EU Risk Management Plan for EndolucinBeta (Lutetium (^{177}Lu) chloride n.c.a.)

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Summary of significant changes in this RMP: Adaptation to new template, updated exposure data included and minor revison of targeted questionnaires. For details refer Annex 8

Other RMP versions under evaluation: Not applicable

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

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1: Product(s) Overview

Active Substance(S) (INN or Common Name):	Lutetium (^{177}Lu) Chloride
Pharmaco-therapeutic Group (ATC Code):	Other therapeutic radiopharmaceuticals (V10X)
Marketing Authorisation Holder	ITM Medical Isotopes GmbH
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	EndolucinBeta
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Radiopharmaceutical precursor.
	Summary of mode of action: ^{177}Lu has no intrinsic pharmacodynamics properties. The mode of action is based on the β- and γ-radiation emitted from this radiopharmaceutical precursor. The exact mode of action will depend on the properties of the final lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with EndolucinBeta, prior to administration.
	Important information about its composition: Non carrier added (n.c.a.) lutetium (^{177}Lu) chloride is produced by the irradiation of highly enriched (> 99 %) Ytterbium (^{176}Yb) in neutron sources.
Hyperlink to the Product Information	eCTD Module 1.3.1
Indication(s) in the EEA	Current: EndolucinBeta 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 EndolucinBeta 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.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution, each 2 mL vial contains an activity ranging from 3 – 80 GBq; each 10 mL vial contains an activity ranging from 8 – 150 GBq
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI- EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Radiopharmaceutical precursor - Not intended for direct use in patients.

Incidence: Not applicable.

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patient.

Prevalence: Not applicable.

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patient.

Demographics of the population in the authorized indication - age, gender, racial and/or ethnic origin and risk factors for the disease: Not applicable.

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patient.

The main existing treatment options: Not applicable.

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patient.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Not applicable.

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patient.

Important co-morbidities: Not applicable.

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patient.

PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

This medicinal product is for radiolabelling use only and is not intended to be injected into the human body. Nevertheless, a dosimetry study ITG-Lu-177-Dosimetry-001 has been conducted in rats to allow the extrapolation of the data in case of accidental injection of this medicinal product to a patient. Several other literature sources relevant to safety are also discussed below.

It should be noted that ^{177}Lu decays completely to ^{177}Hf with a half-life of 6.647 days. Therefore, the safety properties of hafnium must also be considered by the safety evaluation.

Accidental injection of the complete maximum volume of one vial containing 5 ml would therefore result in a maximum single intravenous dose of 73 µg lutetium per person or 1.46 µg lutetium/kg in a 50 kg person. Assuming complete radioactive decay to hafnium, both prior to dosing in the vial, and following administration in the body, this dose would also be the theoretically highest possible single dose exposure to hafnium.

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

Toxicity

Key issues identified from acute or repeat-dose toxicity studies

Lutetium: single dose toxicity

Single dose toxicity information following intravenous administration can be derived from safety pharmacology studies conducted in anaesthetised cats. No pharmacological effects on respiration or on the cardiovascular system were observed in the dose range 1 to 10 mg $LuCl_3$/kg, upon cumulative dosing. The administration of 20 mg/kg was in the lethal dose range in this preparation, resulting in lethality in 5 out of 10 cats. In animals, which did not die upon administration of 20 mg/kg, a transient hypotension with concomitant reduction in blood flow was observed. Respiration was not affected. In animals, which died at this dose or at the highest tested dose of 40 mg/kg, a complete cardiovascular collapse, coupled with respiratory paralysis, was observed, leading to death (Haley et al. 1964). From these data, the intravenous LD_{50} can be estimated to be 20 mg/kg in anaesthetised cats, corresponding to a dose of 12.5 mg lutetium/kg.

Hafnium: single dose toxicity

In rats, an intravenous LD_{50} of 75 – 100 mg hafnium/kg was determined, using the mandelate salt (an exact LD_{50} could not be calculated, since the ratio of hafnium to sodium mandelate was

not given in the report). In cats, the intravenous administration of 10 mg hafnium chloride/kg (corresponding to about 5.56 mg hafnium per kg) was lethal, while a dose of 0.5-2 mg hafnium chloride/kg, corresponding to 0.28 – 1.11 mg hafnium per kg, caused no overt signs of toxicity (BIBRA 1994).

Lutetium: repeat dose toxicity (90 days)

Repeat dose oral toxicity of $LuCl_3$ was evaluated in rats. Animals were fed a diet containing 0.01, 0.1 or 1% $LuCl_3$ for a period of 90 days. Based on a food consumption of 100 mg/kg body weight, this results in a daily exposure of 625 mg lutetium/kg body weight. Animals were monitored throughout the study for signs of toxicity including haematology and at the end of the study the animals were dissected. In addition to macroscopic pathology, a limited number of core organs, i.e., heart, lung, liver, kidney, spleen, pancreas, adrenals and small intestine, were evaluated histologically. The feeding of $LuCl_3$ had no influence on behaviour, growth rate, haematology, and gross pathology.

No signs of toxicity were seen evaluating the histology of the selected organs. Therefore, the NOEL of orally administered lutetium chloride was set at 1% in the diet, corresponding to about 1000 mg lutetium chloride/kg body weight or 625 mg lutetium/kg body weight (Haley et al. 1964).

Hafnium: repeat dose toxicity (up to 90 days)

The repeat dose intraperitoneal toxicity of hafnium gluconate complex was evaluated in rats dosed i.p. about 2-3 g hafnium per kg body weight per day for 10 days. In this study, about 50% of the rats died within the dosing period, but no further details were given (BIBRA 1994).

The effect of repeated intravenous administration of a hafnium salt, bis(1-phenylbutane-1,3-dione) hafnium dichloride was evaluated in 30 rats, compared to 30 control rats. The animals were dosed with the compound twice daily for 10 weeks at a dose of 14 mg/kg body weight. The only sign of toxicity was slower growth. One death in the drug treated group was caused by infection, and not by drug treatment. No further signs of toxicity were reported (BIBRA 1994).

In a different study, survival, growth, a limited number of blood parameters and urinary nitrogen levels were unaffected in an unspecified number of guinea pigs given hafnium dioxide at 2000 mg/kg daily for one month by oral administration. The investigators noted slightly increased liver weights and slightly reduced kidney and spleen weights, though these findings were not statistically significant. Histopathology revealed slight thickening of the alveolar walls in the lung and granularity in cytoplasm of hepatocytes. No NOAEL was determined, since this was a single dose group study (Haley et al. 1964).

In again a different series of studies, hafnium was administered as hafnium sodium mandelate, with an undefined amount of hafnium contained. The oral, subcutaneous and intramuscular route was evaluated. The oral dose of 5-25 mg/rat for up to 16 days was well tolerated, and no signs of toxicity were observed. The subcutaneous and intramuscular administration of up to 35 mg/rat for three weeks resulted in no overt systemic toxicity other than reduced body weight gain, but

animals developed local abscesses related to the dosing site. Examination revealed that hafnium precipitated as insoluble material at the injection site and was taken up by mononuclear phagocytes. Histological evaluation revealed that the insoluble material was also carried to the reticuloendothelial cells of the spleen, liver, lymph nodes and occasionally also the kidneys (Hinerman, Hendrix, and Weller 1954).

Relevance to human usage:

Even with (accidental) injection of the complete volume of 5 ml of $^{177}LuCl_3$ solution at the highest concentration, intended for the chelating reaction, the total amount of lutetium administered would only be 73 µg lutetium, corresponding to a maximum dose of less than 1.5 µg/kg body weight, which is well below the dose of 10 mg/kg of lutetium chloride (6.25 mg lutetium ion/kg) which was found to induce no pharmacological effect, if administered intravenously.

The same dose is the theoretically highest dose of hafnium, assumed that no lutetium is excreted before lutetium decays completely.

Hafnium chloride was also shown to have no pharmacological effect and the compound was found to be very safe. No pharmacological effect was induced upon intravenous administration of up to 2 mg/kg of hafnium chloride (corresponding to a dose of 1.11 mg hafnium ion/kg) in cats.

The data extrapolated from the dosimetry study ITG-Lu-177-Dosimetry-001 show that after (accidental) injection of $^{177}LuCl_3$ in man, the spleen (5.7 mSv/MBq) and the liver (5.6 mSv/MBq) absorb most of the administered radioactive dose, followed by the osteogenic cells (2.2 mSv/MBq). All other organs absorb less than 1 mSv/MBq each, with the red marrow absorbing 0.59 mSv/MBq, the kidneys 0.37 mSv/MBq, the adrenals 0.21 mSv/MBq, and the remainder ≤ 0.1 mSv/MBq each.

