

Common technical documentation Module 1	Section 1.8.2
	Lu 177 n.c.a. MAA Version 1.0

EU Risk Management Plan for iLuzyce, 51.8 GBq/mL, radiopharmaceutical precursor, solution

RMP version to be assessed as part of this application	
RMP Version number	1.0
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Rationale for submitting an updated RMP	Not applicable for initial marketing authorisation application submission
Summary of significant changes in this RMP	Not applicable for initial marketing authorisation application submission

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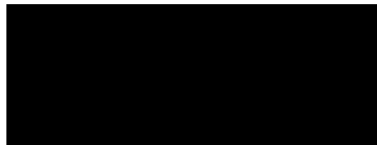


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List of abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMA	Antimitochondrial antibodies
AML	Acute Myeloid Leukaemia
ANA	Antinuclear antibodies
AST	Aspartate aminotransferase
mCPRC	Metastatic castrate-resistant prostate cancer
DSB	Double-Strand Breaks
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
ICRP	International Commission on Radiological Protection
MDS	Myelodysplastic Syndrome
n.c.a.	Non Carrier Added
NET	Neuroendocrine Tumour
PL	Package Leaflet
PRRT	Peptide receptor radionuclide therapy
SMA	Smooth muscle antibodies
SmPC	Summary of Product Characteristics

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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 non carrier added (n.c.a.)
Pharmacotherapeutic group(s) (ATC Code)	Other therapeutic radiopharmaceuticals (V10X)
Marketing Authorisation Applicant	Billev Pharma ApS
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	iLuzyce
Marketing authorisation procedure	Centralised (Well-established use product 10(a))
Brief description of the product	<p><u>Chemical class</u>: Radiopharmaceutical precursor</p> <p>Chemical name: IUPAC Name: lutetium-177(³⁺); trichloride</p> <p>Empirical formula: LuCl₃</p> <p>Molecular weight: 283.3 g/mol</p> <p>Chemical structure:</p> $\begin{array}{ccc} \text{Cl}^- & & \text{Cl}^- \\ & \text{177Lu}^{3+} & \\ & & \text{Cl}^- \end{array}$
	<p>Summary of mode of action</p> <p>Lutetium (¹⁷⁷Lu) chloride n.c.a is a radiopharmaceutical precursor intended to be used for the <i>in vitro</i> radiolabelling of medicinal products (carrier molecules) that have been specifically developed and authorised for radiolabelling with Lutetium (¹⁷⁷Lu) chloride for diagnostic or therapeutic purposes. The radiolabelled medicinal product is subsequently administered by the approved route. The exact mode of action will depend on the properties of the final lutetium (¹⁷⁷Lu)-labelled medicinal product prepared by radiolabelling with iLuzyce prior to administration.</p>

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	<p>Important information about its composition</p> <p>n.c.a. lutetium (¹⁷⁷Lu) chloride is produced by neutron irradiation of enriched Ytterbium (¹⁷⁶Yb).</p>
Hyperlink to the Product Information	eCTD Module 1.3.1.
Indication(s) in the EEA	<p>Current:</p> <p>Not applicable.</p>
	<p>Proposed (if applicable):</p> <p>iLuzyce 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 (¹⁷⁷Lu) chloride.</p>
Dosage in the EEA	<p>Current:</p> <p>Not applicable.</p>
	<p>Proposed (if applicable):</p> <p>The quantity of iLuzyce required for radiolabelling and the quantity of Lutetium (¹⁷⁷Lu)-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.</p>
Pharmaceutical form(s) and strengths	<p>Current (if applicable):</p> <p>Not applicable.</p>
	<p>Proposed (if applicable):</p> <p>Radiopharmaceutical precursor, solution. Clear colourless solution.</p> <p>Each 5 mL vial contains an activity ranging from 5.2 to 207.2 GBq. Each 10 mL vial contains an activity ranging from 5.2 to 414.4 GBq.</p>
Is/will the product be subject to additional monitoring in the EU?	No

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Part II: Safety specification

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

This section is not applicable.

According to Table V.5 of section V.C.1.1 (Summary of minimum RMP requirement for initial marketing authorisation applications) of the Guideline on good Pharmacovigilance practice (GVP) – Module V (Rev 2) this section can be omitted for a well-established medicinal use product.

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

This section is not applicable.

According to Table V.5 of section V.C.1.1 (Summary of minimum RMP requirement for initial marketing authorisation applications) of the Guideline on good Pharmacovigilance practice (GVP) – Module V (Rev 2) this section can be omitted for a well-established medicinal use product.

Part II: Module SIII - Clinical trial exposure

This section is not applicable.

According to Table V.5 of section V.C.1.1 (Summary of minimum RMP requirement for initial marketing authorisation applications) of the Guideline on good Pharmacovigilance practice (GVP) – Module V (Rev 2) this section can be omitted for a well-established medicinal use product.

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

This section is not applicable.

According to Table V.5 of section V.C.1.1 (Summary of minimum RMP requirement for initial marketing authorisation applications) of the Guideline on good Pharmacovigilance practice (GVP) – Module V (Rev 2) this section can be omitted for a well-established medicinal use product.

Part II: Module SV - Post-authorisation experience

This section is not applicable.

According to Table V.5 of section V.C.1.1 (Summary of minimum RMP requirement for initial marketing authorisation applications) of the Guideline on good Pharmacovigilance practice (GVP) – Module V (Rev 2) this section can be omitted for a well-established medicinal use product.

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

This section is not applicable.

According to Table V.5 of section V.C.1.1 (Summary of minimum RMP requirement for initial marketing authorisation applications) of the Guideline on good Pharmacovigilance practice (GVP) – Module V (Rev 2) this section can be omitted for a well-established medicinal use product.

Part II: Module SVII - Identified and potential risks

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

This is the first version of Module SVII for iLuzyce containing Lutetium (¹⁷⁷Lu) chloride n.c.a. iLuzyce is not intended to be administered directly to patients. The safety profile following administration of Lutetium (¹⁷⁷Lu)-labelled medicinal product prepared by radiolabelling with iLuzyce will therefore be dependent on the specific medicinal product being used. The risks associated with the use of Lutetium (¹⁷⁷Lu) chloride are considered well-characterised and the safety profile of Lutetium (¹⁷⁷Lu) can be considered to be well-known.

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
- Hypersensitivity
- Nausea
- Vomiting
- Alopecia

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):

- Extravasation
- Medication errors associated with preparation and procedures

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
- Developmental Toxicity including reproductive toxicity

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Tumour lysis syndrome

Hormone release syndromes

Known risks that do not impact the risk-benefit profile:

None

Other reasons for considering the risks not important:

None

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

Important Identified Risk 1: Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient

The radionuclide ^{177}Lu is a beta-emitting nuclide with a maximal energy of 497 keV and a half-life of 6,647 days (161 h)^{1, 2}. The emission of low energy gamma rays (113 keV and 208 keV)² is of concern with regards to exposure to patients, personnel preparing and administering the radiopharmaceutical as well as to individuals who come into contact with the patient who has received the ^{177}Lu -labelled radiopharmaceutical⁹. Exposure to ionising radiation is known to induce cancer and is potentially mutagenic. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. As a general rule, it is necessary to ensure that the risks of the radiation are lower than from the disease itself and therefore, the radiation exposure by treatment with ^{177}Lu -labelled tracers should be always carefully considered.

