EU Risk Management Plan for Theralugand (lutetium (^{177}Lu) chloride)

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QPPV name: Dr. Iryna Bulyha

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

List of Abbreviations

^{176}Yb	Ytterbium-176
^{177}Hf	Hafnium-177
^{177}Lu	Lutetium-177
^{177}Yb	Ytterbium-177
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Bq	Becquerel
Ca^{2+}	Calcium
CHMP	Committee for Medicinal Products for Human Use
Ci	Curie
DDN	Dendrin
DLP	Data lock point
DNA	Deoxyribonucleic acid
DOTA	1,4,7,10-tetraazacyclododecane-N,N`,N",N"`-tetraacetic acid
DOTATATE	DOTA-D-Phe^1-Tyr^3-Thr^8-octreotate
DTPA	Diethylenetriamine pentaacetate
eCTD	Electronic Common Technical Document
ED_{50}	Median Effective Doses
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
eV	Electronvolt
GABA	γ-aminobutyric acid
GEP	Gastroenteropancreatic
GFR	Glomerular filtration rate
Gy	Gray

HED	Human estimated dose
ICRP	International Commission on Radiological Protection
ICSR	Individual case safety report
IM	Intramuscular
INN	International Nonproprietary Name
IP	Intraperitoneal
IV	Intravenous
$KHSO_4$	Potassium hydrogen sulfate
LD_{50}	Median lethal dose
MAH	Marketing authorisation holder
mCRPC	Metastatic castration-resistant prostate cancer
MDS	Myelodysplastic syndrome
NCA	Non-carrier added
NET	Neuroendocrine tumour
PD	Pharmacodynamics
PK	Pharmacokinetics
PSMA	Prostate-specific membrane antigen
PSUR	Periodic Safety Update Report
RILD	Radiation-induced liver disease
RMP	Risk management plan
SAEs	Serious adverse events
SmPC	Summary of product characteristics
SSR	Somatostatin receptor
Sv	Sievert

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Lutetium (^{177}Lu) chloride
Pharmacotherapeutic group(s) (ATC Code)	Other therapeutic radiopharmaceuticals (V10X)
Marketing Authorisation Holder	Eckert & Ziegler Radiopharma GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Theralugand 40 GBq/ml radiopharmaceutical precursor, solution
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Theralugand 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.
	Summary of mode of action: Lutetium (^{177}Lu) is a radioactive lutetium isotope that emits β-particles of moderate maximum energy (0.498 MeV) upon decay to stable Hafnium (^{177}Hf), with a maximum tissue penetration of approximately 2 mm. Lutetium (^{177}Lu) also emits low-energy gamma-rays which allow scintigraphic, biodistribution and dosimetry studies with the same lutetium (^{177}Lu)-labelled medicinal products.
	Important information about its composition: Lutetium (^{177}Lu) is non-carrier added (n.c.a.) and is produced through the radioactive decay of its mother nuclide ytterbium (^{177}Yb) obtained by irradiation of highly enriched (>99%) ytterbium (^{176}Yb). Lutetium (^{177}Lu) is chemically separated from the irradiated target material via a chromatographic process.
eCTD link to the Product Information	The proposed summary of product characteristics is included within Module 1.3.1 of the initial marketing authorisation application.
Indication(s) in the EEA Current	Theralugand 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.

Dosage in the EEA Current	The quantity of Theralugand required for radiolabelling and the quantity of lutetium (^{177}Lu)-labelled medicinal product that is subsequently administered will depend on the medicinal product to be radiolabelled and its intended use.
Pharmaceutical form(s) and strengths	Radiopharmaceutical precursor, solution; 40 GBq/ml
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: radiolabelling of carrier molecules, developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride

Incidence: Not applicable as lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and thus only incidence of the indications for the radiolabelled medicinal products are relevant. Lutetium (^{177}Lu)-radiolabelled compounds are currently used or investigated in the treatment of neuroendocrine tumours (NETs), non-Hodgkin's lymphoma, brain tumours, small cell lung carcinoma, head, and neck squamous cell carcinoma as well as colorectal, prostate, renal and breast cancers.

Prevalence: Not applicable as lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and thus only prevalence of the indications for the radiolabelled medicinal products are relevant.

Demographics of the population in the authorised age, gender, racial and/or ethnic origin and risk factors for the disease: Not applicable as lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patients. Relevant population will be determined by the radiolabelled medicinal product.

The main existing treatment options: Not applicable as lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patients. Available treatment options will be determined by the radiolabelled medicinal product.

Natural history of the indicated condition in the population, including mortality and morbidity: Not applicable as lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor. Only radiolabelled medicinal products will have characterizable indications with regard to the population. To date, there are two lutetium (^{177}Lu)-radiolabelled agents authorised in the EU/EEA, ^{177}Lu oxodotretotide or ^{177}Lu-DOTATATE (Lutathera), approved for the treatment of gastroenteropancreatic NETs (GEP-NETs) in September 2017, and ^{177}Lu vipivotide tetraxetan or ^{177}Lu-PSMA-617 (Pluvicto), approved for the treatment of prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) in December 2022. Promising therapeutic efficiency of lutetium (^{177}Lu)-based targeted radiotherapies and ongoing discovery of new tumour-specific molecular targets rapidly propel the increasing importance of lutetium (^{177}Lu) for the treatment of various oncological conditions. At the data lock point (DLP) of this RMP, 122 clinical trials with lutetium (^{177}Lu)-radiolabelled agents were either completed, actively recruiting or about to start according to *ClinicalTrials.gov*. As per the final report of co-ordinated approach to the development and supply of radioisotopes in the EU (N°ENER/D3/2019-23), the number of the conditions for which lutetium (^{177}Lu)-radiolabelled agents are being tested and used is constantly growing, so that a dramatic increase in the demand of pharmaceutical-grade lutetium (^{177}Lu) is expected in the future. However, so far its availability is limited by several factors such as small number of manufactures capable of producing pharmaceutical radionuclides, complex manufacturing process and scarcity of raw materials [1, 2].

Important co-morbidities:

Not applicable as lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patients.