Overall, the absorbed radiation doses increase with decreasing age, as with any radionuclide. The total effective dose is 0.534 mSv/MBq in a 73.7 kg adult, increasing to 3.88 mSv/MBq in a 9.7 kg one-year-old. Thus, with accidental injection of for example one GBq $^{177}LuCl_3$ (each vial delivered contains an activity ranging from 1.5 to 300 GBq), the total effective dose would be 0.53 Sv for an adult, associated with first clinical signs of radiation toxicity, such as nausea and fatigue [U.S. Environmental protection, 2012].The same dose accidentally administered to a five-year-old, however, would cause severe radiation toxicity and if administered to a one-year-old, might be fatal. From the results of the dosimetry study ITG-Lu-177-Dosimetry-001 it is clear that even the lowest dose of 1.5 GBq administered accidentally would result in radiation toxicity to individual organs, considerably exceeding the limits set by the FDA for single organs “Guidance for industry and researchers” by the FDA (FDA 2010).

The injection of the whole vial with the maximal activity of 300 GBq will lead to an exposition 160,2 Sv by a 73.7 kg adult. Exposition already to a dose of 20 Sv leads to death in hours to days. The effective dose will be even higher with descending age.

Therefore, $^{177}LuCl_3$ must not be administered directly, but must only be used for radiolabelling.

Reproductive/developmental toxicity

In repeat dose toxicity studies, no toxic effects on reproductive organs were observed following oral dosing of lutetium chloride or hafnium chloride as a food admix for 90 days. The NOEL for lutetium was found to be 625 mg/kg body weight for lutetium and 55.5 mg/kg body weight for hafnium (Haley et al. 1964; Haley et al. 1962).

No further data are available on the chemical toxicity of lutetium or hafnium on the reproductive function, and no data are available evaluating the teratogenic potential of either compound.

As observed in the distribution studies in rats, only very low amounts of radioactivity were found in the reproductive organs (Durbin et al. 1956). Only 0.09% of the injected dose was found in the ovaries per g tissue, 5 min after administration, with no radioactivity found later on. In uterine tissue, no radioactivity above background could be found in this study at any time. The ^{177}Lu distribution to the testes was also very low. Only at 12 h and 48 h after administration, radioactivity barely above background activity could be found, amounting to about 0.01%ID/g.

Thus, based on the low exposure and the lack of accumulation in reproductive organs, no reproductive or developmental toxicity related to ^{177}Lu or its decay product ^{177}Hf is to be expected from administration of ^{177}Lu as a component of radioimmunotherapy, but the potential toxicity and distribution of the carrier molecule should be considered. General radiation considerations apply.

Relevance to human usage:

The use of ^{177}Lu-labelled medicinal product should be avoided during pregnancy; pregnancy should be excluded before use; milk of breast-feeding mothers should be discarded.

Genotoxicity

Genotoxicity is possible in the tissue in which radiopharmaceuticals containing ^{177}Lu is internalized due to the delivery of radiation dose. Treatment is contraindicated in the case when pregnancy is not excluded. Female and male patients must use contraception during the administration of radiopharmaceuticals labelled with ^{177}Lu as described in Summary of product characteristic (SmPC).

Relevance to human usage:

The use of ^{177}Lu-labelled medicinal product should be avoided during pregnancy; pregnancy should be excluded before use; milk of breast-feeding mothers should be discarded.

Carcinogenicity

Radiopharmaceuticals including ^{177}Lu have an inherent carcinogenic potential, derived from the ionising radiation emitted during radioactive decay. The effect of ^{177}Lu retained in the skeleton was studied. In animals examined 12 months after exposure to an estimated dose of 2000 to 8000 rd (20 to 80 Gy), an increased rate of osteosarcoma formation was observed. The increased rate of osteosarcoma formation was comparable to the effect of the radiation from exposure to strontium-90 (Muller, Linzner, and Schaffer 1978).

The main pharmacological and toxic effect is therefore due to the radiation emitted by the decay of lutetium.

Relevance to human usage:

The use of ^{177}Lu-labelled medicinal product should be avoided during pregnancy; pregnancy should be excluded before use; milk of breast-feeding mothers should be discarded.

Safety Pharmacology

Lutetium will be mainly accumulated in liver and spleen after accidental injection.

Lutetium is administered in low amount (consequentially low amount of hafnium appears in the body) so their impact on patient's safety other than radioactivity is negligible. Refer Part II SII under 'Toxicity' for details on hafnium.

Relevance to human usage:

The extrapolated data show that after (accidental) injection of $^{177}LuCl_3$ in man, the spleen (5.7 mSv/MBq) and the liver (5.6 mSv/MBq) absorb most of the administered radioactive dose, followed by the osteogenic cells (2.2 mSv/MBq). All other organs absorb less than 1 mSv/MBq each, with the red marrow absorbing 0.59 mSv/MBq, the kidneys 0.37 mSv/MBq, the adrenals 0.21 mSv/MBq, and the remainder ≤ 0.1 mSv/MBq each. Even with a dose as low as ca 9 MBq, the exposition of liver is as high as 50 mSv, the limit set e.g. by the "Guidance for industry and researchers" by the FDA (FDA 2010). According to the latter, the radiation dose from a single study should not exceed 30 mSv for the whole body, active blood-forming organs, lens of eye and gonads, and should not exceed 50 mSv for other organs.

Mechanisms for drug interactions

Possible drug interactions will depend on the ligand used for the chelation. No mechanisms can be discussed in case of accidental injection of non-chelated $^{177}LuCl_3$.

Relevance to human usage:

There is no relevance for human use, since this medicinal is not intended to be used before chelation with a corresponding ligand.

Other toxicity-related information or data

After intravenous injection of Lu-chloride, lutetium is predominantly but slowly excreted in the urine (O'Mara, McAfee, and Subramanian 1969). According to Durbin *et al.* faecal excretion is also observed (Durbin et al. 1956). The authors found that about 20% of administered radioactivity following intramuscular administration was excreted within 24 hours.

The solution of $^{177}LuCl_3$ in 0.04 M hydrochloric acid solution is acidic at a pH of 1-2. With paravenous injection or infusion into small or collapsed large veins, tissue damage and necrosis can occur, which may be irreversible. In case of accidental administration of lutetium (^{177}Lu) chloride to the patient, the catheter or affected area should be irrigated with isotonic saline solution.

Relevance to human usage:

This data can only be relevant in case of accidental use/medication error, leading to an injection of this radiological precursor in a human body. In this case, the risk of radiologic exposure can be weighted considerably higher. Thus, the risks will be further discussed within the scope of the subordinate risk “accidental use/medication error, resulting in radiation toxicity and/or local tissue damage”.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

No clinical trials have been conducted since this medicinal product is not intended to be used in humans.

PART II: MODULE SIV– POPULATIONS NOT STUDIED IN CLINICAL TRIALS

No clinical trials have been conducted since this medicinal product is not intended to be used in humans.

Therefore, this section is not applicable.

SIV.1 Exclusion Criteria in Pivotal Clinical Trials Within the Development Programme

Not applicable.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Not applicable.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Not applicable.

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV. 1.1 Method Used to Calculate Exposure

Since EndolucinBeta is licensed only for *in vitro* labelling of carrier molecules, such as peptides and monoclonal antibodies, it is hardly possible to estimate even a rough number of patients treated with Lutetium (^{177}Lu) chloride radiolabelled substances. The amount of Lutetium (^{177}Lu) chloride required for labelling and the quantity of Lutetium (^{177}Lu) chloride-labelled medicinal product subsequently administered depends on the medicinal product that is radiolabelled.

Patient exposure is estimated based on the amount of radioactivity sold during the reporting interval to hospitals and research institutes since these sales data are the only data available to the MAH. Data on the use of the final radiolabelled medicinal products in humans or for other purposes is not available.

For the estimation of patient exposure also the shelf-life of 9 days and the short half-life of ^{177}Lu of 6.647 days should be theoretically considered.

Following assumptions can be made:

Based on data from the literature, ^{177}Lu is mainly used for targeted radiopharmaceutical therapy (RPT) indicated for the treatment of neuroendocrine tumours (NETs) using radiolabelled somatostatin analogue ligands and for the treatment of prostate cancer using radiolabelled prostate-specific membrane antigen (PSMA) ligands.