According to the Summary of Product Characteristics (SmPC) for ilLuzyce the point-source approximation shows that the average dose rate experienced 20 hours after administration of a dose of 7.3 GBq ilLuzyce labelled radiopharmaceutical (residual radioactivity 1.5 GBq) by a person at 1 meter distance from the patient's body centre with an abdominal radius of 15 cm is 3.5 $\mu\text{Sv/h}$. Doubling the distance to the patient to 2 meters reduces the dose rate by a factor of 4, to 0.9 $\mu\text{Sv/h}$. The same dose in a patient with an abdominal radius of 25 cm yields a dose rate at 1 meter of 2.6 $\mu\text{Sv/h}$. The generally accepted threshold for discharge of the treated patient from the hospital is 20 $\mu\text{Sv/h}$. In most countries, the exposure limit for hospital staff is set the same as for the general public at 1 mSv/year. When taking the 3.5 $\mu\text{Sv/h}$ dose rate as an average, this would allow hospital staff to work approx. 300 hours/year in close vicinity of patients treated with ilLuzyce labelled radiopharmaceuticals without wearing radiation protection. Of course, the nuclear medicine staff is expected to wear standard radiation protection. Any other person in close vicinity of the treated patient should be informed about possibilities to reduce his/her exposure due to radiation emitted from the patient².

Risk-benefit impact:

The risk is expected to be low. Due to the risk associated with ionising radiation, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

Several studies have been published during the past years investigating the occupational radiation exposure of nuclear medicine personnel as well as patients' household members following administration of ^{177}Lu -labelled tracers for targeted tumour radiotherapy^{3, 4, 5, 6, 7, 8, 9, 10}.

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Altogether, radiation exposure of personnel during labelling and exposure of medical personnel during treatment as well as of the general public was found to be acceptable and within the limits as defined by the International Commission on Radiological Protection (ICRP). However, radiation exposure varies between patients and different radiopharmaceuticals and therefore, additional inpatient and outpatient regulations should be taken into account as well.

Procedural guidelines for the management of radiotherapy, including regulations on patients' discharge, have been developed and should be strictly followed to avoid unnecessary radiation exposure. 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.

Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient is considered an important identified risk associated with the use of ilLuzyce.

Important Identified Risk 2: Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)

Myelosuppression, also referred to as bone marrow suppression, is a decrease in bone marrow activity resulting in reduced production of blood cells. Severe myelosuppression, called myeloablation, can be fatal. Myelosuppression becomes clinically evident as decreased blood count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, and pancytopenia). Pancytopenia is life-threatening. It can cause an oxygen shortage and other immune issues.

A significant side effect of peptide receptor radionuclide therapy (PRRT) using ¹⁷⁷Lu is haematotoxicity (myelosuppression) caused by bone marrow irradiation. Although myelosuppression is mild and self-limiting in many cases, a significant number of patients treated with ¹⁷⁷Lu-DOTATATE developed WHO Grade 3/4 haematotoxicity. Risk factors for development of significant haematotoxicity are poor renal function at baseline and age > 70 years¹³.

According to the information provided in the PSUSAs, haematological disorders including anaemia, thrombocytopenia, leukopenia, neutropenia as well as pancytopenia have been reported with considerable consistency following administration of ¹⁷⁷Lu-labelled tracers for treatment of Neuroendocrine Tumours (NETs) or prostate cancer¹⁴. The EudraVigilance database reported 44 cases of anaemia, 98 cases of thrombocytopenia, 28 cases of leukopenia, nine cases of lymphopenia, 17 cases of neutropenia and nine cases of pancytopenia. Most of the cases were transient and resolved accordingly; fatal outcome (3 cases) was rarely reported¹³.

Haematological disorders have also been observed following ¹⁷⁷Lu-PSMA-targeted therapy for metastatic Castrate-Resistant Prostate Cancer (mCPRC)¹⁴. The association of radioligand therapy with haematotoxicity is biologically plausible based on the known myelosuppressive effects of radiation.

Risk-benefit impact:

Haematological adverse events are assessed as manageable. Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) is considered an important identified risk associated with the use of ilLuzyce. The risk-benefit impact is considered to be moderate.

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Important Identified Risk 3: Myelodysplastic syndrome/Acute myeloid leukaemia

A number of haematological malignancies, most notably myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in clinical studies and in the literature with the use of Lutetium (¹⁷⁷Lu)¹⁵. Although patients had received prior chemotherapy in some studies and the clinical studies were mostly uncontrolled, there was no previous chemotherapy in other studies and the reporting frequency is generally consistent¹⁵. In the EudraVigilance database, 31 cases of MDS have been reported so far; of these, six (19.4%) had fatal outcome. A number of haematological malignancies, most notably MDS and acute myeloid leukaemia (AML) have been reported in clinical studies and in the literature in connection with the use of Lutetium (¹⁷⁷Lu)¹³.

As MDS and AML can be considered possible adverse reactions of ¹⁷⁷Lu-PRRT, these adverse reactions have been included in the product information of medicinal products containing Lutetium (¹⁷⁷Lu). Therefore MDS and AML are considered important identified risks associated with the use of ilLuzyce.

Risk-benefit impact:

The impact on the risk-benefit balance of the product of this risk is still not clear. A number of haematological malignancies, most notably myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been reported in clinical studies and in the literature in connection with the use of lutetium-177¹³.

Important Potential Risk 1: Osteosarcoma

Extrapolation of animal data to man suggest that after accidental injection of the proposed precursor solution ¹⁷⁷Lu chloride n.c.a., the highest absorption is to be expected in osteogenic cells. The total effective dose would be 0.158 mSv/MBq for an adult person. Thus, with accidental injection of for example two GBq ¹⁷⁷LuCl₃ (each vial delivered contains an activity ranging from 3.3 to 192 GBq at activity reference time), the total effective dose would be 0.316 Sv for an adult, which could be associated with first clinical signs of radiation toxicity, such as nausea and fatigue¹⁸. There is the potential risk identified of the development of osteosarcoma as ¹⁷⁷Lu is taken up and accumulated in the bones². It is not possible to describe likelihood and effect of ¹⁷⁷Lu accumulation in bone or liver specifically, as this depends on the labelled compound. The amount of free Lu-ions should be maintained as low as possible to avoid unnecessary accumulation of ¹⁷⁷Lu in the bone. It is recommended to add a binding agent such as DTPA prior to intravenous administration of ¹⁷⁷Lu-labelled conjugates in order to form a complex with free ¹⁷⁷Lu, leading to rapid renal clearance².

