blood and platelet transfusions. It has also been reported that multiple cell lines may be impacted simultaneously in certain patients, leading to pancytopenia, which has sometimes resulted in the discontinuation of treatment. However, with appropriate measures in place to monitor and reduce the risk of hematotoxicity and radiation exposure, the risk-benefit balance of the product is acceptable within the therapeutic context.

Important identified risk: Myelodysplastic syndrome/Acute myeloid leukaemia

Several haematological malignancies, particularly myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), have been documented in association with the use of Lutetium (^{177}Lu) as reported in clinical trials and medical literature (Sabet *et al.*, 2013; Brieau *et al.*, 2016; Vallathol *et al.*, 2020; Almeamar *et al.*, 2022), including fatal cases. While some studies involved patients who had undergone previous chemotherapy treatments and were largely uncontrolled, other studies reported these conditions in patients without any prior chemotherapy. These findings underscore the serious nature of the risk, although the probability of occurrence is low.

Risk-Benefit impact: Clinical research and literature have documented various blood-related cancers, particularly MDS and AML, in relation to the administration of Lutetium (^{177}Lu)-labelled molecules. MDS and AML post-RLT, although serious, appears to be rare.

Important potential risk: Radiation-induced nephropathy

The kidneys are commonly the organs at risk for radiation toxicity, stemming from both non-specific and specific uptake of radiolabelled peptides as well as their renal elimination. The primary cause of renal irradiation is the reabsorption of these peptides in the proximal tubules, which can lead to nephrotoxicity that limits the dose of radiopharmaceutical that can be safely administered (Parihar et al., 2022). Cases of radiation-induced kidney damage, known as radiation-induced nephropathy, have been documented after RLT for neuroendocrine tumours using various radioisotopes (Parihar et al., 2022). However, in a retrospective study in 6 patients with only one functioning kidney undergoing 3 to 5 cycles of treatment with ^{177}Lu-DOTATATE RLT (receiving a total administered activity ranging from 16.6 to 36.2 GBq) none of the patients experienced acute renal toxicity. In terms of chronic renal toxicity, three patients exhibited no toxicity, one had grade II toxicity, and two had grade I toxicity. All patients who showed signs of chronic renal toxicity had pre-existing compromised renal function at the start of the study. The study concluded that with appropriate renal protection

and dose fractionation, 3 to 5 cycles of ^{177}Lu-DOTATATE RLT could be safely administered to patients with NETs who have a single functioning kidney (Ranade *et al.*, 2016).

Risk-Benefit impact: This condition represents a serious adverse reaction, potentially leading to significant disability or incapacity if not managed appropriately. The risk of radiation-induced nephropathy in patients treated with ^{177}Lu-labelled molecules is considered significant due to its possible severe impact on kidney function. However, despite of there is scientific evidence to suspect the possibility of a causal relationship between kidney damage and radiation of ^{177}Lu, the study data does not show a clear relationship between the exposure and the adverse event. As safety precaution, the SmPC recommends close monitoring of renal function before and during the treatment, and intervention to manage any potential kidney issues arising from the treatment. Additionally, renal protection in line with clinical recommendations should be implemented.

Important potential risk: Osteosarcoma

Inferences drawn from animal studies to humans indicate that in the event of an accidental injection of the precursor lutetium (^{177}Lu) chloride, the greatest uptake is likely to occur in osteogenic cells (Müller *et al.*, 1978). The identified potential risk of osteosarcoma development exists due to the uptake and accumulation of ^{177}Lu in bone tissue.

Clinical incidences of osteosarcoma developed after accidental injection of non-labelled lutetium (^{177}Lu) are not known, and the probability of its occurrence is very low.

Non-clinical studies conducted in rats has shown predominant absorption of ^{177}Lu at osteogenic cells, the liver, spleen, red marrow, and kidneys. The long-term effect of intraperitoneal administration of lutetium oxide in NMRI female mice showed an increased rate of osteosarcoma formation after a 12-month exposure period to ^{177}Lu (Müller *et al.*, 1978). Furthermore, studies in mice have demonstrated an increased incidence of osteosarcomas, particularly in long bones and vertebrae, with a significant proportion of subjects exhibiting hematological death shortly after treatment with high doses of stable lutetium (Müller *et al.*, 1980).

Risk-Benefit impact: Osteosarcoma is a life-threatening condition with a high impact on a patient's quality of life. The development of osteosarcoma has been observed only in preclinical studies. The product is a radiopharmaceutical precursor not meant for direct administration to patients but intended for use only in authorized and qualified facilities. As a safety precaution, the SmPC of the product recommends incorporation of a chelating agent like DTPA in the formulation of ^{177}Lu-labelled conjugates to bind any free ^{177}Lu that may exist to minimize the risk of radiotoxicity due to free ^{177}Lu ions, facilitating its rapid elimination through the kidneys.

Important potential risk : Radiation-induced hepatotoxicity

In patients with extensive liver metastases and impaired liver function, there is a possibility of serious liver toxicity. Cases of hepatotoxicity have been documented in patients with liver metastases who are receiving ^{177}Lu-RLT treatments for NETs, as observed in post-marketing surveillance and various medical publications (Kendi *et al.*, 2019; Duan *et al.*, 2022). Additional accounts of hepatotoxicity have emerged from multiple prospective single-arm studies reported in scientific literature, particularly in the context of ^{177}Lu-RLT therapy. Clinical practice guidelines suggest that individuals with liver metastases are at a higher risk for developing hepatotoxicity when undergoing RLT. These guidelines also recommend routine liver function assessments prior to each RLT treatment cycle.