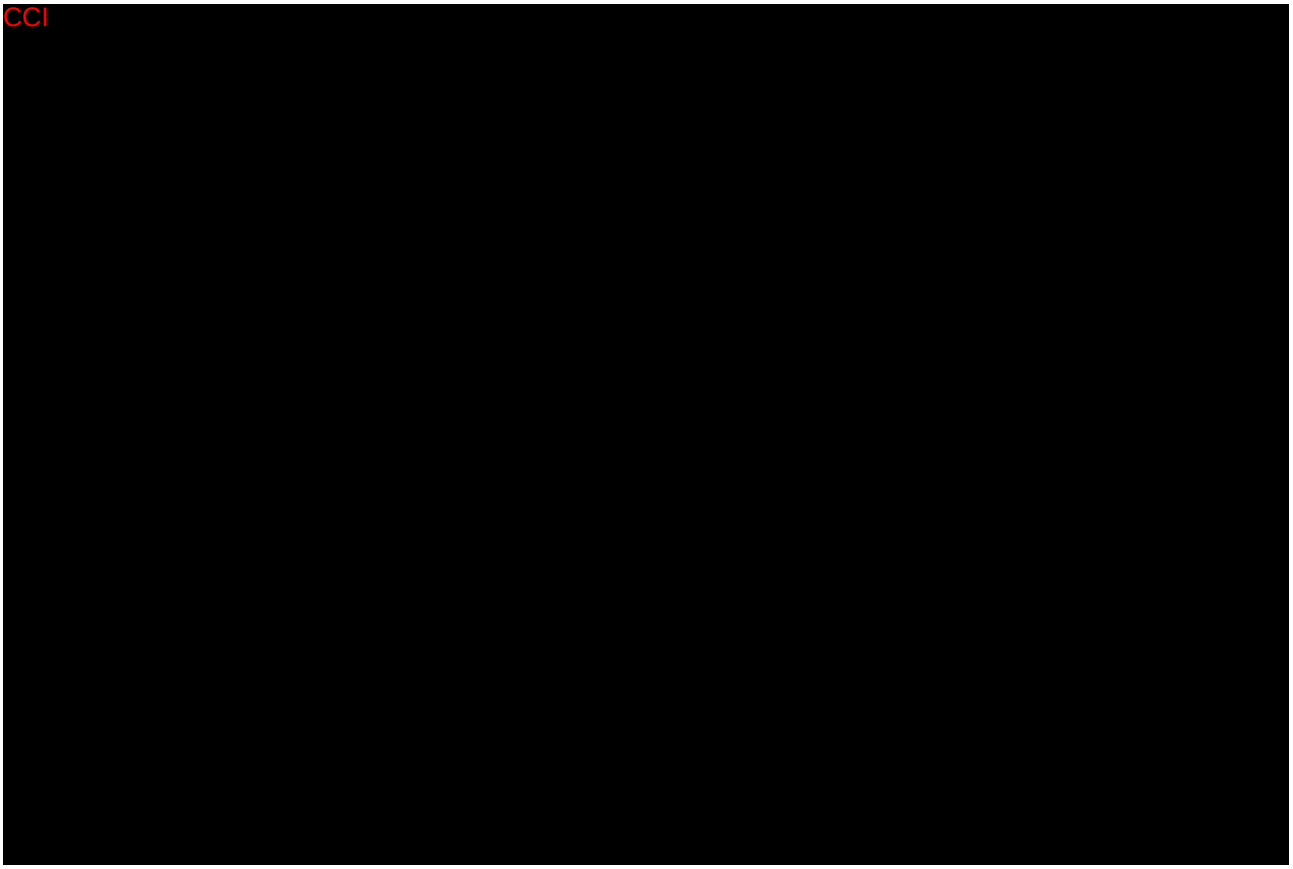
During RPT, somatostatin analogues such as DOTATOC, DOTATATE and DOTANOC are coupled to ^{177}Lu that target somatostatin receptor expressing NETs as *in vivo* radiotherapy.

Based on the assumption that all of the sold Lutetium (^{177}Lu) chloride is solely used to radiolabel PSMA ligands and somatostatin analogues ligands (to equal parts), half of the activity is assumed to have been used for somatostatin analogues ligands and the other half to PSMA ligands.

A joint guidance was released from International Atomic Energy Agency (IAEA), European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging of the USA (SNMMI) regarding RPT using ^{177}Lu that recommends using 5.55-7.4 GBq (on average 6.48 GBq) activity per patient per therapy cycle (Bodei et al. 2013) .

Furthermore, EANM and SNMMI released joint recommendations for therapy with ^{177}Lu-PSMA (Kratochwil et al. 2023). This recommendation includes an average dosage of 7.4 GBq per patient. The number of therapy cycles with ^{177}Lu-PSMA RPT per patient usually varies between 1 and 6 (on average 3.5 cycles).

SV. 1.2 Exposure



Until 31 August 2024, a total amount of [redacted] GBq lutetium (^{177}Lu) chloride were sold since the first marketing authorisation in July 2016.

Based on the assumption described in Part II SV.1.1 that all of the sold lutetium (^{177}Lu) chloride is solely used to radiolabel PSMA ligands and somatostatin analogues ligands (to equal parts), half of the activity is assumed to have been used for somatostatin analogues ligands and the other half to PSMA ligands. Therefore, since the first marketing authorisation (06.07.2016), [redacted] GBq ([redacted] GBq / 2) of lutetium (^{177}Lu) chloride was sold globally for either somatostatin analogues or PSMA ligands.

According to Bodei et al. regarding RPT using ^{177}Lu, recommends using 5.55-7.4 GBq (on average 6.48 GBq) activity per patient per therapy cycle (Bodei et al. 2013). This calculation leads to [redacted] therapy cycles ([redacted] GBq / 6.48 GBq) performed globally since the first marketing authorisation. The number of RPT cycles per patient usually varies between 2 and 6 (on average 4 cycles). Therefore, approximately [redacted] patients ([redacted] therapy cycles / 4 cycles) globally have been exposed to lutetium (^{177}Lu) chloride during therapy with lutetium (^{177}Lu)-radiolabelled somatostatin analogues since the first marketing authorisation. See Part II SV.1.1 for details on calculations.

Kratochwil et al. provided recommendations for therapy with ^{177}Lu-PSMA (Kratochwil et al. 2023) and states an average dosage of 7.4 GBq per patient . The number of therapy cycles with ^{177}Lu-PSMA radioligand therapy per patient usually varies between 1 and 6 (on average 3.5 cycles). Therefore, approximately CCI patients CCI GBq / 7.4 GBq = CCI therapy cycles; CCI therapy cycles / 3.5 cycles = CCI patients) globally have been exposed to Lutetium (^{177}Lu) chloride during ^{177}Lu-PSMA radioligand therapy since the first marketing authorisation in July 2016.

Overall, the estimated number of patients who were exposed to ^{177}Lu from first marketing authorisation in July 2016 was CCI patients (CCI patients + CCI patients) globally.

As the exposure is based on the amount of radioactivity sold and average activity per patient per RPT cycle, further details of the characteristics of the patient population treated with lutetium (^{177}Lu)-radiolabelled somatostatin analogues or PSMA ligands (e.g., sex, age, indication, dose, formulation, region) cannot be estimated.

Further details of the characteristics of the treated patient population (e.g. sex, age, indication, dose, formulation, region) are not available.

PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

This medicinal product contains a highly radioactive substance. The potential for misuse for illegal purposes results from the possibility to cause serious health effects, such as cancer or radiation toxicity, without obvious direct association with the substance uptake.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1: Radiotoxicity including occupational exposure and inadvertent exposure

Risk seriousness:

No seriousness/outcomes are known.

Risk frequency:

No frequency is known. Cancer risk and hereditary disorders are stochastic effects with a combined detriment of ~5%/Sv (ICRP 2007).

Risk-benefit impact:

Severity and nature of risk are low. Sghedoni *et al.* has evaluated the skin equivalent doses during ^{177}Lu-DOTATOC labelling and administration and concluded that the use of appropriate protection devices and procedures allows the observance of generally accepted dose limits for exposed workers (Sghedoni et al. 2011).

At risk are personnel involved in handling this medicinal product, especially the specialists performing chelation with specially developed ligands. Limits according to ICRP 103: effective dose 20 mSv per year; skin and extremity equivalent dose 500 mSv per year (ICRP 2007).

Important Identified Risk 2: Developmental toxicity including reproductive toxicity

Risk seriousness:

No seriousness/outcomes are known.

Risk frequency:

No frequency is known. Cancer risk and hereditary disorders are stochastic effects with a combined detriment of ~5%/Sv (ICRP 2007).

Risk-benefit impact:

Severity is expected to be severe (malformations and/or (permanent) disabilities) to very severe (death). At risk are pregnant and breast-feeding women undergoing radiotherapy.

Important Identified Risk 3: Myelosuppression

Risk seriousness:

This risk is mostly not serious and transient although in some cases patients have required blood and platelet transfusions.

Risk frequency:

Very common.

Risk-benefit impact:

The impact of this risk to the risk-benefit balance is considered to be moderate.

Important Identified Risk 3: Myelodysplastic syndrome / acute myeloid leukaemia

Risk seriousness:

Serious.

Risk frequency:

Uncommon (acute myeloid leukemia) and common (myelodysplastic syndrome)

Risk-benefit impact:

Risk-benefit assessment depends on the final product manufactured as EndolucinBeta.