Risk-benefit impact:

The dosimetry presented in the SmPC of ilLuzyce shows that the bone, liver and kidney are the significant target organs for the biodistribution of ¹⁷⁷Lu. The organ absorbed dose as calculated in QDOSE with the IDAC 2.1 dose calculator after administration of 1000 MBq for bones (cortical bone mineral surface) would be 1.96 mGy/MBq equalling 1.96 Gy².

The risk is considered manageable as the ilLuzyce is only intended to be used for the radiolabelling of carrier molecules. The amount of free ¹⁷⁷Lu is therefore considered to be low. Furthermore, in the SmPC of ilLuzyce it is recommended to add a binding agent such as DTPA prior to intravenous administration of ¹⁷⁷Lu-labelled conjugates in order to form a complex with free ¹⁷⁷Lu if present.

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Important Potential Risk 2: Radiation nephropathy

The kidneys are critical organs because radiolabelled peptides are mainly excreted renally. Radiation nephropathy has been reported following PRRT for NETs using radioisotopes.

A study published in 2016 by Ranade and Basu retrospectively investigated the renal toxicity profile of ¹⁷⁷Lu-DOTATATE PRRT in patients with metastatic NET and a single functioning kidney. Six patients received between 3 and 5 cycles of therapy with a cumulative activity of 16.6-36.2 GBq. The duration of follow-up ranged from 12 to 56 months. The overall toxicity profile (as per the NCI-CTCAE score) showed no acute renal toxicity in any patient. Regarding overall chronic renal toxicity, 3 patients had none, 1 patient had grade II, and 2 patients had grade I. All patients with overall chronic renal toxicity showed compromised renal function at the outset (baseline). The 2 patients with grade I chronic renal toxicity after PRRT had grade II at baseline and gradual improvement over the subsequent cycles. One patient with grade II at baseline showed transient worsening to grade III after the first cycle followed by gradual improvement and a return to baseline after the second cycle. Only 2 patients showed a reduction in GFR (5.3% in one and 13.84% in the other). Four patients showed a reduction in ERPF (31.4% in the patient with the greatest reduction), and all had a rise in filtration fraction signifying that tubular parameters were more affected than glomerular parameters. The authors concluded that 3-5 cycles of ¹⁷⁷Lu-DOTATATE PRRT can be applied to patients with NET and a single functioning kidney, when administered along with renal protection and dose fractionation¹⁹.

Since an association of radiation nephropathy cannot be ruled out and radiation nephropathy has been reported following PRRT for NET using other radioisotopes, radiation nephropathy is considered an important potential risk associated with the use of iLuzyce.

Risk-benefit impact:

The risk is considered manageable through adequate listing and warning in the SmPC, where it is stated that careful consideration of the benefit risk ratio is required in patients with renal impairment, since an increased radiation exposure is possible. It is advisable to assess renal function at baseline and during treatment. Furthermore, renal protection should be considered in accordance with clinical guidance.

Important Potential Risk 3: Radiation-induced hepatotoxicity

Cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with ¹⁷⁷Lu-PRRT for NETs². There have also been reports of hepatotoxicity, particularly following treatment with ¹⁷⁷Lu-PRRT in a number of prospective single-arm studies published in the literature. Clinical guidelines advise that patients with liver metastases may be most susceptible to hepatotoxicity with PRRT and recommend monitoring liver function before each treatment cycle. Therefore, the PRAC considers that advice to healthcare professionals on cases of suspected hepatotoxicity following ¹⁷⁷Lu-PRRT is warranted²⁰.

Hepatotoxicity has been considered an important potential risk associated with the use of iLuzyce.

Risk-benefit impact:

The risk is considered manageable through adequate listing and warning in the SmPC. Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients.

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Missing information

The active substance lutetium (¹⁷⁷Lu) in iLuzyce is a well-known active substance and has well established use in the proposed indication. iLuzyce is not intended to be administered directly to the patients. It is used as radiopharmaceutical precursor and may be coupled to a variety of molecules, facilitating diagnosis and therapy by its radiation properties. Therefore, it is considered that there is no missing information.

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

Not applicable since this is the first version of the 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 – Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient

MedDRA terms	Occupational exposure to radiation (PT)
Potential mechanisms	The unfavourable effects relating to the radioactivity includes carcinogenicity, mutagenicity, and effects on different tissues. The potential mechanism for the radiotoxicity is due to ionising radiation emitted by and the accumulation of ¹⁷⁷ Lu in various tissue. The radioactive decay of the beta particle emitting radionuclides can induce strand breaks of the DNA potentially leading to cell death ^{21,22} .
Evidence source(s) and strength of evidence	It is described in in the published literature and the SmPC that lutetium (¹⁷⁷ Lu) has a half-life of 6.7 days and accumulates in various tissues following administration to the patient. It emits ionising radiation to the surroundings including other persons in close vicinity of the patient during the decay of the radionuclide. The danger of radiation is dependent of the distance the patient who has received treatment with a radionuclide.
Characterisation of the risk	No frequency is known. Hoving B.G. and van der Veen L. D. W. investigated the impact of ¹⁷⁷ Lu-DOTATATE therapy on the radiation dose of

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	the personnel involved in the labelling, quality control, dose administration and imaging procedure. They concluded that the impact of treating 25 patients with ¹⁷⁷ Lu-DOTATATE per year would increase the radiation dose with 1.66 mSv. Due to the different disciplines the dose would be divided over more than 10 persons and therefore still be below the general exposure limits for hospital staff that for most countries is the same as for the general public: 1 mSv/year ²³ .
Risk factors and risk groups	Health care professionals, carers, patients and relatives.
Preventability	The risk can be prevented to a considerable extent if adequate shielding is used and radiation protection precautions are adhered to. Any other person in close vicinity of the treated patient should be informed about possibilities to reduce his/her exposure due to radiation emitted from the patient ³ .
Impact on the risk-benefit balance of the product	The impact on the risk-benefit balance is considered to be low. For each patient the radiation exposure must be justifiable by the likely benefit. For health care professionals, carers and relatives the risk can be minimised by adequate used of shielding and radiation protection. Radiopharmaceuticals should be received, used and administered only by authorised and specially trained persons in designated clinical settings.
Public health impact	There is not considered to be an impact on the public health.