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

Key Safety findings (from non- clinical studies)	Relevance to human usage
Single and repeat-dose toxicity: As per Annex 1 of Dir 2001/83/EC, as amended, in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes, no toxicity studies were conducted by the applicant. Published single-dose and repeat-dose toxicity studies were conducted with different salts of nonradioactive lutetium in mice and rats. **Single-dose toxicity studies** *Mice:* Two acute toxicity studies conducted in mice reported averaged intraperitoneal (IP) LD_{50} of 290 mg/kg (lutetium nitrate) and 315 mg/kg (lutetium chloride), and an oral LD_{50} of 7100 mg/kg (lutetium chloride). A hafnium acute toxicity study conducted in mice reported an intraperitoneal LD_{50} of 112 mg/kg. *Rats:* An acute toxicity study conducted in rats reported an IP LD_{50} of 335 mg/kg for lutetium nitrate and a tolerated IP dose of 1000 mg/kg for lutetium oxide. Intravenous (IV) and oral LD_{50} after single dosing were estimated only for nitrate salts of other lanthanides, incl. ytterbium, and were in the range of above 30 mg/kg for IV administration, and above 3000 mg/kg for oral administration. Necrosis at the injection site, zenobiotic granuloma in the spleen and death was reported following intravenous 50 mg/kg injection of lanthanides. **Repeat-dose toxicity studies** *Rats:* Three chronic toxicity studies were identified. A single chronic toxicity study reported no effect on growth rates, blood cell counts or internal organs following the addition of 0.01, 0.1, or 1% of nonradioactive lutetium chloride into the diet over a period of 90 days. A similar study, investigating the chronic toxicity of adding 0.01, 0.1, or 1% hafnium chloride to the diet over a period of 12 weeks reported no significant effects on body weights, haematology or internal organs, except for liver changes (perinuclear vacuolisation of the parenchymal cells) apparent in some of the animals.	Toxicity studies published in literature revealed no safety concerns for the use of lutetium (^{177}Lu) chloride due to the metallic toxicity of the lutetium itself, or of its decay product hafnium. Acute and chronic toxicity findings for both lutetium and hafnium occurred only at human equivalent doses (HED) of 129 mg/kg when administered orally, thus exceeding by several orders of magnitude their maximum possible amounts in humans for intended lutetium (^{177}Lu) chloride applications. The same HED and conclusions apply to ytterbium. Based on the current available non-clinical data, there is no concern relevant to human usage.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Another study investigated toxicity of hafnium sodium mandelate following its daily administration via a stomach tube at 5-25 mg, and as subcutaneous/intramuscular injection at 10-35 mg. Oral administration caused no detectable accumulation of hafnium in organs and no lesions except aspiration pneumonitis, which however was not attributed to hafnium. Subcutaneously dosed animals showed no systemic toxicity but failed to gain weight when compared to controls. Furthermore, abscesses at the sites of injection were observed, with the rapidity of development and size of the formations being proportional to administered dose.	
Reproductive/Developmental toxicity No fertility and embryofoetal development studies have been conducted by the applicant as they are not required for ^{177}Lu chloride as per Annex 1 of Dir 2001/83/EC and the Committee for Medicinal Products for Human Use (CHMP) draft guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018).	Beta and gamma radiation cause deoxyribonucleic acid (DNA) damage and damage male and female germ cells and a developing foetus.
Genotoxicity: No genotoxicity/mutagenicity studies with lutetium (^{177}Lu) chloride have been conducted by the applicant as they are not required for ^{177}Lu chloride as per as per Annex 1 of Dir 2001/83/EC and the CHMP draft guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018).	Beta and gamma radiation cause DNA damage and are inherently genotoxic.
Carcinogenicity: No carcinogenicity studies with lutetium (^{177}Lu) chloride have been conducted by the applicant as they are not required for ^{177}Lu chloride as per Annex 1 of Dir 2001/83/EC and the CHMP draft guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018). A non-clinical study derived from literature investigating the organ distribution of lutetium (^{177}Lu) chloride following IP injection in mice reported an increased incidence of osteosarcomas observed in animals that received 2000-8000 rad overall absorbed radiation dose at 12 months post-injection.	The osteosarcomogenic effect of lutetium (^{177}Lu) is a serious potential safety concern for clinical use of lutetium (^{177}Lu) chloride, in particular in case of inadvertent direct injection of lutetium (^{177}Lu) chloride.

Key Safety findings (from non- clinical studies)	Relevance to human usage
The late effects of lutetium (^{177}Lu) chloride investigated in a follow-up study by the same group revealed osteosarcomogenic activity. Five groups, each including approximately 50 mice, were exposed to ^{177}Lu chloride at a range of activities from 185 MBq/kg to 1480 MBq/kg (resulting in skeletal radiation doses ranging from 28 to 224 Gy). A total of 50 incidences of osteosarcoma were detected across the five experimental groups, with an activity-dependent threefold increase in the incidence of osteosarcoma from 12.5% for the 185 MBq/kg group to 35.3% and 37.5% for the 370 MBq/kg group and the 740 MBq/kg group respectively. No osteosarcomas were observed in the control group.	
Safety pharmacology: Since lutetium (^{177}Lu) chloride solution is not intended to be administered directly to the patient, no safety pharmacology testing was carried out by Eckert & Ziegler Radiopharma GmbH. However, some potentially relevant pharmacological findings have been derived from literature for lutetium and hafnium. *Lutetium:* Published *in vitro* studies with rat neurons suggest a potentiating influence of nonradioactive lutetium on GABA-induced membrane current, however, it remains unclear whether these effects are reproducible *in vivo* and if they could have any clinical implications. A study investigated the effects of lutetium on cardiovascular and respiratory systems after intravenous administration of 1-40 mg/kg lutetium chloride to ten cats. No effects were observed at 1-10 mg/kg doses. Complete cardiovascular collapse, coupled with respiratory paralysis, was produced by 20 mg/kg dose in five animals, and by 40 mg/kg dose in another five animals. The effects of lutetium on cardiovascular system could not be modified by atropinisation and the collapse could not be counteracted by epinephrine.	Safety-relevant observations for lutetium and hafnium were made in rats and cats only at doses exceeding by several orders of magnitude the maximum possible amounts of these elements that would arise from lutetium (^{177}Lu) chloride applications in clinical setting. Based on the current available non-clinical data, there is no concern relevant to human usage.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Hafnium: A pharmacological study of hafnium chloride conducted in cats resulted in transient hypotension in carotid and femoral blood pressure at a 5 mg/kg IV dose. A respiratory paralysis with complete cardiovascular collapse that could not be counteracted by epinephrine was observed at 10 mg/kg.	
Radiation effects: Three dosimetry studies investigating the distribution of ^{177}Lu in mice following IP administration, as well as three dosimetry studies investigating the distribution of nonradioactive lutetium and of ^{177}Lu in rats following IV and IM administration, were identified in the published literature. *Mice:* One study reported significant accumulation of ^{177}Lu in the liver and spleen 28 hours after administration of ^{177}Lu chloride to Ehrlich's tumour-bearing DDN mice. After 48 hours, ^{177}Lu uptake in liver and spleen decreased, while an increase was detected in bone, kidney and tumour tissue. Another study revealed that approximately 50% of the total radioactivity accumulated in the skeleton after IP injection of up to 60 mCi/kg of a ^{177}Lu preparation containing stable carrier. Only approximately 1 – 5% of the injected activity accumulated in the liver and kidney, and only 0.1- 0.2% in the spleen and lungs. A further report by the same working group described deposition of 60% of the administered ^{177}Lu activity in the skeleton of mice 48 hours post-injection. The radiation burden in the skeleton then gradually decreased over a 14-day observation period. *Rats:* Lutetium (^{177}Lu) deposition was reported in tumour tissue (Yoshida sarcoma), blood, liver, spleen, kidneys, and muscle 3 – 48 hours after IV administration of ^{177}Lu citrate. Lutetium (^{177}Lu) deposition in bone was not assessed in this study.	The studies in mice and rats identified in the published literature report accumulation of ^{177}Lu (and nonradioactive lutetium) in the liver, bones, spleen and kidney. Similar results were obtained in the biodistribution/dosimetry study conducted by the applicant in rats (EZ-Lu177). The absorbed doses estimated based on the dosimetry data of EZ-Lu177 for inadvertently administered free ^{177}Lu fall far below the critical doses for liver, kidney and spleen [3]. However, the estimated bone marrow doses of 3.54 Gy in females and 2.15 Gy in males exceed the recommended for this tissue limit of 2 Gy, and therefore bone marrow toxicity is considered the most prominent safety concern upon inadvertent direct injection lutetium (^{177}Lu) chloride [4].