Important Potential Risk 1: Medication errors associated with preparation and procedures

Risk seriousness:

No seriousness/outcomes are known.

Risk frequency:

No frequency is known.

Risk-benefit impact:

No seriousness/outcomes are known. Nevertheless, based on the fact that the injection of even the lowest activity of 1.5 GBq can lead to an exposure of 0.8 Sv, the effective dose possibly leading to death, the risk is serious.

The severity can be described as severe (induced cancer) to very severe (death).

Important Potential Risk 2: Osteosarcoma

Risk seriousness:

No seriousness/outcomes are known.

Risk frequency:

No frequency is known.

Risk-benefit impact:

In the extremely unlikely event that a full 7.5 GBq dose of nonconjugated dose of EndolucinBeta would be administered to a patient, the osteogenic cell dose that would result according to the dosimetry table for ^{177}Lu in the SmPC would amount to 16.1 Gy. In the only available study on the subject by Müller et al. (Muller et al. 1983), mice were administered carrier added solutions of ^{177}Lu. Although the solution and the route of administration differ from EndolucinBeta, Müller et al. found for a 185 MBq/kg dose a total skeletal dose of 28 Gy, which was associated with a 12.5% incidence of osteosarcomas. The severity would be severe (induced cancer) to very severe (death).

Important Potential Risk 3: Radiation nephropathy

Risk seriousness:

Non serious risk due to mostly mild and reversable changes.

Risk frequency:

No frequency is known.

Risk-benefit impact:

Moderate impact.

Important Potential Risk 4: Radiation-induced hepatotoxicity

Risk seriousness:

Mostly non serious although cases of liver fibrosis and liver failure are reported.

Risk frequency:

No frequency is known.

Risk-benefit impact:

Moderate impact; highly dependent on the liver disease burden.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new safety concern or reclassification in this updated RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk 1: Radiotoxicity including occupational exposure and inadvertent exposure

Potential mechanisms:

This risk is due to ionising radiation, emitted by the isotope ^{177}Lu.

Evidence source(s) and strength of evidence:

Evidence based on literature.

Characterisation of the risk:

No frequency is known. Cancer risk and also hereditary disorders are stochastic effects with a combined detriment of ~5%/Sv (ICRP 2007).

Sghedoni *et al*. has evaluated the skin equivalent doses during ^{177}Lu-DOTATOC labelling and administration and concluded that the use of appropriate protection devices and procedures allows the observance of generally accepted dose limits for exposed workers (Sghedoni et al. 2011).

Risk factors and risk groups:

Personnel involved in handling this medicinal product, especially the specialists performing chelation with specially developed ligands.

Limits according to ICRP 103: effective dose 20mSv per year; skin and extremity equivalent dose 500 mSv per year (ICRP 2007).

Preventability:

This risk can be prevented to a considerable extent if adequate shielding is used and the safety provisions are adhered to.

Impact on the risk-benefit balance of the product:

The impact on the risk-benefit balance is considered to be low as this risk can be minimised by adequate use of shielding and radiation protection. Radiopharmaceuticals should be received, used and administered only by authorised and specially trained persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Public health impact:

The effect on public health is considered to be not present.

Important Identified Risk 2: Developmental toxicity including reproductive toxicity.

Potential mechanisms:

This risk is due to ionising radiation, emitted by the isotope ^{177}Lu.

Evidence source(s) and strength of evidence:

Evidence based on literature and the nonclinical overview.

Characterisation of the risk:

No frequency is known. Cancer risk and also hereditary disorders are stochastic effects with a combined detriment of ~5%/Sv (ICRP 2007).

The severity of this risk is expected to be severe (malformations and/or (permanent) disabilities) to very severe (death).

Risk factors and risk groups:

Pregnant and breast-feeding women undergoing radiotherapy.

Preventability:

This risk can be prevented if pregnant women do not receive any ^{177}Lu-labelled medicinal product, and breastfeeding women express and discard the breast milk.

Impact on the risk-benefit balance of the product:

The risk is considered to have a low impact on the risk-benefit balance of the product as therapy in pregnant women is contraindicated. Breast-feeding women are advised to interrupt breastfeeding and discard the expressed feeds.

Public health impact:

Not applicable – no experience available yet.

Important Identified Risk 3: Myelosuppression

Potential mechanisms:

Bone marrow and kidney are the dose-limiting organs in RPT with ^{177}Lu-DOTA-octreotate (Falconi et al. 2016).

Repeated administration of RPT increases the accumulated dose to normal tissues and thereby increases the risk of accumulation of unrepaired DNA damage that can lead to genetic instability and, potentially, to carcinogenesis (Denoyer et al. 2015).

The spleen has an important role in the haematopoietic system, including being a reservoir for blood cells. It is also the organ that receives the highest mean absorbed dose during ^{177}Lu-DOTATATE treatment. There is some evidence that radiation exposure of the spleen affects overall haematological response during ^{177}Lu-DOTATATE treatment (Svensson et al. 2016).

Evidence source(s) and strength of evidence:

Evidence based on literature.

Characterisation of the risk:

Myelosuppression is reported as being predominantly transient and resolving spontaneously. However, data from clinical trials revealed that in a small fraction of patients treated with ^{177}Lu-DOTATATE thrombocytopenia and leukopenia lasted more than 6 months and required blood transfusion (Bergsma, Konijnenberg, Kam, et al. 2016).

The severity is expected to be mild to severe (infectious or haemorrhagic complications).

Risk factors and risk groups:

Risk factors associated with myelosuppression are previous chemotherapy and anaemia.

Preventability:

The risk is not completely preventable.

It is important that the healthcare specialist is aware of it and it is important to monitor for early symptoms of myelosuppression.

Impact on the risk-benefit balance of the product:

Clinical guidelines recommend blood counts every 2-4 weeks. Following careful clinical assessment, patients with blood values lower than the limits indicated for the first RPT cycle should receive a lower activity and/or the interval to the following RPT cycle should be extended. In severe cases, interruption of RPT might be considered (Bodei et al. 2013). Therefore, the impact of this risk to the risk-benefit balance is considered to moderate.

Public health impact:

In most cases, myelosuppression is mild and resolves spontaneously. Only some cases, where myelosuppression persisted longer than 6 months, required treatment (Bergsma, Konijnenberg, Kam, et al. 2016).

Important Identified Risk 4: Myelodysplastic syndrome / acute myeloid leukaemia

Potential mechanisms:

Myelodysplastic syndrome due to radiation may have different causes including single- or double-strand breaks in the DNA, involving errors in repair mechanisms and genetic mutations with loss of function or oncogene activation. The different sensitivities of DNA to radiation during the cell cycle and intrinsic host repair mechanisms are critical parameters.

Evidence source(s) and strength of evidence:

Evidence based on literature as well as the SmPC of Lutathera. The approved ^{177}Lu-labelled somatostatin analogue Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults. In section 4.4 of the Lutathera SmPC, a warning for MDS is listed with frequency common, and acute myeloid leukaemia, acute leukaemia, and chronic myelomonocytic leukaemia are listed with frequency uncommon in the table in 4.8.

Characterisation of the risk:

The severity would be severe (induced cancer) to very severe (death).

Risk factors and risk groups:

The development of myeloid neoplasms is significantly associated with previous treatments such as chemotherapy (Bodei et al. 2015).

Other risk factors include (Kesavan and Turner 2016):

- Age > 70 years,
- Impaired renal function,
- Baseline cytopenias,
- Prior number of therapies and
- Prior radiation therapy.

In contrast, neither the type nor the amount of radioactive nuclide administered had a significant influence on the occurrence of myeloid neoplasms (Bodei et al. 2016).

Preventability:

The risk is not completely preventable.
It is important that the healthcare specialist is aware of it and it is important to monitor for early symptoms of myeloid neoplasms.

Impact on the risk-benefit balance of the product:

Until now, only a few cases of myelodysplastic syndrome / acute myeloid leukaemia after radioligand therapy with ^{177}Lu have been reported in the literature. On 26 September 2017, the ^{177}Lu-labelled somatostatin analogue Lutathera received marketing authorisation. Late-onset myelodysplastic syndrome and acute leukaemia (AL) have been observed after treatment with Lutathera (SmPC Lutathera section 4.8), occurring approximately 28 months (9 – 41) for myelodysplastic syndrome and 55 months (32 - 125) for AL after the end of treatment. (SmPC Lutathera section 4.4 and SmPC 4.8). Therefore, this risk is now classified as important identified risk.

The use of targeted follow-up questionnaires will further characterise a possible causal relationship and further risk factors.

Public health impact:

Based on the incidence, the risk is estimated to be low.

Important Potential Risk 1: Medication errors associated with preparation and procedures

Potential mechanisms:

Human error.