Important Identified Risk 2 – Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)

MedDRA terms	Myelosuppression (PT) Anaemia (PT) Leukopenia (PT) Thrombocytopenia (PT) Neutropenia (PT) Lymphopenia (PT) Pancytopenia (PT)
Potential mechanisms	PRRT using ¹⁷⁷ Lu-labelled tracers may cause myelosuppression by irradiating the bone marrow, even though it is mild and reversible. However, a significant number of patients treated with ¹⁷⁷ Lu-DOTATATE develop WHO Grade 3/4 haematotoxicity ¹³ . It is known that radiotherapy with ¹⁷⁷ Lu-labelled tracers induces DNA double-strand breaks (DSBs) in white blood

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	cells ^{24, 25, 26, 27, 28} . DSBs may result in cell death, which consequently reduces the white blood cell count, even far below normal values.
Evidence source(s) and strength of evidence	It is described in the published literature and the SmPC that myelosuppression may occur during radioligand therapy with Lutetium (¹⁷⁷ Lu). Anaemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with Lutetium (¹⁷⁷ Lu). Most events are mild and transient, but in some cases, patients have required blood and platelet transfusions. In some patients more than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described.
Characterisation of the risk	Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) is reported as being mild and self-limiting in many cases. However, a significant number of patients treated with ¹⁷⁷ Lu-DOTATATE developed WHO Grade 3/4 haematotoxicity ¹³ .
Risk factors and risk groups	Patients at risk of developing myelosuppression are patient that has previously been treated with chemotherapy and patients with anaemia, poor renal function at baseline and age > 70 years ¹³ .
Preventability	The risk cannot be completely preventable. It is important that the health care professionals are aware of the risk and monitor for early symptoms of myelosuppression. Hence a blood count should be taken at baseline and monitored regularly during treatment.
Impact on the risk-benefit balance of the product	Regular blood counts are recommended throughout the treatment ² . Following careful clinical assessment, patients with blood values lower than the limits indicated for the first PRRT cycle should receive a lower activity and/or the interval to the following PRRT cycle should be extended. In severe cases, interruption of PRRT might be considered ²⁹ .
Public health impact	Myelosuppression is mild and self-limiting in many cases. However, a significant number of patients treated with ¹⁷⁷ Lu-DOTATATE developed WHO Grade 3/4 haematotoxicity ¹³ .

Important Identified Risk 3 – Myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)

MedDRA terms	Myelodysplastic syndrome (PT) / acute myeloid leukaemia (PT)
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Potential mechanisms	Published clinical trials suggest that the combination of alkylating agents and PRRT poses a high risk of MDS and are considered either the consequence of mutational events induced by cytotoxic therapies or to arise via the selection of a myeloid clone with a mutator phenotype that has a markedly elevated risk for mutational events ³⁰ .
Evidence source(s) and strength of evidence	It is described in the published literature and the SmPC that MDS and AML have been observed after treatment with Lutetium (¹⁷⁷ Lu) peptide receptor radionuclide therapy for neuroendocrine tumors.
Characterisation of the risk	In the EudraVigilance database, 31 cases of MDS have been reported so far; of these, six (19.4%) had fatal outcome. A number of haematological malignancies, most notably myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been reported in clinical studies and in the literature in connection with the use of Lutetium (¹⁷⁷ Lu) ¹³ . MDS is listed as “common” and AML is listed as “uncommon” according to the MedDRA convention frequency in the SmPC of ilLuzyce ² and Lutathera ¹⁶ .
Risk factors and risk groups	Patients who have previously received chemotherapy. Other risk factors include ³¹ : Age above 70 years, impaired renal function, baseline cytopenias, prior number of therapies and prior radiation therapy.
Preventability	The risk is not completely preventable. The indication of PRRT should take into consideration the importance of previous chemotherapy. Exposure to alkylating agents should be avoided in patients with low-grade neuroendocrine tumour, who have a long survival expectancy and a significant likelihood of benefiting from the PRRT, because it may compromise the safety and future applicability of this more effective therapy. Regular and prolonged monitoring of blood counts is mandatory, especially in patients experiencing early hematological toxicity after PRRT ³² .
Impact on the risk-benefit balance of the product	The impact on the risk-benefit balance of the product of this risk is still not clear. A number of haematological malignancies, most notably myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been reported in clinical studies and in the literature in connection with the use of lutetium-177 ¹³ .
Public health impact	Based on the incidences so far, the public health impact is considered low.

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Important Potential Risk 1 - Osteosarcoma

MedDRA terms	Osteosarcoma (PT)
Potential mechanisms	The potential mechanism for the radiotoxicity is due to ionising radiation emitted by and the accumulation of ¹⁷⁷ Lu in the bones.
Evidence source(s) and strength of evidence	It is described in the published literature that a large amount of free lutetium (¹⁷⁷ Lu) ions are taken up and accumulated in the bones. This can potentially lead to osteosarcomas. The risk depends on the labelled compound.
Characterisation of the risk	The data available concerning the risk of developing osteosarcoma is based on extrapolation of animal data to man showing that if a large amount of free ¹⁷⁷ Lu would be present it would be accumulated in the bones. After accidental injection of the precursor solution ¹⁷⁷ Lu chloride n.c.a., the highest absorption is to be expected in osteogenic cells. The total effective dose would be 0.158 mSv/MBq for an adult person. Thus, with accidental injection of for example 2 GBq ¹⁷⁷ LuCl ₃ (each vial delivered contains an activity ranging from 3.3 to 192 GBq at activity reference time), the total effective dose would be 0.316 Sv for an adult, which could be associated with first clinical signs of radiation toxicity, such as nausea and fatigue ¹⁸ . There is the potential risk identified of the development of osteosarcoma as ¹⁷⁷ Lu is taken up and accumulated in the bones ² . It is not possible to describe likelihood and effect of ¹⁷⁷ Lu accumulation in bone or liver specifically, as this depends on the labelled compound.
Risk factors and risk groups	Patients.
Preventability	The risk is not completely preventable, but can be reduced if ilLuzyce is only used for the radiolabelling of carrier molecules. Furthermore, it is recommended to add a binding agent such as DTPA prior to intravenous administration of Lutetium (¹⁷⁷ Lu)-labelled conjugates in order to form a complex with free Lutetium (¹⁷⁷ Lu), if present, leading to a rapid renal clearance of Lutetium (¹⁷⁷ Lu) ² .
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 ilLuzyce is a radiopharmaceutical precursor and it is not intended for direct use in patients.
Public health impact	The effect on the quality of life is considered high in the

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	event of the development of osteosarcomas.
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Important Potential Risk 2 – Radiation nephropathy