Risk-Benefit impact: Therefore, to manage the risk, appropriate warnings have been included in the SmPC of the product. Regular monitoring of liver function during the course of treatment of patients at risk is advised. For patients experiencing liver function issues, a dose adjustment may be required.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is the first version of RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and potential identified risks

Important identified risk: Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient

Potential mechanisms: The adverse effects associated with exposure to radioactivity, such as carcinogenicity, mutagenicity, and tissue-damaging outcomes, are due to the ionizing radiation emitted during the decay of ^{177}Lu, which can accumulate in various tissues. This includes the release of beta and low-energy gamma rays, potentially causing breaks in DNA strands and subsequent cellular death (Khazaei Monfared et al., 2023).

Evidence source(s) and strength of evidence: Published studies and the SmPC of the product detail that lutetium (^{177}Lu) emits ionizing radiation that can affect not only the patient but also his healthcare providers, care givers or other people remaining in close proximity to the patient for a prolonged period of time. The risk associated with radiation exposure is influenced by the physical distance from the patient who has undergone radionuclide therapy during the first days following the product administration (Sulieman *et al.*, 2020).

Regarding to occupational exposure, as radiopharmaceuticals are administered by highly qualified professionals in a clinical setting in a highly controlled environment, occupational exposure to radiotoxicity is not considered to constitute a safety concern. In a study on the radiation exposure to personnel involved in various stages of ^{177}Lu-DOTATATE therapy, including the labelling process, quality assurance, dose administration, and imaging procedures found that treating 25 patients annually with ^{177}Lu-DOTATATE would result in an increased radiation dose of 1.66 mSv to staff members. Since the responsibilities are spread across multiple disciplines, this additional dose would be distributed among more than 10 individuals. Consequently, the radiation exposure for each person would remain below the standard occupational limits for hospital staff, which, in many countries, is equivalent to the public exposure limit of 1 mSv per year (Hoving et al., 2016).

Characterisation of the risk: No frequency is known; however, the external dose rate decreases significantly in a short period—with, on average, only 10% of the radiopharmaceutical remaining in the patient 24 hours post-administration—the risk to third parties must be carefully managed. Consequently, the cumulative exposure resulting from repeated treatment cycles heightens the risk for cohabitants and members of the public who are in frequent or prolonged close contact with the patient (Sulieman *et al.*, 2020).

Different studies have assessed the exposure received by third parties. In a study conducted by Calais *et al*., in 2014, it was reported that the mean total exposure to 25 caregivers during the day of therapy and over a period of up to 5 days at home was 90 μSv, with a median exposure of 40 μSv and a range of 10–470 μSv, highlighting varying patient-caregiver behaviours and differences in the retained activity levels in patients (Calais *et al.*, 2014). Furthermore, Sulieman *et al*., measured the radiation exposure at different distances, the reported mean dose-rates (in μSv/h) was 82.0 at 0.3 m, 16.2 at 1 m and 1.1 at 3 m from the patients Although dose rate decreases with distance, the same authors emphasize the need for appropriate radiation protection measures to ensure that doses to family members and the public do not exceed the 1.0 mSv annual limit (Sulieman *et al.*, 2020).

Therefore, the potential for cumulative radiation exposure to uninformed individuals to exceed the recommended public dose limit is considered a significant identified risk.

Risk factors and risk groups: Persons in close proximity to the treated patient.

Preventability: To inform anyone in close proximity to the treated patient about ways to minimize their exposure to radiation from the patient, like increasing the distance with the patient.

Impact on the risk-benefit balance of the product: Considering that the dose rate decreases significantly in a short period (less than 10% of the radiopharmaceutical remaining in the patient 24 hours post-administration), the doses measured in carers in close contact in a cycle generally are 10 times lower than the public exposure limit and that the physicians provide adequate information to patients to aware any other person in close vicinity, the impact on the risk-benefit balance is deemed to be low.

Public health impact: The impact on public health is considered low due to the existence of well-established safety protocols and the extensive experience of healthcare professionals in the field of nuclear medicine.

Healthcare professionals are responsible for instructing patients on the necessary radioprotection measures prior to discharge. The ICRP indicate some instructions to safely manage the unintended exposure to radiopharmaceuticals, including specific recommendations to limit the time and distance of contact with other people, especially with vulnerable groups such as children and pregnant women, ensuring that cumulative exposure to cohabitants and the general public is kept below the established dose limits (ICRP, 2007). Proper adherence to these mitigation guidelines effectively reduces risk, resulting in minimal public health impact.

Important identified risk: Decrease blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)

Potential mechanisms:

The major determinant of radiation exposure of the haematopoietic stem cells is radiopharmaceutical circulation within the bone marrow. However, specific targeting mechanisms to more differentiated blood cell progenitors may also contribute.

RLT with ^{177}Lu-labelled molecules can lead to myelosuppression due to bone marrow irradiation, although typically this condition is mild and temporary. Radioligand therapy with these molecules is known for causing DNA-strand breaks within white blood cells, potentially leading to significant decreases in white blood cell count (Eberlein et al., 2015; Schumann et al., 2019; O'Neill et al., 2020; Salas-Ramirez et al., 2023). These DNA-strand breaks lead to

cell mortality, which in turn can cause a significant decrease in the white blood cell count, potentially dropping to levels well beneath the normal range. Additionally, the overexpression of SSRs on activated leukocyte subtypes, such as lymphocytes and monocytes, in the case of ^{177}Lu-DOTATATE, may result in higher radiation exposure to these cells (Sjogreen Gleisner *et al.*, 2022).