Evidence source(s) and strength of evidence:

Evidence based on literature and CTD module 2.4 (toxicity of free ^{177}Lu)

Characterisation of the risk:

No seriousness/outcomes are known. Nevertheless, based on the fact that the injection of even the lowest activity of 1.5 GBq can lead to an exposure of 0.8 Sv, the effective dose possibly leading to death, the risk is serious (FDA 2010).

Risk factors and risk groups:

Patients undergoing radiotherapy.

Preventability:

This risk can be prevented if a corresponding ample warning is made in the SmPC and the delivery and management are restricted to persons with a dedicated licence to handle radiopharmaceuticals. Consequences (radiation toxicity) can be reduced by administration of a chelate (see SmPC section 4.9).

Impact on the risk-benefit balance of the product:

The impact on the risk-benefit balance is considered to be low as this risk can be minimised. Radiopharmaceuticals should be received, used and administered only by authorised and specially trained persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Public health impact:

The effect on the quality of life is high (possible secondary neoplasms, organ damage) to extreme (death).

Important Potential Risk 2: Osteosarcoma

Potential mechanisms:

This risk is due to ionising radiation, emitted by the isotope ^{177}Lu.

Evidence source(s) and strength of evidence:

Evidence based on literature.

Characterisation of the risk:

In the extremely unlikely event that a full 7.5 GBq dose of non-conjugated dose of EndolucinBeta would be administered to a patient, the osteogenic cell dose that would result according to the dosimetry table for ^{177}Lu in the SmPC would amount to 16.1 Gy. In the only available study on the subject by Müller et al., mice were administered carrier added solutions of ^{177}Lu (Muller, Linzner, and Schaffer 1978). Although the solution and the route of administration differ from EndolucinBeta, Müller et al. found for a 185 MBq/kg dose a total skeletal dose of 28 Gy, which was associated with a 12.5% incidence of osteosarcomas.

The severity would be severe (induced cancer) to very severe (death).

Preventability:

This risk can be prevented to a considerable extent if the medicinal product is only used for the radiolabelling of carrier molecules. Free ^{177}Lu will not be present in the body in clinically relevant amounts after treatment with a labelled conjugate.

Impact on the risk-benefit balance of the product:

The risk is considered to have a low impact on the risk-benefit balance of the product as EndolucinBeta 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.

Public health impact:

The effect on the quality of life is high (neoplasms, organ damage) to extreme (death).

Important Potential Risk 3: Radiation nephropathy

Potential mechanisms:

The mechanism of injury is thought to be radiation injury resulting from the renal excretion of the β-emitting isotope when it is used as a somatostatin conjugate in the treatment of neuroendocrine malignant disease. After being filtered by glomeruli, radiopeptides are reabsorbed and retained from the proximal tubule. Renal toxicity probably occurs because of irradiation of the radiosensitive glomeruli by activity retained in the relatively radioresistant tubular cells.

Evidence source(s) and strength of evidence:

Evidence based on literature.

Characterisation of the risk:

Radiolabelled somatostatin analogues are excreted by the kidney. Radiation nephropathy has already been reported following radionuclide therapy for neuroendocrine tumours using other radioisotopes like ^{90}Y (Paganelli et al. 2001; Bodei et al. 2008; Bodei et al. 2004; De Jong et al. 2002). To a lesser degree, radiation nephropathy can also occur with ^{177}Lu-labeled somatostatin analogues which have a shorter range of tissue penetration of particles emitted (Bodei et al. 2015; Bodei et al. 2008; Paganelli et al. 2014; Kwekkeboom et al. 2005; Kwekkeboom et al. 2008; Kwekkeboom et al. 2003; Bergsma, Konijnenberg, van der Zwan, et al. 2016). Thereby, thrombotic microangiopathy seems to be the major cause for renal failure of patients treated with 90Y (Moll et al. 2001; Stoffel et al. 2001).

Radiation nephropathy develops gradually over months to years and can lead to the development of chronic kidney disease.

Most cases of nephrotoxicity were mild and reversible. Persistent nephrotoxicity after long-term follow-up occurred in 13.4% (95% CI: 10.0-17.9) (Bodei et al. 2015).

Risk factors and risk groups:

Risk factors for radiation-induced nephropathy are:

- Hypertension (Bodei et al. 2015; Paganelli et al. 2001; Bodei et al. 2008; Valkema et al. 2005; Barone et al. 2005),
- Age > 60 years (Bodei et al. 2015; Valkema et al. 2005; Barone et al. 2005; Imhof et al. 2011),
- Diabetes mellitus (Barone et al. 2005),
- Renal morphological abnormalities (Bodei et al. 2008),
- Low baseline glomerular filtration rate (Imhof et al. 2011; Svensson et al. 2015),
- Previous chemotherapy (Bodei et al. 2015),
- Male gender (Bodei et al. 2015) and
- A higher number of concomitant risk factors (Valkema et al. 2005).

Preventability:

The risk is not completely preventable.
It is important that the healthcare specialist is aware of it and it is important to monitor for early symptoms of nephropathy. Renal function should be assessed at baseline and during treatment and renal protection should be considered, in accordance with clinical guidance.

Impact on the risk-benefit balance of the product:

European clinical guidelines recommend the use of amino acid infusions as renal protection (Bodei et al. 2013). This seems to reduce the absorbed radiation dose to the kidney and therefore reduces the risk of radiation nephropathy. Therefore, the impact on the risk-benefit balance is considered to be moderate.

Public health impact:

Most cases of nephrotoxicity are mild and reversible. However, more severe cases could require dialysis and hospitalisation.

Important Potential Risk 4: Radiation-induced hepatotoxicity

Potential mechanisms:

The exact molecular mechanism of radiation-induced hepatotoxicity is still unknown but early effects of irradiation include DNA damage, oxidative stress and reactive oxygen species production leading to hepatocellular apoptosis and acute inflammatory responses in irradiated regions (Robbins and Zhao 2004).

There are two different types of radiation-induced hepatotoxicity: the classic and non-classic type. Patients with classic radiation-induced hepatotoxicity present symptoms like fatigue, abdominal pain, increased abdominal girth, hepatomegaly and ascites 1–3 months after radiotherapy (Lawrence et al. 1995). In addition, the level of alkaline phosphatase (ALP) increases, whereas transaminase and bilirubin levels remain normal. The hallmark histologically is hepatic-venoocclusive disease (Reed and Cox 1966).

Patients with presenting the non-classic type of radiation-induced hepatotoxicity have underlying chronic hepatic diseases, such as cirrhosis and viral hepatitis, and show more dysregulated hepatic functions with jaundice and/or remarkably elevated serum transaminases rather than ALP (Cheng et al. 2004; Reed and Cox 1966).

Evidence source(s) and strength of evidence:

Evidence based on literature and post-marketing experience.

Characterisation of the risk:

Radiation-induced liver injury typically has a time to onset of 4-8 weeks, but has been reported as early as 2 weeks or as late as 7 months after radiation therapy (Benson et al. 2016; Khozouz, Huq, and Perry 2008; Guha and Kavanagh 2011). The majority of patients recover within 3 to 5 months, while some develop worsening liver fibrosis and failure.

Risk factors and risk groups:

The likelihood of radiation-induced hepatotoxicity is related to the extent of liver irradiation, and pre-existing liver dysfunction may make patients more susceptible to lower doses of radiation. The development of radiation-induced hepatotoxicity is significantly associated with pre-existing liver diseases.

Other risk factors include (Pan et al. 2010):

- Prior liver directed therapies,
- Hepatitis B carrier status,
- Portal vein tumour thrombosis,
- Male gender.

Preventability:

The risk is not completely preventable.

It is important that the healthcare specialist is aware of it, and it is important to monitor for early symptoms of hepatotoxicity.

Impact on the risk-benefit balance of the product:

The 2013 Joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours guidelines advise that in patients without or with minor metastatic liver involvement, no significant hepatic toxicity has been reported following RPT (Guha and Kavanagh 2011; Bodei et al. 2013). However, in patients with massive liver metastases and impaired liver function, liver toxicity may occur and this should be considered when choosing the appropriate radioisotope. In such cases, the guidance recommends that ^{177}Lu-labelled peptides should be used and the administered activity should be reduced accordingly. The ENETS guidance on RPT contraindicates RPT in patients with severe hepatic impairment (total bilirubin >3xULN or albumin less than 30g/L and prothrombin time increased). Laboratory evaluations recommended before each therapy cycle include liver function tests.

Public health impact:

Based on the incidence, the risk is estimated to be low.

SVII.3.2 Presentation of the Missing Information

Not applicable.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
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 • Radiation-induced hepatotoxicity
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Specific Adverse Reaction Follow-Up Questionnaires for Safety Concerns:

The objective is to obtain post-marketing data for both safety concerns and evaluation of a true association between radiation nephropathy and myelodysplastic syndrome / acute myeloid leukaemia respectively related to preceding radioligand therapy using ^{177}Lu. The detailed data, especially medical history derived from the questionnaires, will give more insights to distinguish these cases from de novo or other secondary treatment-related malignancies. The questionnaires are implemented in ITM sponsored clinical trials where EndolucinBeta was used to radiolabel the investigational medicinal product.