MedDRA terms	Nephropathy toxic (PT)
Potential mechanisms	Kidneys are usually the critical organs in terms of radiation toxicity due to non-specific or specific accumulation of radiolabelled peptide and renal excretion of radiolabelled peptides. Renal irradiation is mainly caused by reabsorption of radiolabelled peptides in the proximal tubules, causing dose-limiting nephrotoxicity ^{33, 34} .
Evidence source(s) and strength of evidence	It is described in the published literature and the SmPC that radiolabelled peptides are mainly excreted via the kidneys. The kidneys are therefore exposed to radiation due to accumulation of radiolabelled peptide during the excretion process. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using other radioisotopes.
Characterisation of the risk	Radiolabelled peptides are mainly excreted renally. The frequency of radiation nephropathy is not known. Results from different studies are confounded with the use of radioprotective agents such as amino acids or medical history. A study published in 2016 by Ranade and Basu retrospectively investigated the renal toxicity profile of ¹⁷⁷ Lu-DOTATATE PRRT in patients with metastatic NET and a single functioning kidney and showed that 3-5 cycles of ¹⁷⁷ Lu-DOTATATE PRRT can be applied to patients with NET and a single functioning kidney, when administered along with renal protection and dose fractionation ¹⁹ .
Risk factors and risk groups	Identified risk factors for radiation-induced nephropathy are: <ul style="list-style-type: none"> • Hypertension^{33, 35, 36} • Diabetes mellitus^{33, 36} • Age >60 years^{33, 35, 37} • Renal morphological abnormalities³⁸ • Low baseline glomerular filtration rate^{37, 39} • Previous chemotherapy³⁶ • Male gender³⁸ • A higher number of concomitant risk factors³⁵
Preventability	The risk is not completely preventable. Healthcare professionals should be aware of the risk and 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

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	guidance ² . Renal protection could be facilitated by the use of amino acid infusions ²⁹ . This seems to reduce the absorbed radiation dose to the kidney and therefore reduces the risk of radiation nephropathy.
Impact on the risk-benefit balance of the product	Provided that protective measures such as monitoring the renal function and amino acid infusions are taken, the impact on the risk-benefit balance is considered to be moderate.
Public health impact	The severity of the nephrotoxicity cases is expected to be mild and reversible. However, more severe cases could require dialysis and hospitalisation.

Important Potential Risk 3 – Radiation-induced hepatotoxicity

MedDRA terms	Drug-induced liver injury (PT)
Potential mechanisms	<p>In the literature two different types of radiation-induced hepatotoxicity is described: the classic type and the non-classic type. The classic type presents with anicteric hepatomegaly, ascites and elevated liver enzymes, especially alkaline phosphatase 2 weeks to 4 months after radiation. The non-classic type presents with markedly elevated serum transaminases and jaundice^{39, 40}.</p> <p>The mechanism of hepatic injury was classically veno-occlusive disease secondary to fibrosis. The mechanism for non-classic RILD is less well understood but may involve the loss of regenerating hepatocytes and reactivation of hepatitis^{39, 40}.</p>
Evidence source(s) and strength of evidence	It is described in the SmPC that cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with Lutetium (¹⁷⁷ Lu) peptide receptor radionuclide therapy for neuroendocrine tumors.
Characterisation of the risk	The frequency of radiation-induced hepatotoxicity is not known. Classic radiation induced liver disease was historically the dose limiting complication of liver radiation with onset 2 weeks to 4 months post whole hepatic radiation. In the current era of CT (computer tomography) based radiation planning classic radiation induced liver disease is very rare. The non-classic radiation induced liver disease is much more common ³⁹ .
Risk factors and risk groups	The risk factors associated with the classic type radiation-induced hepatotoxicity includes:

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	<ul style="list-style-type: none"> • High mean liver dose • Primary liver cancer • Male gender • Hepatic intra-arterial chemotherapy <p>The risk factors associated with the non-classic type radiation-induced hepatotoxicity is related to underlying liver disease such as hepatitis B or cirrhosis³⁹.</p>
Preventability	The risk is not completely preventable. Healthcare professionals should be aware of the risk and monitor for early symptoms of symptoms of hepatotoxicity. Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients.
Impact on the risk-benefit balance of the product	No significant hepatic toxicity has been reported in patients without or with minor metastatic liver involvement. In patients with massive liver metastases and impaired liver function, liver toxicity may occur and this should be considered when choosing the appropriate radioisotope and dosing. In such cases it is recommended to reduce the administered activity accordingly ²⁹ .
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 the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Osteosarcoma • Radiation nephropathy • Radiation-induced Hepatotoxicity
Missing information	None

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Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

In accordance with Article 8(3)(ia) of Directive 2001/83/EC as amended the Applicant has the services of a Qualified Person Responsible for Pharmacovigilance, an assigned Deputy and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third Country.

Routine pharmacovigilance activities are conducted and processes and systems are in place to ensure that information on all suspected adverse reactions related to ilLuzyce and the active substance Lutetium (¹⁷⁷Lu) chloride n.c.a. that are reported to the company are collected and collated in order to be accessible at least at one point within the EU.

Specific adverse drug reaction follow-up forms will be used to collect data to help further characterize the risks of "Myelodysplastic syndrome/Acute myeloid leukaemia", "Radiation nephropathy" and "Radiation-induced hepatotoxicity". Please refer to Annex 4.

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

No Post-authorisation efficacy studies are planned.

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	<p><u>Routine risk communication:</u></p> <p>Warning about exposure to radioactivity in SmPC section 4.4. and Package Leaflet (PL) section 1.</p> <p>Adverse reactions including induction of certain risk of cancer and development of hereditary effects included in SmPC section 4.8 and PL section 4.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Contains a general warning on radiation protection in SmPC section 4.4.</p> <p>Recommendation to administer the smallest quantity to the patient to achieve the appropriate outcome included in PL section 3.</p> <p>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.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling.
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	<p><u>Routine risk communication:</u></p> <p>Warning concerning haematological side effects and myelosuppression included in SmPC section 4.4 and PL section 2.</p> <p>Anaemia, thrombocytopenia, leukopenia and lymphopenia are</p>

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	<p>listed as adverse reactions in SmPC section 4.8 and PL section 4.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>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.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> • Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> • The symbol "radioactive" is given on the labelling.
Myelodysplastic syndrome/Acute myeloid leukaemia	<p><u>Routine risk communication:</u></p> <p>Warning about MDS and AML in SmPC section 4.4 and PL section 2.</p> <p>MDS is listed as common and AML as uncommon adverse reactions in SmPC section 4.8 and PL section 4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> • Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> • The symbol "radioactive" is given on the labelling.
Osteosarcoma	<p><u>Routine risk communication:</u></p> <p>Warning in SmPC section 12 concerning the uptake and accumulation of free Lutetium ¹⁷⁷Lu in the bones, which could potentially result in osteosarcomas.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation to use a binding agent such as DTPA prior to intravenous administration of ¹⁷⁷Lu labelled conjugates in SmPC section 12.</p>

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	<p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling.
Radiation nephropathy	<p><u>Routine risk communication:</u></p> <p>Warning concerning the excretion of radiolabelled somatostatin analogues by the kidneys in SmPC section 4.4 and PL section 2.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation for assessment of the renal functions at baseline and during treatment in SmPC section 4.4 and PL section 2.</p> <p>Recommendation to consider renal protection in SmPC section 4.4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling.
Radiation-induced hepatotoxicity	<p><u>Routine risk communication:</u></p> <p>Warning about hepatotoxicity in SmPC section 4.4 and PL section 2.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation to monitor the liver function regularly during treatment in SmPC section 4.4 and PL section 2.</p> <p>Recommendation to consider dose reduction in affected patients in SmPC section 4.4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p>