Key Safety findings (from non- clinical studies)	Relevance to human usage
Accumulation of nonradioactive lutetium in bones, liver, spleen, and, to a lesser degree, in kidneys and lungs, were detected in a study with rats receiving IV injection of lutetium chloride. The blood cells vs. serum distribution was measured at 2-hours post-injection revealing significantly higher proportion of lutetium in serum than in blood cells. A comprehensive study investigated the distribution of radioactivity following IM injection of lutetium (^{177}Lu) at doses of 7.3 to 29 µCi, with 0.5-1.9 µg stable carrier. Over 60% of lutetium (^{177}Lu) were deposited in the skeleton, whilst the liver was a second deposition site, containing < 5% of the injected activity. Blood contained less than 0.02% injected activity per mL at 1-day post-injection, with undetectable levels thereafter. Muscle concentration was similar to the levels in blood but declined at a slower rate. Compared to blood, 10-fold higher levels of ^{177}Lu were found in the gastrointestinal tract and 3-4-fold higher levels in skin samples. Kidneys accumulated only about 0.9% activity dose/g. The applicant conducted a study (EZ-Lu177) investigating the biodistribution of 30 MBq of lutetium (^{177}Lu) chloride injected via IV to male and female rats. The results of this study were extrapolated to provide estimates for Theralugand distribution and dosimetry in humans. The effective dose coefficients determined based on the obtained animal data in line with International Commission on Radiological Protection (ICRP) 60 provisions are 0.143 mSv/MBq and 0.304 mSv/MBq for male and female adult patients, respectively. With ICRP 103 provisions applied, the sex-averaged adult effective dose coefficient is 0.19 mSv/MBq. The estimated absorbed dose coefficients in adult female patients were the greatest for spleen (2.61 mGy/MBq), liver (2.28 mGy/MBq), bone marrow (0.48 mGy/MBq), kidneys (0.28 mGy/MBq), and bone surface (endosteum) (0.26 mGy/MBq). Similarly, for male patients, the estimated absorbed doses were greatest for the liver (1.06 mGy/MBq), spleen (0.91 mGy/MBq), bone marrow and kidneys (0.29 mGy/MBq, each), and bone surface (0.17 mGy/MBq).	

Key Safety findings (from non- clinical studies)	Relevance to human usage
Consequently, in case of an accidental direct IV injection of 7.4 GBq, the activity usually applied for a single treatment cycle with most commonly used 177Lu-labelled radiopharmaceuticals, organ doses of 19.31 Gy, 16.87 Gy, 3.54 Gy, 2.04 Gy, and 1.95 Gy would be reached for spleen, liver, bone marrow, kidneys, and bone surface in female patients, respectively. In men, these values would be lower, at 6.73 Gy (spleen), 7.84 Gy (liver), 2.15 Gy (bone marrow and kidneys, each), and 1.26 Gy (bone surface), respectively.	
Local tolerance: Ocular irritation and skin tolerance to nonradioactive lutetium chloride was investigated in guinea pigs (skin tolerance) and rabbits (ocular and skin tolerance). **Guinea pigs** Dilutions of 1:10, 1:100 and 1:1000 nonradioactive lutetium chloride were intradermally administered to three guinea pigs. Necrosis was observed within one (1) hour, with the highest irritation index of eight at 1:10 dilution, persisting for seven days. Complete healing was not observed within 5-week observation period. For higher dilutions up to $1:10^6$, an irritation index of 2 was observed, with healing accompanied by nodule formation within 46 days. Dissection of the nodules revealed crystalline deposits, hypothesised to be due to a reaction between lutetium and tissue phosphate. **Rabbits** Ocular irritation in rabbits following instillation of nonradioactive lutetium chloride resulted in swelling and profuse discharge one hour after administration, however no effects on the cornea were detected. Following skin exposure to 0.5 g crystalline lutetium chloride, no effects on intact skin were observed, whereas abraded skin areas developed high irritation (irritation index value: 8) but healed with scar formation in 35 days.	Based on the data derived from published local tolerance studies, there are no observations with clinical relevance for human usage of lutetium (^{177}Lu) chloride.

Other toxicity studies: ***Ex vivo*** In a series of studies, the effects of nonradioactive lutetium chloride on the preparation of isolated rabbit ileum in the presence of acetylcholine (2.5 µg) or nicotine (0.5 µg) were assessed. In the dosage range of 10 to 40 mg, an increase in depression of intestinal tonus and contractility of the ileum resulting in a non-reversible paralysis was induced. This effect counteracted the spasmogenic effect of acetylcholine and nicotine. The antispasmodic median effective doses (ED_{50}) were 0.6 mg/ml and 0.5 mg/ml, respectively. **Hepatotoxicity** A study investigated the hepatotoxicity of IV administered nonradioactive lutetium chloride in rats. Animals received 10 mg/kg lutetium chloride and were sacrificed on day 1 and day 3 with blood and liver extraction. The examinations did not reveal any statistically significant changes in hepatic lipids, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, as well as in serum bilirubin and total bile acids concentrations. **Nephrotoxicity** Toxicity studies with free lutetium (^{177}Lu) in mice and rats report no adverse effects to kidneys, however numerous articles describing renal damage in rats with one of the most commonly used ^{177}Lu-labelled radiopharmaceutical, ^{177}Lu-DOTATATE, were identified. The administration of 555 MBq ^{177}Lu-DOTATATE IV dose resulted in severe damage of tubular function in rats, with changes in proximal and distal tubules, while no changes occurred in the glomeruli. These effects were accompanied by proteinuria and increased serum creatinine levels compared to control. In 278 MBq group, while not as many tubules were damaged and less severe increase in creatinine levels was noticed, histological findings did not differ at a statistically significant level from 555 MBq group. At kidney cortex level, these doses would correspond to 46 and 92 Gy absorbed doses, respectively. Importantly, 23 Gy kidney dose is recommended for patient treatment based on external beam radiotherapy experience [4].	Non-clinical *ex vivo* data does not contain any findings with clinical relevance for human usage of lutetium (^{177}Lu) chloride. No clinically-relevant hepato-toxicities were reported in the available non-clinical data on lutetium (^{177}Lu) chloride. However, cases of hepatotoxicity were reported in some of the clinical studies with ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 (see Part II: Module SIII – Clinical trial exposure) and, therefore, radiation-induced hepatotoxicity is considered a safety concern for lutetium (^{177}Lu) chloride. Whilst no occurrence of nephrotoxicity with free ^{177}Lu were identified in the non-clinical data, significant evidence for the nephrotoxicity of the ^{177}Lu-radiolabelled agent ^{177}Lu-DOTA-TATE highlights nephrotoxicity as an important risk in human usage at least for some of the radiolabelled with lutetium (^{177}Lu) radiopharmaceuticals. Furthermore, radiation-induced nephropathy has been reported in multiple clinical studies with ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 (see Part II: Module SIII – Clinical trial exposure), and, therefore, radiation-induced nephropathy is included as a safety concern for lutetium (^{177}Lu) chloride.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Studies in mice confirmed that renal damage occurred at a certain absorbed dose threshold and was dose dependent. Doses of 0.26, 2.4, and 8.2 MBq of ^{177}Lu-DOTATATE corresponding to 0.3, 3, and 10 Gy absorbed doses, respectively, induced minor morphological changes in kidney cortex after 140 days post-injection. Administration of 90, 120, and 150 MBq of ^{177}Lu-DOTATATE, corresponding to 35, 47, and 58 Gy absorbed doses, respectively, however caused long-term renal toxicity with the most pronounced histological changes in the cortex at 58 Gy. Studies in rats report that addition of protective agents such as lysine and amifostine prevent or decrease ^{177}Lu-DOTATATE-induced kidney damage as judged by reduced proteinuria and normalised creatinine levels.	