Evidence source(s) and strength of evidence: Published studies indicate that myelosuppression is a possible side effect of radioligand therapy with Lutetium (^{177}Lu)-labelled molecules. Haematological toxicity, including anaemia, leukopenia, and thrombocytopenia, with varying grades have been observed across different studies with various ^{177}Lu-labelled molecules, such as ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC or ^{177}Lu-PSMA-617 (Bodei *et al.*, 2011; Horsch *et al.*, 2016; Khreish *et al.*, 2022; Sundlov *et al.*, 2022; Zidan *et al.*, 2022; Patell *et al.*, 2023)

Characterisation of the risk: Generally, the haematological toxicity is commonly reported due to the radiation of the bone marrow after the treatment with ^{177}Lu-labelled molecules. In a retrospective study enrolling patients with NENs treated with 7.4 GBq/dose of 177Lu-DOTATATE, the 29.8% of the patients reported haematological toxicity (Mitjavila *et al.*, 2023). In a prospective, real-world evidence, long-term study, aimed at assessing the outcomes and toxicities of targeted radionuclide therapies in patients with advanced prostate cancer in clinical practice showed that, of the 254 patients treated with 177Lu-PSMA-617, 18–20% reported thrombocytopenia or lymphopenia (Khreish *et al.*, 2022).

On the other hand, although less frequent, severe cases of haematological toxicity have been reported after the treatment with ^{177}Lu-labelled molecules. Khreish *et al.*, reported even lower frequencies of grade 3-4 thrombocytopenia (4.3%) and lymphopenia (2.8%) cases (Khreish *et al.*, 2022).In the retrospective study by Mitjavila et. al., among the 522 subjects with different NETs treated with ^{177}Lu-DOTATATE, grade 5 haematological toxicities were also identified, including two cases of pancytopenia, as well one case of leukemia and two cases of myelodysplastic syndrome (MSD) (Mitjavila *et al.*, 2023).

Therefore, a reduction in blood cell count, including conditions such as anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, and pancytopenia, is often described after the treatment with ^{177}Lu-labelled molecules. Generally, these cases are mild, being resolved on its own in numerous instances. However, a few proportion of patients undergoing treatment with ^{177}Lu-labelled molecules have experienced severe hematotoxicity, reaching Grade 3/4 severity, leading to treatment discontinuation and/or requiring blood and platelet transfusions.

Risk factors and risk groups: Patients at higher risk for myelosuppression include those who have undergone prior chemotherapy treatments, as well as individuals presenting with anaemia (Bodei *et al.*, 2015). Baseline renal impairment, and patients aged over 70 years have also been considered as risk factors for developing myelosuppression.

Preventability: While the risk cannot be entirely prevented, it is crucial for healthcare professionals to be aware of the risk and to monitor for initial signs of myelosuppression, including conducting a blood counts at baseline and during treatment, in accordance with clinical guidance.

Impact on the risk-benefit balance of the product: While the risk of decrease blood count is not negligible, the potential clinical benefits for patients with specific cancer types, combined with the measures in place to monitor and reduce the risk of hematotoxicity, indicated that the impact on the risk-benefit balance of the product is acceptable within the therapeutic context.

Public health impact: Myelosuppression is typically mild, but severe hematotoxicity has been observed in a subset of patients receiving ^{177}Lu-DOTATATE therapy . Therefore, the public health impact is considered medium.

Important identified risk: Myelodysplastic syndrome/Acute myeloid leukaemia

Potential mechanisms: Clinical research indicates that using alkylating agents in conjunction with RLT significantly increases the risk of developing MDS and AML (Brieau et al., 2016). These occurrences are thought to result from either mutations triggered by cytotoxic treatments or the emergence of a myeloid clone that exhibits a mutator phenotype, which is highly susceptible to mutations.

Evidence source(s) and strength of evidence: Published literature, clinical studies and post-marketing experience document cases where MDS and AML have occurred following the administration of Lutetium (^{177}Lu)-labelled molecules in the treatment of neuroendocrine tumours. The occurrence of these conditions has been consistently reported across various studies, reinforcing the strength of evidence. Clinical research and literature have documented various blood-related cancers, particularly MDS and AML, in relation to the administration of ^{177}Lu-labelled molecules (Sabet *et al.*, 2013; Kesavan *et al.*, 2014; Brieau *et al.*, 2016; Mitjavila *et al.*, 2023). .

Characterisation of the risk: The induction of secondary malignancies by radiation is a complex process that originates as a result of single or double strand breaks in the DNA and involves errors in the repair mechanisms leading to genetic mutations, with loss of function or oncogene activation (Bodei *et al.*, 2015). Clinical research and medical publications have noted various haematological malignancies, particularly MDS and AML, in association with the utilization of Lutetium (^{177} Lu)-labelled agents. Sabet *et al.*, reported 3 cases of MDS (1.4%) which were reported 14, 29, and 34 months after the treatment with 7.9 GBq of 177Lu-octreotate (4 courses at standard intervals of 3 months), and one patient developed AML 36 months after the last cycle (Sabet *et al.*, 2013). In a long-term follow up (5 years) of 65 patients treated with 4 cycles of 7.8 GBq ^{177}Lu-octreotate, 1,650 mg/m^2 capecitabine (n = 28) and 1,500 mg/m^2 capecitabine with 200 mg/m^2 temozolomide (n = 37), Kesavan et al., reported 2 cases of MSD, which corresponds to the 3% of the included patients, and none of them developed leukemia (Kesavan *et al.*, 2014). On the other hand, Mitjavila *et al.*, reported one case of leukemia and two cases of MSD among the 522 subjects with different NETs treated with ^{177}Lu-DOTATATE included in the cases series review (Mitjavila *et al.*, 2023). In another study that prospectively enrolled 807 patients who received RLT with 177Lu (34.4%), 90Y (44.4%), both (19.2%) or combinations of RLT and other agents (2%), at a median follow-up of 30 months, MSD occurred in 2.35 % of patients and acute leukemias in 1.1 % of patients, which included 3 cases of AML (Bodei *et al.*, 2015). These findings underscore the serious nature of the risk, although the probability of occurrence is low.