	<p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling.
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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
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	<p><u>Routine risk communication:</u></p> <p>Warning about exposure to radioactivity in SmPC section 4.4. and PL section 1.</p> <p>Adverse reactions including induction of certain risk of cancer and development of hereditary effects included in SmPC section 4.8 and PL section 4.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Contains a general warning on radiation protection in SmPC section 4.4.</p> <p>Recommendation to administer the smallest quantity to the patient to achieve the appropriate outcome included in PL section 3.</p> <p>Contains information about</p>	Routine pharmacovigilance activities.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	<p>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.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <p>The symbol "radioactive" is given on the labelling.</p>	
<p>Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)</p>	<p><u>Routine risk communication:</u></p> <p>Warning concerning haematological side effects and myelosuppression included in SmPC section 4.4 and PL section 2.</p> <p>Anaemia, thrombocytopenia, leukopenia and lymphopenia are listed as adverse reactions in SmPC section 4.8 and PL section 4.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>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.</p> <p><u>Other routine risk minimisation</u></p>	<p>Routine pharmacovigilance activities.</p>

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Safety concern	Risk minimisation measures	Pharmacovigilance activities
	<p><u>measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling. 	
Myelodysplastic syndrome/Acute myeloid leukaemia	<p><u>Routine risk communication:</u></p> <p>Warning about MDS and AML in SmPC section 4.4 and PL section 2.</p> <p>MDS is listed as common and AML as uncommon adverse reactions in SmPC section 4.8 and PL section 4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling. 	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>Targeted follow-up questionnaires for adverse reaction reports of myelodysplastic syndrome / acute myeloid leukaemia.</p>
Osteosarcoma	<p><u>Routine risk communications:</u></p> <p>Warning in SmPC section 12 concerning the uptake and accumulation of free Lutetium ¹⁷⁷Lu in the bones, which could potentially result in osteosarcomas.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to</u></p>	Routine pharmacovigilance activities.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	<p><u>address the risk:</u></p> <p>Recommendation to use a binding agent such as DTPA prior to intravenous administration of ¹⁷⁷Lu labelled conjugates in SmPC section 12.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling. 	
Radiation nephropathy	<p><u>Routine risk communication:</u></p> <p>Warning concerning the excretion of radiolabelled somatostatin analogues by the kidneys in SmPC section 4.4 and PL section 2.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation for assessment of the renal functions at baseline and during treatment in SmPC section 4.4 and PL section 2.</p> <p>Recommendation to consider renal protection in SmPC section 4.4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>Targeted follow-up questionnaires for adverse reaction reports of radiation nephropathy.</p>

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	<p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling. 	
Radiation-induced hepatotoxicity	<p><u>Routine risk communication:</u></p> <p>Warning about hepatotoxicity in SmPC section 4.4 and PL section 2.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation to monitor the liver function regularly during treatment in SmPC section 4.4 and PL section 2.</p> <p>Recommendation to consider dose reduction in affected patients in SmPC section 4.4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling. 	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>Targeted follow-up questionnaires for adverse reaction reports of radiation-induced hepatotoxicity.</p>

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Part VI: Summary of the risk management plan

Summary of risk management plan for ilLuzyce (Lutetium (¹⁷⁷Lu) chloride non carrier added)

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

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

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

I. The medicine and what it is used for

ilLuzyce is a radiolabelling precursor and as such with no direct indication. It is authorised for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with Lutetium (¹⁷⁷Lu) chloride (see SmPC for the full indication). When linked to the appropriate carrier molecule, ilLuzyce can be used in several oncologic indications depending on the carrier molecule.

Further information about the evaluation of ilLuzyce's benefits can be found in ilLuzyce'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 ilLuzyce, together with measures to minimise such risks and the proposed studies for learning more about ilLuzyce'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;

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- 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 ilLuzyce 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 ilLuzyce. 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Osteosarcoma • Radiation nephropathy • Radiation-induced hepatotoxicity
Missing information	None

II.B Summary of important risks

Important identified risk 1 – 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	It is described in in the published literature and the SmPC that lutetium (¹⁷⁷ Lu) has a half-life of 6.7 days and accumulates in various tissues following administration to the patient. It emits ionising radiation to the surroundings including other persons in close vicinity of the patient during the decay of the radionuclide. The danger of radiation is dependent of the distance the patient who has received treatment with a radionuclide.
Risk factors and risk groups	Health care professionals, carers, patients and relatives.

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Risk minimisation measures	<p><u>Routine risk communication:</u></p> <p>Warning about exposure to radioactivity in SmPC section 4.4. and PL section 1.</p> <p>Adverse reactions including induction of certain risk of cancer and development of hereditary effects included in SmPC section 4.8 and PL section 4.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Contains a general warning on radiation protection in SmPC section 4.4.</p> <p>Recommendation to administer the smallest quantity to the patient to achieve the appropriate outcome included in PL section 3.</p> <p>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.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> • Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> • The symbol "radioactive" is given on the labelling.
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Important identified risk 2 - Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	
Evidence for linking the risk to the medicine	It is described in the published literature and the SmPC that myelosuppression may occur during radioligand therapy with Lutetium (¹⁷⁷ Lu). Anaemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with Lutetium (¹⁷⁷ Lu). Most events are mild and transient, but in some cases patients have required blood and platelet transfusions. In some patients more than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described.
Risk factors and risk groups	Patients at risk of developing myelosuppression are patient that has previously been treated with chemotherapy and

	patients with anaemia, poor renal function at baseline and age > 70 years ¹³ .
Risk minimisation measures	<p><u>Routine risk communication:</u></p> <p>Warning concerning haematological side effects and myelosuppression included in SmPC section 4.4 and PL section 2.</p> <p>Anaemia, thrombocytopenia, leukopenia and lymphopenia are listed as adverse reactions in SmPC section 4.8 and PL section 4.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>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.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> • Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> • The symbol "radioactive" is given on the labelling.
Important identified risk 3 – Myelodysplastic syndrome/Acute myeloid leukaemia	
Evidence for linking the risk to the medicine	It is described in the published literature and the SmPC that MDS and AML have been observed after treatment with Lutetium (¹⁷⁷ Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.
Risk factors and risk groups	Patients who have previously received chemotherapy. Other risk factors include ³¹ : Age above 70 years, impaired renal function, baseline cytopenias, prior number of therapies and prior radiation therapy.
Risk minimisation measures	<p><u>Routine risk communication:</u></p> <p>Warning about MDS and AML in SmPC section 4.4 and PL section 2.</p> <p>MDS is listed as common and AML as uncommon adverse reactions in SmPC section 4.8 and PL section 4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p>