Note: for all non-clinical references refer to CTD module 2.4.

Part II: Module SIII – Clinical trial exposure

For all clinical studies described below refer to the CTD module 2.5.

Lutetium (^{177}Lu) chloride is not directly administered to patients, and therefore no clinical studies can be carried out with this product itself. However clinical studies with the two most commonly used and well established in the clinical practice ^{177}Lu-labelled agents, ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617, were identified in the published literature. ^{177}Lu-DOTATATE is used for the treatment of somatostatin receptor (SSR)-positive NETs, whereas ^{177}Lu-PSMA-617 is applied for the treatment of metastatic castration-resistant prostate cancer (mCRPC).

^{177}Lu-DOTATATE:

In addition to numerous, supportive, retrospective safety-relevant studies, the safety evaluation of ^{177}Lu-DOTATATE therapy for treatment of SSTR-positive NETs is predominantly based on two prospective clinical trials.

An open-label, randomised, comparator-controlled Phase III trial (NETTER-1), investigating the safety of ^{177}Lu-DOTATATE in 231 patients with advanced, inoperable, well-differentiated SSTR-positive midgut NETs, reported the onset of grade 3 or worse treatment-related serious adverse events (SAEs) in 6% (n=7) of patients in the ^{177}Lu-DOTATATE group. In total, 87% (n=200) of patients entered long-term follow-up, including 86% (n=101) of 117 patients in the ^{177}Lu-DOTATATE group and 87% (n=99) of 114 patients in the control group. The incidence of treatment-related SAEs in the ^{177}Lu-DOTATATE group was low during long-term follow-up, occurring in 3% (n=3) of 101 patients. One (1) patient died from myelodysplastic syndrome (MDS) (grade 5), one (1) patient had grade 3 respiratory tract infection and grade 3 refractory cytopenia with multilineage dysplasia, which led to study discontinuation; one (1) patient had grade 2 breast cancer. At the time of the final analysis, 142 patients had died: 73 (62%) of 117 patients in the ^{177}Lu-DOTATATE group and 69 (61%) of 114 patients in the control group. Death due to disease progression was the leading cause of death in both groups.

Two (2%) ^{177}Lu-DOTATATE treated patients developed MDS. One (1) of these patients developed refractory cytopenia with unilineage dysplasia, confirmed as MDS, which occurred about 14 months after receiving the first of four doses of ^{177}Lu-DOTATATE. This patient died 33 months after randomisation because of MDS, which was the only reported ^{177}Lu-DOTATATE treatment-related death. The other patient developed refractory cytopenia with multilineage dysplasia, occurring about 8 months after receiving the first of three doses of ^{177}Lu-DOTATATE.

Nephrotoxicity of grade 3 or worse, regardless of causality, was reported in six (5.4%) of 111 patients in the ^{177}Lu-DOTATATE group and four (3.6%) of 112 patients in the control group. Only one (1%) of 111 patients in the ^{177}Lu-DOTATATE group had grade 3 increased serum creatinine. Creatinine clearance over time was analysed in both study groups to clinically evaluate long-term renal function. Mean change from baseline in creatinine clearance over time was similar for both.

In total, 201 patients (95% of patients in the ^{177}Lu-DOTATATE group and 86% of patients in the control group) had at least one (1) adverse event (AE) during the trial, of which 95 patients (86%) in the ^{177}Lu-DOTATATE group and 34 patients (31%) in the control group reported AEs that were considered related to trial treatment by the investigator. The rates of grade 3/4 AEs were similar in the two groups; however, transient grade 3/4 neutropenia, thrombocytopenia, and lymphopenia were reported in 1%, 2%, and 9% of patients, respectively, in the ^{177}Lu-DOTATATE group versus no patients in the control group.

A single-arm Phase II trial (ILUMINET) evaluating safety and efficacy of individualised, dosimetry-based ^{177}Lu-DOTATATE treatment in 96 patients (42 female, 54 male) with NETs reported rather mild toxicity with few grade 3/4 AEs. The most common clinical events were grade 1/2 fatigue, nausea, pain, diarrhoea, abdominal pain, flushing, and alopecia. Haematological AEs were common, with grade 1/2 anaemia and thrombocytopenia occurring in more than half of the patients. Grade 3/4 laboratory findings were observed in 1-9% of patients, including haematological AEs and liver enzyme increase. Overall, grade 3/4 toxicity occurred in <10% of patients and was mostly haematological, with no grade 3/4 renal toxicity.

Regarding late AEs, the only clinical AE occurring in >5% of the patients and persisting 12 months after treatment was grade 1 fatigue. There was also one grade 3/4 clinical AE, a thromboembolic event. The only persisting laboratory findings were grade 1/2 haematological AEs, whereas all grade 3/4 laboratory findings occurred in <5% of the patients at 12 months.

During follow-up, two patients were diagnosed with acute myeloid leukaemia 2 and 4 years after the first cycle of ^{177}Lu-DOTATATE.

Plasma creatinine levels increased over time, leading to an increase in the frequency of grade 1 toxicity. Less patients had a glomerular filtration rate (GFR) >60 after treatment compared with baseline. There was one case of grade 3 toxicity related to intercurrent nephrolithiasis. There was one case of grade 2 renal toxicity and no grade 3/4 events.

^{177}Lu-PSMA-617:

The safety evaluation of ^{177}Lu-PSMA-617 therapy for treatment of mCRPCS is predominantly based on five prospective clinical trials.