The forms are provided in Annex 4 of the risk management plan (RMP).

Other Forms of Routine Pharmacovigilance Activities for Safety Concerns:

Not applicable

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This medicinal product is a radiopharmaceutical precursor and is not intended to be used directly. No efficacy studies can be conducted due to the negative risk/benefit ratio in this case.

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 Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Radiotoxicity including occupational exposure and inadvertent exposure	Routine risk communication: SmPC section 4.1, 4.2, 6.4, 6.6, 12 PL section 1, 3, 4, 5 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Developmental toxicity including reproductive toxicity	Routine risk communication: SmPC section 4.3, 4.6, 4.8, 6.6, 12 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.
Myelosuppression	Routine risk communication: SmPC section 4.4, 4.8 PL section 2, 4 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Myelodysplastic syndrome / acute myeloid leukaemia	Routine risk communication: SmPC section 4.4 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.
Medication errors associated with preparation and procedures	Routine risk communication: SmPC section 4.1, 4.2, 4.4, 6.6 PL section 1, 2, 3 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Osteosarcoma	Routine risk communication: SmPC section 4.8, 12 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.
Radiation nephropathy	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: recommendation for assessment of renal function at baseline and during treatment is included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Radiation-induced hepatotoxicity	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: recommendation to monitor liver function regularly during treatment is included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as 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 Measures	Pharmacovigilance Activities
Radiotoxicity including occupational exposure and inadvertent exposure	Routine risk communication: SmPC section 4.1, 4.2, 6.4, 6.6, 12 PL section 1, 3, 4, 5 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.	Routine pharmacovigilance activities

Developmental toxicity including reproductive toxicity	Routine risk communication: SmPC section 4.3, 4.6, 4.8, 6.6, 12 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol "radioactive" is given on the labelling.	Routine pharmacovigilance activities
Myelosuppression	**Routine risk communication:** SmPC section 4.4, 4.8 PL section 2, 4 **Other routine risk minimisation measures beyond the Product Information:** Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol "radioactive" is given on the labelling.	Routine pharmacovigilance activities

Myelodysplastic syndrome / acute myeloid leukaemia	Routine risk communication: SmPC section 4.4 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol "radioactive" is given on the labelling.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: targeted follow-up questionnaires for adverse event reports of myelodysplastic syndrome / acute myeloid leukaemia
Medication errors associated with preparation and procedures	Routine risk communication: SmPC section 4.1, 4.2, 4.4, 6.6 PL section 1, 2, 3, Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol "radioactive" is given on the labelling.	Routine pharmacovigilance activities

Osteosarcoma	Routine risk communication: SmPC section 4.8, 12 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.	Routine pharmacovigilance activities

Radiation nephropathy	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: recommendation for assessment of renal function at baseline and during treatment is included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: targeted follow-up questionnaires for adverse event reports of radiation nephropathy

Radiation-induced hepatotoxicity	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: recommendation to monitor liver function regularly during treatment is included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.	Routine pharmacovigilance activities

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for EndolucinBeta (Lutetium (^{177}Lu) chloride n.c.a.)

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

EndolucinBeta's SmPC and its package leaflet give essential information to healthcare professionals and patients on how EndolucinBeta should be used.

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

I. The medicine and what it is used for

EndolucinBeta is authorised as 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. It contains Lutetium (^{177}Lu) chloride n.c.a. as the active substance and it is not intended for direct use in patients.

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

II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

II.A List of important risks and missing information

Important risks of EndolucinBeta 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 EndolucinBeta. 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 • Radiation-induced hepatotoxicity
Missing information	None

II.B. Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk: Radiotoxicity Including Occupational Exposure and Inadvertent Exposure	
Evidence for linking the risk to the medicine	Evidence based on literature.
Risk factors and risk groups	Personnel involved in handling this medicinal product, especially the specialists performing chelation with specially developed ligands Limits according to ICRP 103: effective dose 20mSv per year; skin and extremity equivalent dose 500 mSv per year.
Risk minimization measures	Routine risk communication: SmPC section 4.1, 4.2, 6.4, 6.6, 12 PL section 1, 3, 4, 5 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Important identified Risk: Developmental toxicity including reproductive toxicity	
Evidence for linking the risk to the medicine	Evidence based on literature and the nonclinical overview.
Risk factors and risk groups	Pregnant and breast-feeding women undergoing radiotherapy.
Risk minimization measures	Routine risk communication: SmPC section 4.3, 4.6, 4.8, 6.6, 12 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Important Identified Risk: Myelosuppression	
Evidence for linking the risk to the medicine	Evidence based on literature.
Risk factors and risk groups	Risk factors associated with myelosuppression are previous chemotherapy and anaemia.
Risk minimization measures	Routine risk communication: SmPC section 4.4, 4.8 PL section 2, 4 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. 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	Evidence based on literature.
Risk factors and risk groups	The development of myeloid neoplasms is significantly associated with previous treatments such as chemotherapy. Other risk factors include: Age > 70 years, Impaired renal function, Baseline cytopenias, Prior number of therapies and Prior radiation therapy. In contrast, neither the type nor the amount of radioactive nuclide administered had an significant influence on the occurrence of myeloid neoplasms.
Risk minimization measures	<u>Routine risk communication:</u> SmPC section 4.4 PL section 2 <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling. <u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • targeted follow-up questionnaires for adverse event reports of radiation nephropathy

Important Potential Risk: Medication Errors Associated with Preparation and Procedures	
Evidence for linking the risk to the medicine	Evidence based on literature.
Risk factors and risk groups	Patients undergoing radiotherapy.
Risk minimization measures	Routine risk communication: SmPC section 4.1, 4.2, 4.4, 6.6 PL section 1, 2, 3, Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Important Potential Risk: Osteosarcoma	
Evidence for linking the risk to the medicine	Evidence based on literature.
Risk factors and risk groups	Patients undergoing radiotherapy.
Risk minimization measures	Routine risk communication: SmPC section 4.8, 12 Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling.

Important Potential Risk: Radiation Nephropathy	
Evidence for linking the risk to the medicine	Evidence based on literature.
Risk factors and risk groups	Risk factors for radiation-induced nephropathy are: • Hypertension, • Age > 60 years, • Diabetes mellitus, • Renal morphological abnormalities, • Low baseline glomerular filtration rate, • Previous chemotherapy, • Male gender and • A higher number of concomitant risk factors.
Risk minimization measures	<u>Routine risk communication:</u> SmPC section 4.4 PL section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> recommendation for assessment of renal function at baseline and during treatment is included in SmPC section 4.4 <u>Other routine risk minimisation measures beyond the Product Information:</u> • Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. Labelling: • The symbol “radioactive” is given on the labelling. <u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> targeted follow-up questionnaires for adverse event reports of radiation nephropathy

Important Potential Risk: Radiation-Induced Hepatotoxicity	
Evidence for linking the risk to the medicine	Evidence based on literature and post-marketing experience.
Risk factors and risk groups	The likelihood of radiation-induced hepatotoxicity is related to the extent of liver irradiation, and pre-existing liver dysfunction may make patients more susceptible to lower doses of radiation. The development of radiation-induced hepatotoxicity is significantly associated with pre-existing liver diseases Other risk factors include: • Prior liver directed therapies, • Hepatitis B carrier status, • Portal vein tumour thrombosis, • Male gender.
Risk minimization measures	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: recommendation to monitor liver function regularly during treatment is included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: • Legal status: • Use only by trained specialists. • Sale limited to licenced nuclear medicine sites: the product will only be sent out to users with a dedicated (i.e. ^{177}Lu) licence for handling of open radioactive sources. 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 EndolucinBeta.

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

There are no studies required for EndolucinBeta.

PART VII: ANNEXES

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Annex 1 - EudraVigilance Interface

Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Not applicable.

Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Not applicable.

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Myelodysplastic syndrome / acute myeloid leukaemia Follow-up questionnaire **Case ID:**

Part 1: Patient		
Initials:	**Age:** |_____| year(s)	**Ethnic origin:**
Gender: ☐ Male ☐ Female		

Part 2: Medicinal product		
Product name:	**Coupled with (non-active precursor):**	**Administered activity:**
Dosage:	**Batch/expiration date, if given:**	**Route of administration:**
Indication for use:	**Treatment cycles administered:** |_____|	
Start date (first treatment cycle): |___|___|_____| DD MM YYYY	**Stop date (last treatment cycle):** |___|___|_____| DD MM YYYY or ☐ Not applicable	**Was the medication stopped due to the adverse event(s)?** ☐ Yes ☐ No ☐ Not applicable
Did the reaction abate after stopping the medication? ☐ Yes ☐ No ☐ Not applicable	**Was the medicinal product reintroduced?** ☐ Yes ☐ No ☐ Not applicable	**Did the reaction reappear after reintroduction?** ☐ Yes, permanently ☐ No ☐ Yes, temporarily ☐ Unknown

Part 3: Adverse event (Please attach further pages, if needed.)