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	<p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> The symbol "radioactive" is given on the labelling. <p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>Targeted follow-up questionnaires for adverse reaction reports of myelodysplastic syndrome / acute myeloid leukaemia.</p>
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Important potential risk 1 - Osteosarcoma	
Evidence for linking the risk to the medicine	It is described in the published literature that a large amount of free lutetium (¹⁷⁷ Lu) ions are taken up and accumulated in the bones. This can potentially lead to osteosarcomas. The risk depends on the labelled compound.
Risk factors and risk groups	Patients.
Risk minimisation measures	<p><u>Routine risk communications:</u></p> <p>Warning in SmPC section 12 concerning the uptake and accumulation of free Lutetium ¹⁷⁷Lu in the bones, which could potentially result in osteosarcomas.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation to use a binding agent such as DTPA prior to intravenous administration of ¹⁷⁷Lu labelled conjugates in SmPC section 12.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <p>The symbol "radioactive" is given on the labelling</p>

Important potential risk 2 – Radiation nephropathy	
Evidence for linking the risk to the medicine	It is described in the published literature and the SmPC that radiolabelled peptides are mainly excreted via the kidneys. The kidneys are therefore exposed to radiation due to accumulation of radiolabelled peptide during the excretion process. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using other radioisotopes.
Risk factors and risk groups	<p>Identified risk factors for radiation-induced nephropathy are:</p> <ul style="list-style-type: none"> • Hypertension^{33, 35, 36} • Diabetes mellitus^{33, 36} • Age >60 years^{33, 35, 37} • Renal morphological abnormalities³⁸ • Low baseline glomerular filtration rate^{37, 39} • Previous chemotherapy³⁶ • Male gender³⁸ <p>A higher number of concomitant risk factors³⁵.</p>
Risk minimisation measures	<p><u>Routine risk communication:</u></p> <p>Warning concerning the excretion of radiolabelled somatostatin analogues by the kidneys in SmPC section 4.4 and PL section 2.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation for assessment of the renal functions at baseline and during treatment in SmPC section 4.4 and PL section 2.</p> <p>Recommendation to consider renal protection in SmPC section 4.4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> • Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> • The symbol “radioactive” is given on the labelling. <p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p>

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	Targeted follow-up questionnaires for adverse reaction reports of radiation nephropathy.
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Important potential risk 3 – Radiation induced hepatotoxicity	
Evidence for linking the risk to the medicine	It is described in the SmPC that cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with Lutetium (¹⁷⁷ Lu) peptide receptor radionuclide therapy for neuroendocrine tumors.
Risk factors and risk groups	<p>The risk factors associated with the classic type radiation-induced hepatotoxicity includes:</p> <ul style="list-style-type: none"> • High mean liver dose • Primary liver cancer • Male gender • Hepatic intra-arterial chemotherapy <p>The risk factors associated with the non-classic type radiation-induced hepatotoxicity is related to underlying liver disease such as hepatitis B or cirrhosis⁴².</p>
Risk minimisation measures	<p><u>Routine risk communication:</u></p> <p>Warning about hepatotoxicity in SmPC section 4.4 and PL section 2.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>Recommendation to monitor the liver function regularly during treatment in SmPC section 4.4 and PL section 2.</p> <p>Recommendation to consider dose reduction in affected patients in SmPC section 4.4.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status:</p> <ul style="list-style-type: none"> • Use only by specialists experienced with <i>in vitro</i> radiolabelling <p>Labelling:</p> <ul style="list-style-type: none"> • The symbol "radioactive" is given on the labelling. <p><u>Routine pharmacovigilance activities beyond adverse</u></p>

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	<u>reactions reporting and signal detection:</u> Targeted follow-up questionnaires for adverse reaction reports of radiation-induced hepatotoxicity.
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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 iLLuzyce.

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

There are no studies required for iLLuzyce.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

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Initial receipt date:

Case ID number:

**Targeted follow-up questionnaire
Myelodysplastic syndrome / acute myeloid leukaemia**

In addition to collecting routine information for this adverse event, please provide the following information

1. Did the patient have any of the following signs or symptoms after starting the therapy with the medicinal product?		
<input type="checkbox"/> Tiredness	<input type="checkbox"/> Bleeding	<input type="checkbox"/> Chest pain
<input type="checkbox"/> Shortness of breath	<input type="checkbox"/> Chilled sensation	<input type="checkbox"/> Hepatomegaly
<input type="checkbox"/> Purpura or petechiae	<input type="checkbox"/> Splenomegaly	<input type="checkbox"/> Other, please specify:
<input type="checkbox"/> Increased number of infections	<input type="checkbox"/> Ecchymosis	
Please provide details by symptom, including start/stop date and treatment:		
Did the patient require dialysis?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		
If yes, please provide further details:		
<input type="checkbox"/> Temporary <input type="checkbox"/> Ongoing		
If temporary:	Start date:	/ / (DD/MM/YYYY)
	Stop date:	/ / (DD/MM/YYYY)

2. Risk factors/medical history		
Has there been any previous chemotherapy?		
<input type="checkbox"/> Yes, chemotherapy	<input type="checkbox"/> Yes, radiotherapy	<input type="checkbox"/> 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:

Has there been any previous radionuclide 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 Cytopenia

Exposure to certain chemicals, including tobacco smoke, pesticides, fertilisers, and solvents such as benzene

Exposure to heavy metals, such as mercury or lead

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

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

3. Laboratory results

Laboratory result(s) available: Yes No unknown If yes, please give details below.

Laboratory result(s) report enclosed: <input type="checkbox"/> Yes <input type="checkbox"/> No				
Lab parameter	Test date	Value	Normal range	Interpretation
Blood count red blood cells	/ / (DD/MM/YYYY)			
Blood count platelets	/ / (DD/MM/YYYY)			
Blood count white blood cells	/ / (DD/MM/YYYY)			
Hemoglobin	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Serum creatinine	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Myoglobinuria	/ / (DD/MM/YYYY)			
Proteinuria	/ / (DD/MM/YYYY)			
Hematuria	/ / (DD/MM/YYYY)			

4. Other investigations
<input type="checkbox"/> Bone marrow biopsy <input type="checkbox"/> Bone marrow aspiration
<p>If yes, please specify further investigation of bone marrow and list details in the panel below.</p> <input type="checkbox"/> Cytogenetic analysis <input type="checkbox"/> Immunochemistry <input type="checkbox"/> Immunophenotyping <input type="checkbox"/> Flow cytometry <input type="checkbox"/> FISH (Flouorescence in situ hybridisation)
<input type="checkbox"/> Sonography of the following area: _____
<input type="checkbox"/> Other, please specify:
<p>Please provide details by test, including date and result:</p>

<p>5. Diagnosis</p> <p>Affected myeloid cell lineage</p> <p><input type="checkbox"/> Myeloblasts <input type="checkbox"/> Promyelocytes <input type="checkbox"/> Myelomonocytes <input type="checkbox"/> Monoblasts</p> <p><input type="checkbox"/> Monocytes <input type="checkbox"/> Erythroid <input type="checkbox"/> Megakaryoblasts <input type="checkbox"/> Other (please specify)</p>