Risk factors and risk groups: Patients previously treated with chemotherapy, especially with alkylating agents, are at increased risk (Brieau *et al.*, 2016). Other risk factors include advanced age, compromised kidney function, low baseline blood cell counts and a history of multiple treatments (Kesavan et al., 2016).

Preventability: The risk cannot be completely prevented but can be mitigated considering the patient's prior chemotherapy treatments before RLT. It is recommended to avoid alkylating agents in patients with low-grade neuroendocrine tumours who are expected to live longer and have a substantial chance of benefiting from RLT, as these agents could jeopardize the safety

and future viability of this more effective treatment. It is essential to conduct consistent and extended monitoring of blood counts, particularly for patients who exhibit early signs of haematological toxicity following RLT.

Impact on the risk-benefit balance of the product: The risk of developing MDS and AML post-RLT, although serious, is relatively rare. The impact of this risk in the risk-benefit balance provided that there is careful patient selection and monitoring is acceptable.

Public health impact: Given the low incidence MDS/AML, but the serious consequences of the risk, the public health impact is considered medium.

Important potential risk: Radiation-induced nephropathy

Potential mechanisms: Dosimetry studies have indicated that the kidneys are a main target organ for radiation exposure following the injection of $^{177}LuCl_3$ (Sjogreen Gleisner *et al.*, 2022). Consequently, the renal system, particularly the kidneys, is highly susceptible to radiation toxicity, which can result from both non-specific uptake and renal elimination of radiolabelled peptides. The primary cause of renal irradiation is the reabsorption of these peptides in the proximal tubules, which can lead to nephrotoxicity that limits the dose of radiation that can be safely administered (Parihar et al., 2022).

Evidence source(s) and strength of evidence: Published studies and the SmPC of the related products indicate that radiolabelled peptides are predominantly eliminated through the kidneys, leading to radiation exposure from the accumulation of these peptides during excretion. The excessive exposure and accumulation may increase the risk of developing nephropathies.

Characterisation of the risk: While radiolabelled peptides are primarily eliminated through the kidneys, the incidence rate of radiation-induced kidney damage, or radiation nephropathy, is not clearly established. On one hand, cases of radiation-induced kidney damage, known as radiation nephropathy, have been documented after RLT for neuroendocrine tumours using various radioisotopes, especially for the treatments with ^{90}Y (Parihar et al., 2022), suggesting a possible relationship between the exposure to the radiation and kidney damage.

However, this relationship between the treatment with other radioligands and nephropathies has not been clearly stabilised, and ^{177}Lu is an example of this.

To establish a comparison between ^{90}Y and ^{177}Lu, both commonly radioligands used in the clinical practice for the treatment of certain neuroendocrine tumours, ^{177}Lu leads to lower irradiation of the glomerulus post peptide receptor radionuclide therapy (Parihar et al., 2022). This lower exposure to radiation suggests that the overall lower risk of nephrotoxicity would be lower than the therapy with ^{90}Y, which at high doses (6.7 GBq/cycle) produced severe nephrotoxicity rates up to 14% and increased the probability of renal toxicities in long-term outcome of a phase I dose escalation study (Marincek et al. 2013).

Different studies have assessed the potential nephrotoxicity of the treatment with ^{177}Lu. For example, in a long-term follow-up study of a phase II prospective clinical trial evaluated the effects, including related toxicities, of ^{177}Lu-PSMA-617 treatment in patients with metastatic prostatic cancer. A total of 50 patients with metastatic castration-resistant prostate cancer received up to 4 cycles of ^{177}Lu-PSMA-617 every 6 weeks, even 15 patients who initially responded but then progressed, received additional doses (median of 2 cycles commencing 359 d from enrolment). Different tests and assessments of the renal function were conducted throughout all the study (median follow up: 31.4 months) and only grade 1–2 renal injury

occurred in 10% of patients; and in 28 patients reported a mean decline of 11.7 mL/min (95% CI, -19 to -4 mL/min) 3 months after completion of ^{177}Lu-PSMA. The authors indicated that the loss of renal cortical mass due to the age of the population (median age: 71 years) and prior obstructive uropathy may render men with advanced prostate cancer at increased risk of progressive renal impairment, so the renal function must be monitored during the treatment (Violet *et al.*, 2020).

On the other hand, in a review of the different studies using ^{177}Lu as radionuclide therapy some nephrotoxicity effects, but mainly in low grade. However, many of these studies included patients with factors that should be accounted for the correct evaluation of this risk, like natural decline in glomerular filtration rate (GFR) with increasing age, institution of other nephrotoxic treatments, history of previous kidney damage, etc., (Parihar et al., 2022). Furthermore, results of a study assessing the renal toxicity of ^{177}Lu-DOTATATE RLT in patients with metastatic NET who have only one working kidney indicated that patients with NETs and a single functioning kidney can safely undergo 3-5 cycles of ^{177}Lu-DOTATATE RLT, provided that it is accompanied by renal protective measures and dose fractionation (Ranade et al., 2016).