An open-label, randomised, Phase III trial (VISION) evaluating the clinical safety profile of ^{177}Lu-PSMA-617 in 831 patients who previously had mCRPC treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regimens reported a higher incidence of AEs of grade 3 or above in the ^{177}Lu-PSMA-617 group compared to the control group (52.7% vs. 38.0%). Fatigue (n=228), dry mouth (n=205), and nausea (n=187) were the most common AEs in the ^{177}Lu-PSMA-617 group. The incidence of SAEs was 31.9% in the ^{177}Lu-PSMA-617 group and 25.4% in the control group. Drug-related SAEs were reported in 8.1% of patients in the ^{177}Lu-PSMA-617 group and in 2.4% in the control group. Grade 5 treatment-related AEs occurred in five (5; 0.9%) patients in the ^{177}Lu-PSMA-617 group, including pancytopenia (n=2), bone marrow failure (n=1). subdural haematoma (n=1) and intracranial haemorrhage (n=1), whilst none occurred in the control group.

A single-arm, single-centre, randomised, phase II trial (TheraP) comparing ^{177}Lu-PSMA-617 with cabazitaxel for treatment of mCRPC in 200 male patients reported grade 3/4 AEs in 32 (33%) of 98 men in the ^{177}Lu-PSMA-617 group versus 45 (53%) of 85 men in the cabazitaxel group. Grade 3/4 thrombocytopenia was more common with ^{177}Lu-PSMA-617 than with cabazitaxel (11% vs 0%), and grade 3/4 neutropenia was less common with ^{177}Lu-PSMA-617 (4% vs 13%), with no episodes of febrile neutropenia (0% vs 8%). Study treatment was discontinued because of toxicity in one man (1%) in the ^{177}Lu-PSMA-617 group. No deaths were attributed to study treatment.

A prospective, multicenter, randomised phase II trial (RESIST-PC) investigating the efficacy profile of two (2) activity doses (6 GBq vs 7.4 GBq) of ^{177}Lu-PSMA therapy in 64 patients with progressive mCRPC reported the following most common treatment-emergent AEs of any grade in the 6.0 GBq arm, the 7.4 GBq arm, and overall: dry mouth (47.8%; 63.4%; 57.8%, respectively), fatigue (56.5%; 51.2%; 53.1%, respectively), nausea (52.2%; 43.9%; 46.9%, respectively), and diarrhoea (13.0%; 31.7%; 25.0%, respectively). Serious treatment-emergent AEs were reported for five (5; 7.8%) patients overall, including one (1) subdural haematoma grade 4, one (1) anaemia grade 3, one (1) thrombocytopenia grade 4, one (1) gastrointestinal haemorrhage grade 3, and one (1) acute kidney injury grade 3, however all were considered as possibly but not probably or definitely related to treatment. No trend to creatinine increases or any abnormal changes in haematologic parameters were noted.

A prospective, single-arm, single-institutional study evaluating the efficacy and safety of ^{177}Lu-PSMA-617 radioligand therapy in 90 patients with mCRPC reported transient grade 1/2 fatigue in 26 patients (28.8%) and nausea in 23 patients (25.5%). Other transient toxicities included diarrhoea in six patients (6.6%), dry mouth in nine patients (11%). Only two patients reported grade 3 anaemia, and one (1) patient experienced grade 3 thrombocytopenia. A significant decrease was observed in the haemoglobin levels post radioligand therapy, but the mean level was in normal limits. No grade 3/4 leukopenia, hepatotoxicity or nephrotoxicity were observed in the patients.

A study evaluating the long-term outcomes of radioligand therapy with ^{177}Lu-PSMA-617 in 121 heavily pre-treated mCRPC patients reported transient grade 1/2 toxicities which included fatigue (34.7%), nausea (33%), dry mouth (24.7%) and diarrhoea (14%). Grade 3 anaemia was noted in 3 patients. Regarding nephrotoxicity, 2 patients with grade 1 at the baseline marginally increased to grade 2, but no higher-grade renal toxicity was observed. This study confirmed that ^{177}Lu-PSMA-617 RLT is associated with low treatment-related toxicities, even after a long evaluation period.

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

As lutetium (^{177}Lu) chloride is not administered to patient directly, the European Medicines Agency (EMA) has waived the obligation to submit the results of the studies with ^{117}Lu chloride in all subsets of the paediatric population on grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. The use of Theralugand in case of established/suspected pregnancy, or when pregnancy has not been excluded, is contraindicated for the product.

Part II: Module SV - Post-authorisation experience

The section is not applicable as Theralugand is not registered as a medicinal product in any country worldwide.

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

As the distribution of this radioactive medicinal product is strictly regulated and it may be purchased only by the authorised medical facilities, where it is also handled exclusively by trained and duly authorised personnel, and as it is not psychologically or physically addictive, there is no feasible risk of misuse for recreational and/or illegal purposes.

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

Reproductive toxicity

Reasons for omission from the list of safety concerns:

Lutetium (^{177}Lu) chloride is a genotoxic drug by virtue of its radioactivity. Additionally, the use of the product is contraindicated in incidences of established/suspected pregnancy. This risk requires no further characterisation. Any reports of reproductive toxicity are followed up via routine pharmacovigilance, i.e., through signal detection and adverse reaction reporting. Moreover, the product information of Theralugand contains appropriate messages intended to minimise the risk.

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

Important Identified Risks:

1) **Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient**

Risk-benefit impact:

Unintended exposure to radiation of health care personnel (occupational exposure) and of other persons in the close vicinity of the patient (e.g., family members) is categorised as an important identified risk predominantly due to its inherent reproductive and carcinogenic toxicity. Lutetium (^{177}Lu) chloride is not intended to be directly administered to patients and is to be used only for the radiolabelling of specifically developed therefor carrier molecules. The amount of radioactivity administered to patients will depend on the carrier molecule to be radiolabelled and its indicated use. Moreover, the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the carrier molecule to be radiolabelled will affect the distribution and elimination of the radioactivity. Thus, the levels of radiation emission, the incidence and severity of this important identified risk, as well as its impact on the risk-benefit balance of Theralugand largely depend on the characteristics of medicinal product utilising radiolabelling with lutetium (^{177}Lu).

The unintended radiation exposure of health care personnel and patient's social environment from the currently highest single radiation dose (7.4 GBq) recommended for lutetium (^{177}Lu)-labelled radiopharmaceuticals is deemed to be acceptable based on the limits defined by the ICRP. In particular, it is estimated that nuclear medicine staff should be able to work 300 hours/year with patients receiving lutetium (^{177}Lu)-labelled radiopharmaceuticals without exceeding the recommended annual exposure limit. Nevertheless, reports found in the literature indicated that cumulative radiation doses in close proximity to the patients could potentially exceed over time the ICRP-recommended annual limit. This risk is however counteracted by procedural guidelines for the management of radiotherapy, including regulations on patients' discharge (see CTD module 2.5 for further details).