Adverse event	Onset	Start date	Stop date	Severity	Outcome	Relatedness to medicinal product
	☐ Before therapy start ☐ After therapy start	|___|___|_____| DD MM YYYY	|___|___|_____| DD MM YYYY	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered ☐ Recovered with sequelae ☐ Ongoing ☐ Patient died ☐ Unknown	☐ Related ☐ Not related
	☐ Before therapy start ☐ After therapy start	|___|___|_____| DD MM YYYY	|___|___|_____| DD MM YYYY	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered ☐ Recovered with sequelae ☐ Ongoing ☐ Patient died ☐ Unknown	☐ Related ☐ Not related
	☐ Before therapy start ☐ After therapy start	|___|___|_____| DD MM YYYY	|___|___|_____| DD MM YYYY	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered ☐ Recovered with sequelae ☐ Ongoing ☐ Patient died ☐ Unknown	☐ Related ☐ Not related

Seriousness:

☐ Life-threatening ☐ Disability/incapacity ☐ Congenital anomaly/birth defect ☐ Medically significant event

☐ Hospitalisation/prolonged hospitalisation, if yes: Admission date: \|___\|___\|_____\| DD MM YYYY
Discharge date: \|___\|___\|_____\| DD MM YYYY

☐ Death, if yes: Date of death: \|___\|___\|_____\| DD MM YYYY

Autopsy performed: ☐ Yes ☐ No

Autopsy report attached: ☐ Yes ☐ No

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Myelodysplastic syndrome / acute myeloid leukaemia Case ID:
Follow-up questionnaire

Special situation:

☐ Abuse ☐ Breastfeeding ☐ Lack of effect ☐ Medication error ☐ Misuse
☐ Occupational exposure ☐ Off-label use ☐ Overdose ☐ Counterfeit
☐ Pregnancy ☐ Suspected transmission via a medicinal product of an infectious agent

Did the patient have any of the following sign or symptoms after starting the therapy with the medicinal product?

☐ Tiredness ☐ Bleeding ☐ Ecchymosis
☐ Shortness of breath ☐ Chilled sensation ☐ Chest pain
☐ Purpura or petechiae ☐ Splenomegaly ☐ Hepatomegaly
☐ Increased number of infections ☐ Other, please specify:

Please provide details by symptom, including start/stop date and treatment:

Did the patient require dialysis?
☐ Yes ☐ No
If yes, please provide further details:
☐ Temporary Start date: |___|___|_____| DD MM YYYY Stop date: |___|___|_____| DD MM YYYY
☐ Permanent Start date: |___|___|_____| DD MM YYYY

Part 4: Risk factors/medical history

Has there been any previous chemotherapy or radiation therapy?
☐ Yes, chemotherapy ☐ Yes, radiation therapy ☐ No

If yes, please specify:
Medicinal product:

Treatment start date: |___|___|_____| DD MM YYYY
Treatment stop date: | | | | DD MM YYYY

Have there been any adverse events?
☐ Yes ☐ No
If yes, please specify:

Does the patient have any of the following risk factors currently?

☐ Renal disease ☐ Impaired renal function ☐ Anemia ☐ Cytopenia
☐ Exposure to certain chemicals, including tobacco smoke, pesticides, fertilizers, and solvents such as benzene
☐ Exposure to heavy metals, such as mercury or lead

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Myelodysplastic syndrome / acute myeloid leukaemia Follow-up questionnaire **Case ID:**

Please provide details by risk factor, including onset date and treatment:
Please provide details to the medical history (patient or family):

Part 5: Concomitant treatment						
Concomitant medications: ☐ Yes ☐ No ☐ Unknown (Exclude drugs to treat the adverse event)						
Name of medicinal product (generic name)	**Indication**	**Suspected**	**Dosage**	**Start date Stop date**	**Treatment stopped? If yes, before/ after adverse event**	**If yes, did event improve after withdrawal?**
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No

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Myelodysplastic syndrome / acute myeloid leukaemia Case ID:
Follow-up questionnaire

Part 5: Concomitant treatment						
Name of medicinal product (generic name)	**Indication**	**Suspected**	**Dosage**	**Start date Stop date**	**Treatment stopped? If yes, before/ after adverse event**	**If yes, did event improve after withdrawal?**
		☐ Yes ☐ No		|__|__|_____| DD MM YYYY |__|__|_____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No

Part 6: Laboratory results				
Laboratory result(s) available: ☐ Yes ☐ No ☐ Unknown If yes, please give details below.				
Laboratory results report enclosed: ☐ Yes ☐ No				
Lab parameter	**Test date**	**Value**	**Normal Range**	**Interpretation:**
Blood count red blood cells	|__|__|_____| DD MM YYYY			☐ Normal ☐ Decreased
Blood count platelets	|__|__|_____| DD MM YYYY			☐ Normal ☐ Decreased
Blood count white blood cells	|__|__|_____| DD MM YYYY			☐ Normal ☐ Decreased
Hemoglobin	|__|__|_____| DD MM YYYY			☐ Normal ☐ Decreased
Serum creatinine	|__|__|_____| DD MM YYYY			☐ Normal ☐ Elevated
Myoglobinuria	|__|__|_____| DD MM YYYY		-	
Proteinuria	|__|__|_____| DD MM YYYY		-	
Hematuria	|__|__|_____| DD MM YYYY		-	

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Myelodysplastic syndrome / acute myeloid leukaemia Case ID:
Follow-up questionnaire

Part 7: Other investigations
☐ Bone marrow biopsy☐ Bone marrow aspiration If yes, please specify further investigation of bone marrow and list details in the panel below: ☐ Cytogenetic analysis ☐ Immunocytochemistry ☐ Immunophenotyping ☐ Flow cytometry ☐ FISH (fluorescence in situ hybridisation) ☐ Sonography of the following area: _____ ☐ Other, please specify:
Please provide details by test, including date and result:

Part 8: Administrative data		
Report date: |___|___|_____| DD MM YYYY		Number of pages including attachments:
Reporter: Name: Date: ☐ Health care professional ☐ Other	Address: Phone: E-mail:	Signature:
Will be sent to:	☐ E-mail: safety-reporting@itm-radiopharma.com ☐ Fax: +49 89 329 8986 6068 **(only if communication per e-mail failed!)**	

Thank you for completing this form!

itm

Radiation nephropathy
Follow-up questionnaire

Case ID:

Part 1: Patient		
Initials:	Age: |_____| year(s)	**Ethnic origin:**
Gender: ☐ Male ☐ Female		

Part 2: Medicinal product		
Product name:	**Coupled with:**	**Activity:**
Dosage:	**Batch/expiration date, if given:**	**Route of administration:**
Indication for use:	**Treatment cycles administered:** |_____|	
Start date: |___|___|_____| DD MM YYYY	**Stop date:** |___|___|_____| DD MM YYYY or ☐ Not applicable	**Was the medication stopped due to the adverse event(s)?** ☐ Yes ☐ No ☐ Not applicable
Did the reaction abate after stopping the medication? ☐ Yes ☐ No ☐ Not applicable	**Was the medicinal product reintroduced?** ☐ Yes ☐ No ☐ Not applicable	**Did the reaction reappear after reintroduction?** ☐ Yes, permanently ☐ No ☐ Yes, temporarily ☐ Unknown

Part 3: Adverse event (Please attach further pages, if needed.)

Adverse event	**Onset**	**Start date**	**Stop date**	**Severity**	**Outcome**	**Relatedness to medicinal product**
	☐ Before therapy start ☐ After therapy start	|___|___|_____| DD MM YYYY	|___|___|_____| DD MM YYYY	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered ☐ Recovered with sequelae ☐ Ongoing ☐ Patient died ☐ Unknown	☐ Related ☐ Not related
	☐ Before therapy start ☐ After therapy start	|___|___|_____| DD MM YYYY	|___|___|_____| DD MM YYYY	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered ☐ Recovered with sequelae ☐ Ongoing ☐ Patient died ☐ Unknown	☐ Related ☐ Not related
	☐ Before therapy start ☐ After therapy start	|___|___|_____| DD MM YYYY	|___|___|_____| DD MM YYYY	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered ☐ Recovered with sequelae ☐ Ongoing ☐ Patient died ☐ Unknown	☐ Related ☐ Not related

Seriousness:

☐ Life-threatening ☐ Disability/incapacity ☐ Congenital anomaly/birth defect ☐ Medically significant event

☐ Hospitalisation/prolonged hospitalisation, if yes: Admission date: |___|___|_____| DD MM YYYY
Discharge date: |___|___|_____| DD MM YYYY

☐ Death, if yes: Date of death: |___|___|_____| DD MM YYYY

Autopsy performed: ☐ Yes ☐ No

Autopsy report attached: ☐ Yes ☐ No

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Radiation nephropathy
Follow-up questionnaire

Case ID:

Special situation:

☐ Abuse ☐ Breastfeeding ☐ Lack of effect ☐ Medication error ☐ Misuse
☐ Occupational exposure ☐ Off-label use ☐ Overdose ☐ Counterfeit
☐ Pregnancy ☐ Suspected transmission via a medicinal product of an infectious agent

Did the patient have any of the following symptoms after starting the therapy with the medicinal product?