Taken together all the studies discussed, there is scientific evidence to suspect the possibility of a causal relationship between kidney damage and radiation of ^{177}Lu but study data are not clear-cut.

Risk factors and risk groups: Identified risk factors for radiation-induced nephropathy include: hypertension, diabetes mellitus, age over 60, renal morphological abnormalities, low base glomerular filtration rate, previous chemotherapy and male gender (Parihar et al., 2022). The current threshold of toxicity for the absorbed kidney dose established for External Beam Radiation Therapy (EBRT) is 23 Gy. However, in practice, different types of radiation treatment require different thresholds, as kidney tolerance depends, among others, on emission type and range, radiation energy, and dose distribution of the radiation (de Roode *et al.*, 2024). Also, the existence of risk factors, such as renal impairment, shall be considered due to the potential impact that a compromised renal function can have on the PK of radiopharmaceuticals that are eliminated by the kidney, with the consequent increased risk of reaching systemic exposures associated with the onset of toxicological effects.

Preventability: The risk cannot be entirely prevented, but early detection of kidney damage is crucial. Healthcare professionals should be informed about the risk, and renal function including GFR should be evaluated before starting treatment and continuously monitored during treatment. Renal protective measures should be considered, in accordance with clinical guidance, to reduce radiation absorption by the kidneys (Parihar et al., 2022), thereby lowering the likelihood of radiation-induced nephropathy.

Impact on the risk-benefit balance of the product: With the implementation of kidney protection measures and amino acid infusions, the impact on the risk-benefit balance is considered acceptable.

Public health impact: Nephrotoxicity events are generally mild, with more serious cases requiring dialysis and hospitalization being rare.

Important potential risk: Osteosarcoma

Potential mechanisms: The potential mechanism behind radiotoxicity is attributed to the ionizing radiation released by ^{177}Lu and its accumulation within the bones following administration of non-labelled ^{177}Lu.

Evidence source(s) and strength of evidence: Published studies indicate that a substantial uptake and retention of free lutetium (^{177}Lu) ions in the bones can occur (Müller *et al.*, 1978; Repetto-Llamazares *et al.*, 2013) following administration of free ^{177}Lu, which may increase the risk of developing osteosarcomas.

Characterisation of the risk: Clinical data of this risk is not available. Non-clinical studies conducted in rats has shown predominant absorption of ^{177}Lu at osteogenic cells, the liver, spleen, red marrow, and kidneys. The long-term effect of intraperitoneal administration of lutetium oxide in NMRI female mice showed an increased rate of osteosarcoma formation after a 12-month exposure period to ^{177}Lu (Müller *et al.*, 1978). Furthermore, studies in mice have demonstrated an increased incidence of osteosarcomas, particularly in long bones and vertebrae, with a significant proportion of subjects exhibiting hematological death shortly after treatment with high doses of stable lutetium (Müller *et al.*, 1980).

Inferences drawn from animal studies to humans indicate that in the event of an accidental injection of the ^{177}Lu chloride the greatest uptake is likely to occur in osteogenic cells (Müller *et al.*, 1978). For an adult, the overall effective dose is estimated to be 0.158 mSv/MBq. For an adult, the overall effective dose is estimated to be between 0.122 and 0.132 mSv/MBq (for man and women, respectively) Consequently, if an adult were to accidentally receive an accidental injection of $^{177}LuCl_3$ with volumetric activity of 37 GBq/mL, the volume required to observe the first effects of acute radiation toxicity (1 Sv) would be between 204-221 µL, and to observe the first effects on blood cell counts [0.5Sv] 102-110 µL (more than the whole content of the lowest volume of the product [50 µL] included in a 2 mL vial). This level of exposure could correlate with the initial clinical indicators of radiation toxicity. The identified potential risk of osteosarcoma development exists due to the uptake and accumulation of ^{177}Lu in bone tissue.

Risk factors and risk groups: The level of risk is contingent upon the procedures of handling of Lu in the specialised facilities.

Preventability: While the risk cannot be entirely prevented, it is mitigated since the product is exclusively utilized for the radiolabelling of carrier molecules. To minimize the undesired accumulation of ^{177}Lu in the bone, it is crucial to keep the concentration of free Lu-ions to the lowest level feasible. The incorporation of a chelating agent like DTPA in the formulation of Lutetium (^{177}Lu)-labelled conjugates can minimize the risk of radiotoxicity due to free ^{177}Lu ions, facilitating its rapid elimination through the kidneys.

Impact on the risk-benefit balance of the product: The risk is considered to have a low impact on the risk-benefit ratio of the product, considering that the product is a radiopharmaceutical precursor not meant for direct administration to patients and that has been observed only in preclinical studies.

Public health impact: Osteosarcoma is a life-threatening condition with a high impact on a patient's quality of life.

Important potential risk: Radiation-induced hepatotoxicity

Potential mechanisms: In patients with extensive liver metastases and impaired liver function, there is a possibility of serious liver toxicity coming from excessive irradiation of the liver tissue located in the proximity of the metastases. The literature describes two distinct forms of radiation-induced hepatotoxicity: classic and non-classic. The classic form is characterized by the absence of jaundice but includes hepatomegaly, ascites, and elevated liver enzyme levels, particularly alkaline phosphatase, occurring from two weeks to four months post-radiation. On the other hand, the non-classic form is identified by significantly increased levels of serum transaminases and the presence of jaundice (Kim et al., 2017).