2) **Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)**

Risk-benefit impact:

No evidence of haematotoxicity following administration of free lutetium (^{177}Lu) was reported in the non-clinical studies. However, haematotoxicity of varying severity is commonly reported with ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 in the clinical studies discussed in Part II: Module SIII – Clinical trial exposure and in the CTD module 2.5, and is subsequently categorised as an important identified risk. Severe haematotoxicity (myelosuppression) may also predispose the patient to opportunistic infections, bleeding, and secondary malignancies. Lutetium (^{177}Lu) chloride is not intended to be directly administered to patients and is to be used only for the radiolabelling of specifically developed therefor carrier molecules. The PK and PD properties of the carrier molecule will affect the distribution and elimination of the radiation. The quantity of lutetium (^{177}Lu) chloride required for radiolabelling and the quantity of lutetium (^{177}Lu)-labelled medicinal product for the intended use will influence the incidence and severity of haematotoxicity. Measures such as monitoring of the patient's blood counts prior to administration and throughout the duration of treatment, as well as intervention options that include administration of blood and platelet transfusions and discontinuation of treatment, are applied to mitigate the risk.

3) Myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)

Risk-benefit impact:

Secondary post-treatment haematological malignancies MDS and AML are reported in several clinical studies with ^{177}Lu-DOTATATE. The incidences vary between approx. 1 and 7% and risk factors such as prior or concurrent chemotherapy appear to contribute to development of these toxicities (see CTD module 2.5 for further details). Lutetium (^{177}Lu) chloride is not intended to be directly administered to patients and is to be used only for the radiolabelling of specifically developed therefor carrier molecules. Hence, the PK and PD properties of the carrier molecule will affect the distribution and elimination of the radiation, determining particularly the radiation dose deposited to bone marrow and thereby also the incidence and severity of the haematological malignancies. In line with this, MDS and AML do not occur with ^{177}Lu-PSMA-617, although its total cumulative dose of radiation applied to patients per treatment is higher than the dose established for ^{177}Lu-DOTATATE (6 cycles with 7.4 GBq/cycle vs. 4 cycles with 7.4 GBq/cycle, respectively).

Despite the obvious specificity of MDS and AML occurrence for a particular carrier molecule type, the risk is considered important for Theralugand due to the inherent severity of these conditions and as the relevance for other carrier molecules developed in the future cannot be excluded. As stated in the SmPC of Theralugand, the risk of MDS and AML should be carefully considered for weighing up benefits and risks of a ^{177}Lu-based therapy for each patient.

Important Potential Risks:

1) Osteosarcoma

Risk-benefit impact:

Osteosarcoma caused by lutetium (^{177}Lu) was included as an important potential risk based on two nonclinical studies describing osteosarcoma occurrence in mice after IP injection of varying lutetium (^{177}Lu) activities (see CTD module 2.4 for details). However, no reports of osteosarcoma onset in clinical use of lutetium (^{177}Lu)-labelled radiopharmaceuticals were identified in the literature. Lutetium (^{177}Lu) chloride is not intended to be directly administered to patients and is to be used only for the

radiolabelling of specifically developed therefor carrier molecules. Therefore, and as such products are handled only by trained and experienced nuclear medicine professionals, inadvertent direct injection of lutetium (^{177}Lu) chloride is considered as a highly unlikely event. Up to the DLP of this RMP, no clinical reports of inadvertent direct administration of free lutetium (^{177}Lu) have been discovered by the applicant. Due to reliable, persistent stability of radionuclide complexes with commonly employed in radiolabelling chelators, release of free lutetium (^{177}Lu) from radiolabelled compounds is also deemed very improbable. If required, elimination of free lutetium (^{177}Lu) from the body can be increased using appropriate chelating agents to prevent potential radiotoxic effects (see Theralugand SmPC).

2) Radiation-induced nephropathy

Risk-benefit impact:

Radiation-induced nephropathy has been reported in several non-clinical and multiple clinical studies with ^{177}Lu-DOTATATE and to a lower extent with ^{177}Lu-PSMA-617 discussed in Part II: Module SIII – Clinical trial exposure (see CTD modules 2.4 and 2.5 for details). Since lutetium (^{177}Lu) chloride is not intended to be directly administered to patients, the PK and PD properties of the radiolabelled carrier molecules will determine the distribution and elimination of the radioactivity defining this particular risk and the degree of radiation-induced nephropathy.

3) Radiation-induced hepatotoxicity

Risk-benefit impact:

Cases of radiation-induced hepatotoxicity have been reported in some of the studies with ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 discussed in Part II: Module SIII – Clinical trial exposure and CTD module 2.5. Most of the observed liver function related events were however mild in severity. Overall, due to rather low incidences, especially of serious and long-lasting hepatotoxicities, this risk is not regarded to have substantial impact on the benefit-risk ratio of Theralugand. Moreover, since lutetium (^{177}Lu) chloride is not intended to be directly administered to patients, the risk and the degree of radiation-induced hepatotoxicity will be always specific for each radiolabelled carrier molecule, depending on its molecular properties, dose, distribution, route of elimination and the nature of diseases it is applied for. In line with this, reports of hepatotoxicity are markedly more common for therapies with ^{177}Lu-DOTATATE than with ^{177}Lu-PSMA-617.

Missing Information:

None

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

Not applicable for this initial 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 Risks:

1) Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient

Potential mechanisms:

Lutetium (^{177}Lu) has a half-life of 6.647 days and decays to stable ^{177}Hf. Thereby lutetium (^{177}Lu) emits beta-particles with mean energies of 47, 111 and 149 KeV, with the most abundant being 149 KeV (79.4%), and a moderate maximum energy of 498 KeV. The beta-emission of lutetium (^{177}Lu) is accompanied by the emission of gamma-photons with energies of 113 keV (6.2%) and 208 keV (11%). The emitted radiation may promote cellular and DNA damage via direct and indirect radioactive ionisation [5].

Evidence source(s) and strength of evidence:

Studies investigating the occupational exposure as well as exposure to family members and the public from patients treated with ^{177}Lu-PSMA-617 or ^{177}Lu-DOTATATE report that cumulative radiation doses in close proximity to the patients could potentially exceed over time the ICRP-recommended annual limit of 1 mSv per year, in particular in the absence of contact restrictions (see CTD module 2.5 for further details).

Characterisation of the risk:

Unintended exposure of nuclear medicine staff to ionising radiation in the process of handling lutetium (^{177}Lu) chloride and lutetium (^{177}Lu)-labelled radiopharmaceuticals, as well as of family members or public being in close proximity to a treated patient, may result in direct damage to DNA affecting the ability of the cell to replicate and survive, as well as in indirect damage via radiolytic decomposition of intracellular water (H_2O) leading to the formation of reactive oxygen species and cell death [6]. The frequency and degree to which health care professionals and members of the public are exposed to radiation from lutetium (^{177}Lu)-labelled radiopharmaceuticals cannot be quantified as radiation exposure varies between patients and different radiopharmaceuticals. However, given the short penetration range of beta-particles and the half-life of lutetium (^{177}Lu) (approximately 6.7 days), the annual limit of 1 mSv for the recommended total effective dose is rather unlikely to be exceeded for individuals in proximity to treated patients if the appropriate radiation safety and patient management guidelines (incl. regulations on patient's discharge) are followed [7].