<p>6. Treatment</p> <p>Was the myelodysplastic syndrome / acute myeloid leukaemia treated?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If yes, please specify: Medicinal product:</p> <p>Treatment start date: / / (DD/MM/YYYY) Treatment stop date: / / (DD/MM/YYYY)</p>

<p>7. Outcome</p> <p><input type="checkbox"/> Recovered <input type="checkbox"/> Not recovered <input type="checkbox"/> Death <input type="checkbox"/> Unknown</p>

8. Administrative data		
Report date: / / (DD/MM/YYYY)		Number of pages including attachments:
Reporter: Name: <input type="checkbox"/> Health care professional <input type="checkbox"/> Other, please specify:	Address: Phone: E-mail:	Signature:
Please send to: E-mail: -@-.com		

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Initial receipt date:

Case ID number:

**Targeted follow-up questionnaire
Radiation nephropathy**

In addition to collecting routine information for this adverse event, please provide the following information

1. Did the patient have any of the following signs or symptoms after starting the therapy with the medicinal product?		
<input type="checkbox"/> Fever	<input type="checkbox"/> Dehydration	<input type="checkbox"/> Changes in urine colour
<input type="checkbox"/> Changes in urine frequency	<input type="checkbox"/> Changes in urine volume	<input type="checkbox"/> Other, please specify:
<input type="checkbox"/> Changes in urine odour	<input type="checkbox"/> No urination	
Please provide details by symptom, including start/stop date and treatment:		
Did the patient require dialysis?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		
If yes, please provide further details:		
<input type="checkbox"/> Temporary <input type="checkbox"/> Ongoing		
If temporary:	Start date:	/ / (DD/MM/YYYY)
	Stop date:	/ / (DD/MM/YYYY)

2. Risk factors/medical history		
Has there been any previous chemotherapy?		
<input type="checkbox"/> Yes, chemotherapy	<input type="checkbox"/> Yes, radiotherapy	<input type="checkbox"/> 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?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		
If yes, please specify:		

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:

3. Laboratory results

Laboratory result(s) available: Yes No unknown If yes, please give details below.

Laboratory result(s) report enclosed: Yes No

Lab parameter	Test date	Value	Normal range	Interpretation
Hemoglobin	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Serum creatinine	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Myoglobinuria	/ / (DD/MM/YYYY)		-	
Proteinuria	/ / (DD/MM/YYYY)		-	
Hematuria	/ / (DD/MM/YYYY)		-	
Urea	/ / (DD/MM/YYYY)			
Electrolytes	/ / (DD/MM/YYYY)			
Glomerular filtration rate (GFR)	/ / (DD/MM/YYYY)			
Casts	/ / (DD/MM/YYYY)		-	

4. Other investigations

Renal sonography Renal biopsy CT

Other, please specify:

Please provide details by test, including date and result:

5. Treatment	
Was the radiation nephropathy treated?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
If yes, please specify:	
Medicinal product:	
Treatment start date:	/ / (DD/MM/YYYY)
Treatment stop date:	/ / (DD/MM/YYYY)

6. Outcome			
<input type="checkbox"/> Recovered	<input type="checkbox"/> Not recovered	<input type="checkbox"/> Death	<input type="checkbox"/> Unknown

7. Administrative data		
Report date: / / (DD/MM/YYYY)		Number of pages including attachments:
Reporter: Name:	Address:	Signature:
<input type="checkbox"/> Health care professional	Phone:	
<input type="checkbox"/> Other, please specify:	E-mail:	
Please send to: E-mail: -@-.com		

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Initial receipt date:

Case ID number:

**Targeted follow-up questionnaire
Radiation-induced hepatotoxicity**

In addition to collecting routine information for this adverse event, please provide the following information

1. Did the patient have any of the following signs or symptoms after starting the therapy with the medicinal product?		
<input type="checkbox"/> Rash	<input type="checkbox"/> Stomach pain	<input type="checkbox"/> Fatigue
<input type="checkbox"/> Nausea and vomiting	<input type="checkbox"/> Loss of appetite	<input type="checkbox"/> Fever
<input type="checkbox"/> Changes in faeces colour	<input type="checkbox"/> Changes in urine colour	<input type="checkbox"/> Other, please specify:
<input type="checkbox"/> Yellow skin and eyes		
Please provide details by symptom, including start/stop date and treatment:		

2. Risk factors/medical history		
Has there been any previous chemotherapy?		
<input type="checkbox"/> Yes, radionuclide therapy	<input type="checkbox"/> Yes, chemotherapy	<input type="checkbox"/> Yes, radiation therapy
<input type="checkbox"/> 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?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		
If yes, please specify:		

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?
 Acute/chronic liver disease Non-alcoholic fatty liver disease
 Viral hepatitis Alcohol intake

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

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

Has there been any co-administration of hepatotoxic agents prior to or together with the administration of the medicinal product?
 Yes No

If yes, please specify:

3. Laboratory results				
Laboratory result(s) available: <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> unknown If yes, please give details below.				
Laboratory result(s) report enclosed: <input type="checkbox"/> Yes <input type="checkbox"/> No				
Lab parameter	Test date	Value	Normal range	Interpretation
Full blood count	/ / (DD/MM/YYYY)			
Urea and electrolytes	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated

Alkaline phosphatase (ALP)	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Aspartate aminotransferase (AST)	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Alanine transaminase (ALT)	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Gamma-glutamyl transferase (GGT)	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
International Normalised Ratio (INR)	/ / (DD/MM/YYYY)			<input type="checkbox"/> Normal <input type="checkbox"/> Elevated
Viral markers (Hepatitis A, B, C)	/ / (DD/MM/YYYY)			
Antinuclear antibodies (ANA)	/ / (DD/MM/YYYY)			
Smooth muscle antibodies (SMA)	/ / (DD/MM/YYYY)			
Antimitochondrial antibodies (AMA)	/ / (DD/MM/YYYY)			
Serum protein	/ / (DD/MM/YYYY)			

4. Other investigations
<input type="checkbox"/> Imaging results <input type="checkbox"/> Liver biopsy <input type="checkbox"/> Other, please specify:
Please provide details by test, including date and result:

5. Treatment
Was the radiation-induced hepatotoxicity treated? <input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, please specify: Medicinal product:

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Treatment start date:	/ /	(DD/MM/YYYY)
Treatment stop date:	/ /	(DD/MM/YYYY)

6. Outcome			
<input type="checkbox"/> Recovered	<input type="checkbox"/> Not recovered	<input type="checkbox"/> Death	<input type="checkbox"/> Unknown

7. Administrative data		
Report date: / / (DD/MM/YYYY)		Number of pages including attachments:
Reporter: Name:	Address:	Signature:
<input type="checkbox"/> Health care professional	Phone:	
<input type="checkbox"/> Other, please specify:	E-mail:	
Please send to: E-mail: -@-.com		

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

Not applicable.