The mechanism behind the classic radiation-induced hepatotoxicity is veno-occlusive disease secondary to fibrosis. In contrast, the mechanism for non-classic hepatotoxicity is less understood, but may involve the loss of regenerating hepatocytes and reactivation of hepatitis (Koay et al., 2018).

Evidence source(s) and strength of evidence: The SmPC of the related products indicate that instances of liver toxicity have been documented in post-marketing surveillance and in medical literature among patients with liver metastases who are receiving Lutetium (^{177}Lu)-labelled somatostatin receptor targeting RLT for the treatment of neuroendocrine tumours.

However, AEs related to liver function in clinical studies with the use of ^{177}Lu-labelled radiopharmaceuticals are difficult to disentangle from the natural course of liver deterioration caused by the disease (Bober *et al.*, 2022). Recent studies with ^{177}Lu-labelled radiopharmaceuticals suggest that underlying liver insufficiency is not significantly exacerbated by the product, even in patients with pre-existing liver metastases (Bober *et al.*, 2022).

Characterisation of the risk: Cases of liver toxicity have been more frequently reported in patients with NET and liver metastasis, who did not respond to conventional treatment and were then treated with ^{177}Lu and/or ^{90}Y PRRT (Riff *et al.*, 2015). Yet, the casual relationship is not possible to be established, as the late on the onset of the treatment could lead to hepatic damage and the use of locoregional therapies may cause that the liver is exposed to radiation and increase the liver damage. On the other hand, in a retrospective longitudinal observational study reported only one case of severe liver injury after the treatment with 177Lu-PRRT. Liver parameters deteriorated within weeks after the first administration and the patient died of liver failure weeks later. However, the rest of patients included (35) did not report signs of liver injury (Abou Jokh Casas *et al.*, 2020). Therefore, the available evidence published in the literature suggests that hepatotoxicity related to ^{177}Lu-PRRT has been reported primarily in cases with severe liver metastases. This underscores the need for close monitoring of patients with liver metastasis undergoing this treatment. .

Risk factors and risk groups: The risk factors linked with classic-type radiation-induced hepatotoxicity include high mean liver dose, primary liver cancer, male gender and hepatic intra-arterial chemotherapy. The risk factors associated with the non-classic type radiation-induced hepatotoxicity are related to underlying liver disease such as hepatitis B or cirrhosis (Koay et al., 2018). It is not clear the impact of ^{177}Lu-radiopharmaceuticals in the deterioration of liver function in patients that present a compromised liver function prior the initiation of the treatment (Khreish *et al.*, 2021; Bober *et al.*, 2022).

Preventability: Healthcare professionals should monitor for early symptoms of hepatotoxicity and regularly check liver function during treatment. Dosage adjustments may be necessary if hepatotoxicity is observed.

Impact on the risk-benefit balance of the product: Patients with minor or without liver metastases have not experienced notable hepatic toxicity. However, in patients with extensive liver metastases and impaired liver function, there is a possibility of serious liver toxicity.

Public health impact: The risk is considered low based on the incidence.

SVII.3.2 Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) Myelodysplastic syndrome/Acute myeloid leukaemia
Important potential risks	Osteosarcoma Radiation-induced nephropathy Radiation-induced hepatotoxicity
Missing information	None

PART III- Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including the collection, processing and analysis of individual case safety reports, the review and reporting on aggregate data, and a signal detection system are conducted for Ilumira 37 GBq/mL radiopharmaceutical precursor, solution. Routine PV activities are consistent with the EMA Guidelines on Good Pharmacovigilance Practices (GVP). A comprehensive description of all aspects of the PV system is provided in the Pharmacovigilance System Master File (PSMF), which is available upon request.

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place for the product included in this RMP.

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable since there are no additional pharmacovigilance activities proposed.

PART IV- Plans for post-authorisation efficacy studies

Efficacy of the product has been widely confirmed, as has been used for more than 10 years in Europe and its safety and efficacy has been well characterised. To date, no factors which might affect the efficacy of the product in medical practice have been identified for in its authorised indications and in the target population. There are no studies which are conditions of the marketing authorisation or specific obligation of Ilumira.

Based on the current knowledge, the MAH considers that there are no gaps in knowledge about efficacy of Ilumira requiring for post-authorisation efficacy studies. Furthermore, it is pertinent to highlight that Ilumira is not designed for direct administration to patients. Therefore, if necessary, post-authorisation efficacy evaluation would be done for the molecule radiolabelled with Ilumira, rather than the precursor product.

PART V- Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V. 1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	Routine risk communication: Warning about exposure to radioactivity in SmPC section 4.4. and Package Leaflet (PL) section 1. Adverse reactions including induction of certain risk of cancer and development of hereditary effects included in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Contains a general warning on radiation protection in SmPC section 4.4. and the indication that the product is to be used by specialists experienced with *in vitro* radiolabelling in SmPC section 4.2. Recommendation to administer the smallest quantity to the patient to achieve the appropriate outcome included in PL section 3. Contains information about precautions to be taken during the receipt, handling and storage of the radiopharmaceutical in SmPC sections 6.4, 6.6 and 12 and PL sections 3 and 5. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	Routine risk communication: Warning concerning haematological side effects and myelosuppression included in SmPC section 4.4 and PL section 2.