Risk factors and risk groups:

Health care professionals, carers, relatives, and all other individuals of prolonged close proximity to a treated patient.

Preventability:

Only nuclear medicine specialists qualified by training and experience with access to necessary shielding equipment are authorised to handle radiopharmaceuticals, mitigating the risk of occupational exposure.

The risk of unintended radiation exposure to the public and family members in prolonged close proximity to a treated patient is mitigated by procedural guidelines for the management of radiotherapy, including regulations on patients' discharge, developed to avoid unnecessary radiation

exposure. Any adverse events associated with the occupational or unintended exposure of other individuals to radiation from lutetium (^{177}Lu) have to be reported immediately.

Impact on the risk-benefit balance of the product:

There is currently no available data to quantify the frequency of unintended radioactivity exposure exceeding the ICRP-recommended annual limit due to lutetium (^{177}Lu)-based radiotherapies. Given the physical constraints of the radionuclide (short half-life and range of beta-particles), available preventability measures, and awareness among health care professionals, particularly raised via the product information for Theralugand, the impact of this risk on the benefit-risk balance of the product is considered low.

Public health impact:

The overall impact to public health is expected to be minimal.

2) Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)

Potential mechanisms:

Lutetium (^{177}Lu)-radiolabelled agents likely exhibit myelosuppressive effect via radiation-induced damage and diminution of haematopoietic cells in the bone marrow, which results in decreased blood cell count.

Evidence source(s) and strength of evidence:

Myelosuppression/ decreased blood cell counts may occur during therapy with lutetium (^{177}Lu)-labelled radiopharmaceuticals. Cases of anaemia, thrombocytopenia, leukopenia, lymphopenia, and less commonly neutropenia have been reported with radioligand therapy using ^{177}Lu-PSMA-617 and ^{177}Lu-DOTATATE (see CTD module 2.5 for details). Most events are mild and transient, however treatment with blood and platelet transfusions may be required. More than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described.

Characterisation of the risk:

Most events reported in literature are mild and transient, however acute disruption of the production of blood cells in the bone marrow may lead to the onset of other adverse effects including severe infections and bleeding which may result in serious outcomes.

Risk factors and risk groups:

Previous chemotherapy and high bone tumour burden are reported in the literature as possible risk factors for decreased blood cell counts (see CTD module 2.5).

Preventability:

To prevent/mitigate the risk of lutetium (^{177}Lu)-induced cytopenias and myelosuppression, blood cell counts should be monitored throughout treatment (Theralugand SmPC). Blood and platelet transfusions may be given to the patient and discontinuation of treatment may be considered if haematological abnormalities are detected.

Impact on the risk-benefit balance of the product:

This risk does not change the overall benefit-risk balance of Theralugand since decreased blood cell counts and myelosuppression are known adverse effects of lutetium (^{177}Lu)-labelled

radiopharmaceuticals like ^{177}Lu-PSMA-617 and ^{177}Lu-DOTATATE but do not outweigh the clinical benefits of these therapies. Moreover, measures such as ongoing haematological monitoring before and during the treatment, blood and platelet transfusions and the option of treatment discontinuation are applied to mitigate the risk.

Public health impact:

The impact to public health is expected to be minimal.

3) Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)

Potential mechanisms:

Unintended co-exposure of bone marrow to some amount of radiation upon treatment with lutetium (^{177}Lu)-labelled radiopharmaceuticals may cause mutations in haematopoietic stem cells leading to aberrant or decreased production of myeloid blood cells.

Evidence source(s) and strength of evidence:

Occurrence of MDS and AML has been reported in several clinical studies that describe treatment of NETs with peptide receptor radionuclide therapy utilising ^{177}Lu-DOTATATE (see CTD module 2.5).

Characterisation of the risk:

MDS and AML are rare late side effects of ^{177}Lu-DOTATATE therapy, with reported incidences ranging between approximately 1% and 7% and potential serious outcomes of disability and death. Hence, the applicant regards MDS and AML as an important risk for Theralugand at least in the context of some lutetium (^{177}Lu)-radiolabelled agents.

Risk factors and risk groups:

Risk factors include previous or concurrent chemotherapy (in particular with alkylating agents), prior radiation therapy, number of prior therapies, age above 70 years, impaired renal function, baseline cytopenias and presence of bone metastases (see CTD module 2.5 and [8]).

Preventability:

The increased distribution of radiation to the bone marrow appears to be an intrinsic property of the particular radiolabelled product.

As stated in the SmPC of Theralugand, potential risk factors like prior chemotherapies should be assessed for each patient considered for a therapy with ^{177}Lu-DOTATATE or similar compounds known to cause MDS and AML. Generally, as also stated in the SmPC, the radiation exposure must be justifiable by the likely benefit for each patient. Ongoing blood cell counts monitoring throughout the treatment with lutetium (^{177}Lu)-labelled radiopharmaceuticals is essential to predict and detect possible haematological toxicities.

Impact on the risk-benefit balance of the product:

So far, MDS and AML are considered to have a limited impact on the risk-benefit balance of Theralugand itself, as their occurrence is restricted to particular radiolabelled compounds (^{177}Lu-DOTATATE) and predominantly to patient populations with certain risk factors (e.g., prior exposure to chemotherapeutic agents).

Public health impact:

The impact to public health is considered low as MDS and AML have only been reported for certain lutetium (^{177}Lu)-labelled radiopharmaceuticals and with rather low overall incidences.

Important Potential Risks:

1) Osteosarcoma

Potential mechanisms:

Extrapolation of nonclinical data from the applicant's dosimetry study EZ-Lu177 to human use suggests that after direct injection of lutetium (^{177}Lu) chloride (unbound ^{177}Lu), particularly high radioactivity doses are distributed to bone tissue. The retentiveness of lanthanides such as lutetium in the bone is hypothesised to arise from some chemical similarity to Ca^{2+}. The accumulation of lutetium (^{177}Lu) in the skeleton may cause radiation-induced DNA damages and mutations in surrounding cells like osteoblasts or their precursors leading to formation of osteosarcoma (see CTD module 2.4).

Evidence source(s) and strength of evidence:

Nonclinical data indicate that the injection of free lutetium (^{177}Lu) leads to the increased accumulation of the radioisotope in the bones measurable over several weeks after injection. This can potentially trigger the development of osteosarcomas, main evidence for which was presented in a nonclinical study with more than 200 mice treated using a ^{177}Lu - $KHSO_4$ complex (see CTD module 2.4). There are however no available clinical reports of osteosarcoma caused by lutetium (^{177}Lu).

Characterisation of the risk:

As malignant tumours of the bone with the possibility of life threatening and fatal outcomes, osteosarcomas must be considered as a serious potential consequence of a direct administration of free lutetium (^{177}Lu). Studies report a 5-year survival rate for primary osteosarcomas of approximately 65%-70% [9, 10].