☐ Fever ☐ Dehydration ☐ No urination
☐ Changes in urine frequency ☐ Changes in urine volume ☐ Changes in urine colour
☐ Changes in urine odour ☐ Other, please specify:

Please provide details by symptom, including start/stop date and treatment:

Did the patient require dialysis?
☐ Yes ☐ No
If yes, please provide further details:
☐ Temporary Start date: |___|___|_____| DD MM YYYY Stop date: |___|___|_____| DD MM YYYY
☐ Permanent Start date: |___|___|_____| DD MM YYYY

Part 4: Risk factors/medical history

Has there been any previous chemotherapy or radiation therapy?
☐ Yes, chemotherapy ☐ Yes, radiation therapy ☐ No

If yes, please specify:
Medicinal product:

Treatment start date: | | | | DD MM YYYY
Treatment stop date: | | | | DD MM YYYY

Have there been any adverse events?
☐ Yes ☐ No
If yes, please specify:

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Radiation nephropathy
Follow-up questionnaire

Case ID:

Is the patient suffering from diabetes?
☐ Yes, currently ☐ Yes, in the past ☐ No

If yes, please provide further details:

Onset date: |___|___|_____| DD MM YYYY

Latest HbA_{1c}:

Does the patient have any of the following risk factors currently?

☐ Renal disease ☐ Congestive heart failure ☐ Hypertension ☐ Kidney stones
☐ Enlarged prostate ☐ Dehydration ☐ Urinary tract infection ☐ Direct trauma
☐ Diabetes mellitus ☐ Previous nephrotoxic chemotherapy or trans-arterial chemoembolisation

Please provide details by risk factor, including onset date and treatment:

Please provide details to the medical history (patient or family):

Has there been any co-administration of basic amino acids, bovine gelatine-containing solution or albumin fragments prior to or together with the administration of the medicinal product?
☐ Yes ☐ No

If yes, please specify:

Part 5: Concomitant treatment

Concomitant medications: ☐ Yes ☐ No ☐ Unknown (Exclude drugs to treat the adverse event)

Name of medicinal product (generic name)	Indication	Suspected	Dosage	Start date Stop date	Treatment stopped? If yes, before/ after adverse event	If yes, did event improve after withdrawal?
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No

Page 3 of 5

Radiation nephropathy
Follow-up questionnaire

Case ID:

Part 5: Concomitant treatment						
Name of medicinal product (generic name)	**Indication**	**Suspected**	**Dosage**	**Start date Stop date**	**Treatment stopped? If yes, before/ after adverse event**	**If yes, did event improve after withdrawal?**
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No
		☐ Yes ☐ No		|__|__|____| DD MM YYYY |__|__|____| DD MM YYYY	☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No

Part 6: Laboratory results				
Laboratory result(s) available: ☐ Yes ☐ No ☐ Unknown If yes, please give details below.				
Laboratory results report enclosed: ☐ Yes ☐ No				
Lab parameter	**Test date**	**Value**	**Normal Range**	**Interpretation:**
Hemoglobin	|__|__|____| DD MM YYYY			☐ Normal ☐ Decreased
Serum creatinine	|__|__|____| DD MM YYYY			☐ Normal ☐ Elevated
Myoglobinuria	|__|__|____| DD MM YYYY		-	
Proteinuria	|__|__|____| DD MM YYYY		-	
Hematuria	|__|__|____| DD MM YYYY		-	
Casts	|__|__|____| DD MM YYYY		-	

Radiation nephropathy
Follow-up questionnaire

Case ID:

Part 7: Other investigations		
☐ Renal sonography ☐ Other, please specify:	☐ Renal biopsy	☐ CT
Please provide details by test, including date and result:		

Part 8: Administrative data		
Report date: |___|___|_____| DD MM YYYY		Number of pages including attachments:
Reporter: Name: Date: ☐ Health care professional ☐ Other	Address: Phone: E-mail:	Signature:
Will be sent to:	☐ E-mail: safety-reporting@itm-radiopharma.com ☐ Fax: +49 89 329 8986 6068 **(only if communication per e-mail failed!)**	

Thank you for completing this form!

Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.

Annex 7 – Other Supporting Data (Including Reference Material)

Barone, R., F. Borson-Chazot, R. Valkema, S. Walrand, F. Chauvin, L. Gogou, L. K. Kvols, E. P. Krenning, F. Jamar, and S. Pauwels. 2005. 'Patient-specific dosimetry in predicting renal toxicity with (90)Y-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship', *J Nucl Med*, 46 Suppl 1: 99S-106S.

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Annex 8 – Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
01	01/04/2015	Initial version
02	18/12/2015 Marketing authorisation application (EMEA/H/C/003999/0000)	Safety concerns • Important identified risk radiotoxicity including occupational exposure and inadvertent exposure added • Important potential risk osteosarcoma added • Important potential risk medication errors associated with preparation and procedures renamed • Important potential risk occupational exposure resulting in radiation toxicity removed
03	24/08/2017 Adaption due to PSUSA (EMEA/H/C/PSUSA/00010391/201612)	Safety concerns • Important identified risk myelosuppression added • Important potential risk radiation nephropathy added • Important potential risk myelodysplastic syndrome / acute myeloid leukaemia added Annexes Annex 7: • Specific adverse drug reaction follow up forms for myelodysplastic syndrome / acute myeloid leukaemia added • Specific adverse drug reaction follow up forms for radiation nephropathy added

04	06/12/2017 Adaption due to PSUSA (EMEA/H/C/PSUSA/00010391/201706)	<u>Annexes</u> Annex 7: • Specific adverse drug reaction follow up forms for myelodysplastic syndrome / acute myeloid leukaemia modified <u>Pharmacovigilance Plan</u> • Additional pharmacovigilance activities: Additional pharmacovigilance activities for myelodysplastic syndrome / acute myeloid leukaemia and radiation nephropathy added
05	04/01/2018 Adaption due to variation report (EMEA/H/C/003999/IB/0005)	<u>Pharmacovigilance Plan</u> • Additional pharmacovigilance activities: Additional pharmacovigilance activities for myelodysplastic syndrome / acute myeloid leukaemia and radiation nephropathy removed
06	18.02.2019 Adaption due to PSUSAs (EMEA/H/C/PSUSA/00010391/201712, EMEA/H/C/PSUSA/00010391/201806)	<u>Safety concerns</u> • Important potential risk radiation-induced hepatotoxicity added • Important potential risk myelodysplastic syndrome / acute myeloid leukaemia reclassified as important identified risk

7.0	Information will be added after regulatory approval	New template used Sponsor's name was updated from ITG Isotope Technologies Garching GmbH to ITM Medical Isotopes GmbH Peptide receptor radionuclide therapy (PRRT) was replaced with radiopharmaceutical therapy (RPT) due to internal agreement Safety concern Toxicity • Text organised under new subheadings reproductive/developmental toxicity and genotoxicity. Populations Not Studied in Clinical Trials • Text rewritten for better readability. Exposure • Added new exposure data to this report. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP • Myelosuppression and myelodysplastic syndrome / acute myeloid leukaemia added as important identified risks. • Radiation nephropathy and radiation-induced hepatotoxicity are added as important potential risks. • No new safety concerns were found in this RMP. This statement was added under new safety concerns. Pharmacovigilance Plan Other forms of routine pharmacovigilance activities for safety concerns • Text was deleted because information about following myelodysplastic syndrome / acute myeloid leukaemia in COMPETE is redundant since oversight of the safety of participants in clinical trials is routinely performed through regular activities (collection and analysis of adverse events and safety surveillance). There are no myelodysplastic syndrome / acute myeloid

		leukaemia database to which ITM can access in order to analyse data, thus removing the commitment that is not plausible. <u>Risk Minimisation Plan</u> • Routine Risk Minimisation Measures: The statement "The delivery will only follow to the hands of a responsible radiation protection officer." was deleted throughout the document because current delivery practice was followed for delivery receipt. <u>Annexes</u> • Annex 4: Specific adverse drug reaction follow-up forms updated. Minor adaptation of questionnaires due to determined deficiencies