Safety concern	Routine risk minimisation activities
	Anaemia, thrombocytopenia, leukopenia, lymphopenia and pancytopenia are listed as adverse reactions in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Instruction to perform blood count test at baseline and monitor the blood count regularly during treatment included in SmPC section 4.4 and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Myelodysplastic syndrome /Acute myeloid leukaemia	Routine risk communication: Warning about MDS and AML in SmPC section 4.4 and PL section 2. MDS is listed as common and AML as uncommon adverse reactions in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: The section 4.4 included a statement encouraging to the healthcare professionals to consider this possible risk when the patient presents a risk factor. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Radiation-induced nephropathy	Routine risk communication: Warning concerning the excretion of radiolabelled somatostatin analogues by the kidneys in SmPC section 4.4 and PL section 2.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for assessment of the renal functions at baseline and during treatment in SmPC section 4.4 and PL section 2. Recommendation to consider renal protection in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Osteosarcoma	Routine risk communication: Explanation in SmPC section 4.8 that exposure to ionising radiation is linked with cancer induction and may result in higher incidence of cancer. Warning in SmPC section 12 concerning the uptake and accumulation of free Lutetium ^{177}Lu in the bones, which could potentially result in osteosarcomas. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to use a binding agent such as DTPA prior to intravenous administration of ^{177}Lu labelled conjugates in SmPC section 12. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Radiation-induced hepatotoxicity	Routine risk communication: Warning about hepatotoxicity in SmPC section 4.4 and PL section 2.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to monitor the liver function regularly during treatment in SmPC section 4.4 and PL section 2. Recommendation to consider dose reduction in affected patients in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V. 3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	Routine risk communication: Warning in SmPC section 4.4. and PL section 1. Adverse reactions included in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Indications and warnings on radiation protection in SmPC sections 4.2 and 4.4. Recommendation to administer the smallest quantity to achieve the	Routine pharmacovigilance activities

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	appropriate outcome included in PL section 3. Information about precautions for the reception, handling and storage in SmPC sections 6.4, 6.6 and 12 and PL sections 3 and 5. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	Routine risk communication: Warning in SmPC section 4.4 and PL section 2. Adverse reactions listed in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Instruction to monitor the blood count in SmPC section 4.4 and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	Routine pharmacovigilance activities
Myelodysplastic syndrome /Acute myeloid leukaemia	Routine risk communication: Warning about MDS and AML in SmPC section 4.4 and PL section 2.	Routine pharmacovigilance activities

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	MDS and AML are listed in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: The section 4.4 included a statement encouraging to the healthcare professionals to consider this possible risk when the patient presents a risk factor. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	
Radiation-induced nephropathy	Routine risk communication: Warning in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for assessment of the renal functions in SmPC section 4.4 and PL section 2. Recommendation to consider renal protection in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling:	Routine pharmacovigilance activities

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	• The symbol "radioactive" is given on the labelling.	
Osteosarcoma	Routine risk communication: Explanation in SmPC section 4.8 and warning in SmPC section 12. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to use a binding agent in SmPC section 12. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	Routine pharmacovigilance activities
Radiation-induced hepatotoxicity	Routine risk communication: Warning in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to monitor the liver function in SmPC section 4.4 and PL section 2. Recommendation to consider dose reduction in affected patients in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling	Routine pharmacovigilance activities

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	Labelling: • The symbol "radioactive" is given on the labelling.	

PART VI- Summary of the risk management plan

Summary of risk management plan for Ilumira (Lutetium (^{177}Lu) chloride)

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

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

This summary of the RMP for Ilumira 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 Ilumira's RMP.

I. The medicine and what it is used for

Ilumira is a radiopharmaceutical precursor, and is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride (see SmPC for the full indication). It contains lutetium (^{177}Lu) chloride and intended for *in vitro* radiolabelling of medicinal products which are subsequently administered by the approved route.

Further information about the evaluation of Ilumira's benefits can be found in Ilumira's EPAR, including in its plain-language summary, available on the EMA website, under the medicine´s webpage <link to the EPAR summary landing page>.

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

Important risks of Ilumira, together with measures to minimise such risks and the proposed studies for learning more about Ilumira'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.

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.*

II.A List of important risks and missing information

Important risks of Ilumira 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 Ilumira. 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	Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) Myelodysplastic syndrome/Acute myeloid leukaemia
Important potential risks	Osteosarcoma Radiation-induced nephropathy Radiation-induced hepatotoxicity
Missing information	None

II.B Summary of important risks

Important identified risk: Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	
Evidence for linking the risk to the medicine	Published studies and the SmPC of the product detail that lutetium (^{177}Lu) emits ionizing radiation that can affect not only the patient but also his healthcare providers, caregivers or other people remaining in close proximity to the patient for a prolonged period of time. The risk associated with radiation exposure is influenced by the physical distance from the patient who has undergone radionuclide therapy during the first days following the product administration.
Risk factors and risk groups	Persons in in close proximity to the treated patient.
Risk minimisation measures	<u>Routine risk communication</u>: Warning in SmPC section 4.4. and PL section 1. Adverse reactions included in SmPC section 4.8 and PL section 4. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk</u>: Indications and warnings on radiation protection in SmPC sections 4.2 and 4.4. Recommendation to administer the smallest quantity to achieve the appropriate outcome included in PL section 3. Information about precautions for the reception, handling and storage in SmPC sections 6.4, 6.6 and 12 and PL sections 3 and 5. <u>Other routine risk minimisation measures beyond the Product Information</u>: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Important identified risk: Decrease blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	

Evidence for linking the risk to the medicine	Published studies and the SmPC of the product indicate that myelosuppression is a possible side effect of radioligand therapy with Lutetium (^{177}Lu)-labelled molecules. Haematological toxicity, including anaemia, leukopenia, and thrombocytopenia, with varying grades have been observed across different studies with various 177Lu-labelled molecules, such as ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC or ^{177}Lu-PSMA-617 (Bodei *et al.*, 2011; Horsch *et al.*, 2016; Khreish *et al.*, 2022; Sundlov *et al.*, 2022; Zidan *et al.*, 2022; Patell *et al.*, 2023)
Risk factors and risk groups	Patients at higher risk for myelosuppression include those who have undergone prior chemotherapy treatments, as well as individuals presenting with anaemia (Bodei *et al.*, 2015).Baseline renal impairment, and patients aged over 70 years have also been considered as risk factors for developing myelosuppression.
Risk minimisation measures	Routine risk communication: Warning in SmPC section 4.4 and PL section 2. Adverse reactions listed in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Instruction to monitor the blood count in SmPC section 4.4 and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Important identified risk: Myelodysplastic syndrome/Acute myeloid leukaemia	
Evidence for linking the risk to the medicine	Published literature, clinical studies and post-marketing experience document cases where MDS and AML have occurred following the administration of Lutetium (^{177}Lu)-labelled molecules in the treatment of neuroendocrine tumours. The occurrence of these conditions has been consistently reported across various studies, reinforcing the strength of evidence. Clinical research and literature

	have documented various blood-related cancers, particularly MDS and AML, in relation to the administration of ^{177}Lu-labelled molecules (Sabet *et al.*, 2013; Kesavan *et al.*, 2014; Brieau *et al.*, 2016; Mitjavila *et al.*, 2023).
Risk factors and risk groups	Patients previously treated with chemotherapy, especially with alkylating agents, are at increased risk. Other risk factors include advanced age, compromised kidney function, low baseline blood cell counts and a history of multiple treatments (Kesavan et al., 2016).
Risk minimisation measures	Routine risk communication: Warning about MDS and AML in SmPC section 4.4 and PL section 2. MDS and AML are listed in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: The section 4.4 included a statement encouraging to the healthcare professionals to consider this possible risk when the patient presents a risk factor. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Important identified risk: Radiation-induced nephropathy	
Evidence for linking the risk to the medicine	Published studies and the SmPC of the related products indicate that radiolabelled peptides are predominantly eliminated through the kidneys, leading to radiation exposure from the accumulation of these peptides during excretion. Cases of radiation-induced kidney damage, known as radiation nephropathy, have been documented after RLT for neuroendocrine tumours using various radioisotopes (Parihar et al., 2022).
Risk factors and risk groups	Identified risk factors for radiation-induced nephropathy include: hypertension, diabetes mellitus, age over 60,

	renal morphological abnormalities, low base glomerular filtration rate, previous chemotherapy and male gender (Parihar et al., 2022). The current threshold of toxicity for the absorbed kidney dose established for External Beam Radiation Therapy (EBRT) is 23 Gy. However, in practice, different types of radiation treatment require different thresholds, as kidney tolerance depends, among others, on emission type and range, radiation energy, and dose distribution of the radiation (de Roode *et al.*, 2024). Also, the existence of risk factors, such as renal impairment, shall be considered due to the potential impact that a compromised renal function can have on the PK of radiopharmaceuticals that are eliminated by the kidney, with the consequent increased risk of reaching systemic exposures associated with the onset of toxicological effects.
Risk minimisation measures	Routine risk communication: Warning in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for assessment of the renal functions in SmPC section 4.4 and PL section 2. Recommendation to consider renal protection in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Important potential risk: Osteosarcoma	
Evidence for linking the risk to the medicine	Published studies indicate that a substantial uptake and retention of free lutetium (^{177}Lu) ions in the bones can occur (Müller *et al.*, 1978; Repetto-Llamazares *et al.*, 2013) following administration of free ^{177}Lu, which may increase the risk of developing osteosarcomas.

Risk factors and risk groups	The level of risk is contingent upon the procedures of handling of Lu in the specialised facilities.
Risk minimisation measures	Routine risk communication: Explanation in SmPC section 4.8 and warning in SmPC section 12. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to use a binding agent in SmPC section 12. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Important potential risk: Radiation-induced hepatotoxicity	
Evidence for linking the risk to the medicine	The SmPC of the related products indicate that instances of liver toxicity have been documented in post-marketing surveillance and in medical literature among patients with liver metastases who are receiving Lutetium (^{177}Lu)-labelled somatostatin receptor targeting RLT for the treatment of neuroendocrine tumours. However, AEs related to liver function in clinical studies with the use of ^{177}Lu-radiopharmaceuticals are difficult to disentangle from the natural course of liver deterioration caused by the disease (Bober *et al.*, 2022). Recent studies with ^{177}Lu-radiopharmaceuticals suggest that underlying liver insufficiency is not significantly exacerbated by the product, even in patients with pre-existing liver metastases (Bober *et al.*, 2022).
Risk factors and risk groups	The risk factors linked with classic-type radiation-induced hepatotoxicity include high mean liver dose, primary liver cancer, male gender and hepatic intra-arterial chemotherapy. The risk factors associated with the non-classic type radiation-induced hepatotoxicity are related to underlying liver disease such as hepatitis B or cirrhosis (Koay et al., 2018). It is not clear the impact of ^{177}Lu-radiopharmaceuticals in the deterioration of liver function

	in patients that present a compromised liver function prior the initiation of the treatment (Khreish *et al.*, 2021; Bober *et al.*, 2022).
Risk minimisation measures	Routine risk communication: Warning in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to monitor the liver function in SmPC section 4.4 and PL section 2. Recommendation to consider dose reduction in affected patients in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.

II.C Post-authorisation development plan

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

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

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

There are no studies required for Ilumira.

PART VII: ANNEXES

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

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

Not applicable.