There have been no lutetium (^{177}Lu)-related reports of osteosarcomas in humans, however the incidence of osteosarcomas in mice following IP administration of lutetium (^{177}Lu) was activity-dependent, increasing from 12.5% in the 185 MBq/kg group to 35.3% and 37.5% in the 370 MBq/kg and the 740 MBq/kg groups, respectively (see CTD module 2.4).

Risk factors and risk groups:

Inadvertent direct injection of lutetium (^{177}Lu) chloride is considered to pose the highest risk for osteosarcoma.

Preventability:

As per the indication of Theralugand, lutetium (^{177}Lu) chloride is not intended to be directly administered to patients and 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. Established use of bifunctional radiolabelling chelators with proven clinical suitability, especially in terms of radionuclide-chelator complex stability, prevents the release of free lutetium (^{177}Lu) from radiolabelled compounds. If required (in particular, in case of inadvertent direct administration of ^{177}Lu chloride), chelators like DTPA may be administered to patients to increase the elimination of lutetium (^{177}Lu) from the body.

Impact on the risk-benefit balance of the product:

There is no clinical data available providing evidence for the development of osteosarcomas in patients receiving lutetium (^{177}Lu). So far, osteosarcomogenic activity of free lutetium (^{177}Lu) has been reported only in mice dosed via IP injection. Since no incidences in patients have been identified, and the likelihood of inadvertent direct lutetium (^{177}Lu) chloride administration or lutetium (^{177}Lu) release from radiolabelled compounds is very low, the impact on the benefit-risk balance of the product is considered negligible.

Public health impact:

Currently, the overall impact to public health is considered negligible.

2) Radiation-induced nephropathy

Potential mechanisms:

Multiple studies in literature report the onset of nephrotoxicity in animals and in patients receiving lutetium (^{177}Lu)-labelled radiopharmaceuticals, especially ^{177}Lu-DOTATATE (see CTD module 2.5). Physiological and morphological changes thereby observed in nonclinical studies include proteinuria, elevated serum creatinine, and changes in proximal and distal tubules. The molecular and cellular mechanisms leading to radiation-induced nephropathy are not fully known. Hypothesised plausible mechanisms may involve ionisation events in the DNA, altered regulation of genes responsible for renal necrosis and apoptosis, generation of reactive oxygen species causing chronic oxidative stress, inflammation, and radiation-activation of the renin-angiotensin system leading to glomerular injury with scar formation [11, 12, 13, 14, 15, 16].

Evidence source(s) and strength of evidence:

Nephrotoxicity is reported in humans following administration of lutetium (^{177}Lu)-labelled radiopharmaceuticals ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 and is listed in the product information of corresponding marketing authorisations (for medicinal products Lutathera and Pluvicto, respectively) (see CTD module 2.5, [8] and [17]. However, only Luthatera's product information explicitly describes nephropathy among known adverse reactions.

Characterisation of the risk:

Symptoms of acute radiation-induced nephropathy may include new-onset hypertension, azotaemia, proteinuria, headaches, fatigue, and anaemia. Chronic radiation-induced nephropathy presents with signs of chronic kidney disease, in particular hypertension, proteinuria, anaemia, kidney atrophy (renal volume loss), and chronic kidney failure [12, 14].

As the risk of radiation-induced nephropathy is dependent on the characteristics of the radiolabelled carrier molecules, the incidence cannot be reliably estimated.

Risk factors and risk groups:

Identified risk factors for nephrotoxicity following radionuclide therapies include hypertension, diabetes mellitus, advanced age (>60 years old), medical and surgical co-morbidities (nephrotic syndrome, congestive cardiac failure, renal insufficiency, sepsis, hypovolemia, prior nephrectomy, obstructive uropathy), nephrotoxic medications and thrombotic microangiopathy [12].

Preventability:

Preventability measures include:

- avoidance of use in the presence of known risk factors or risk groups

- assessment of renal function including glomerular filtration rate (GFR) at baseline and during treatment
- coadministration of compounds commonly used for nephroprotection in accordance with clinical guidance valid for the radiolabelled medicinal product.

Impact on the risk-benefit balance of the product:

Whilst radioactive nephropathy is a potentially serious consequence of renal accumulation of lutetium (^{177}Lu)-labelled radiopharmaceuticals, avoidance of the risk factors/groups, assessment of renal function throughout treatment, the availability of nephroprotective agents, and strict adherence to the product information of lutetium (^{177}Lu)-labelled radiopharmaceuticals considerably decrease the likelihood of serious outcomes. Hence, this risk does not substantially affect the positive benefit-risk balance of Theralugand.

Public health impact:

The impact to public health is expected to be minimal.

3) Radiation-induced hepatotoxicity

Potential mechanisms:

Radiotherapies targeting or involving liver tissue pose a risk of radiation-induced hepatotoxicity, potentially leading to the development of the clinical syndrome of radiation-induced liver disease (RILD). Predominantly occurring after high-dose radiotherapy of hepatic cancers [18], RILD of classic type is associated with hepatic veno-occlusive abnormalities, elevated alkaline phosphatase levels, and symptoms such as fatigue, abdominal pain, hepatomegaly, and ascites [19, 20]. In literature, occurrence of the classical RILD was described in patients receiving large liver volumes or the whole-liver doses above the tolerance value of 30-35 Gy and was reported to decrease with the advent of highly conformal radiotherapy methods such as stereotactic body therapy and particle beam therapy [19, 20].

Other radiation-related hepatotoxicities, usually observed in patients with preexisting liver diseases and characterised by symptoms mainly comprising jaundice and markedly elevated serum transaminases, are summarised under the term non-classic RILD [19, 20, 21]. The exact pathogenic mechanisms of radiation-induced hepatotoxicity/RILD are not completely understood so far, but likely involve a causal chain of cellular and physiological events, starting with radiation-induced DNA damage in liver cells, oxidative stress, formation of reactive oxygen species and hepatocellular apoptosis triggering profound inflammation, which subsequently facilitates apoptotic, necrotic and fibrotic reactions in the liver tissue, causing, among others, blood vessel injuries and blood flow impairment and, ultimately, hepatic dysfunction or even hepatic failure [19, 20, 22].

Evidence source(s) and strength of evidence:

Several published clinical studies, predominantly with lutetium (^{177}Lu)-labelled radiopharmaceutical ^{177}Lu-DOTATATE, report acute hepatoxicity of various - but mostly mild and moderate - severity grades [23, 24, 25]. Hepatic adverse reactions are also included in the product information of the authorised ^{177}Lu-DOTATATE medicinal product Lutathera.

Characterisation of the risk:

Hepatotoxic adverse events reported in clinical studies with ^{177}Lu-DOTATATE mainly include elevated liver enzymes and bilirubin levels as well as decrease in serum albumin. The incidences of clinically

significant, serious or life-threatening hepatotoxic events (grades 3 and 4) ranged between 1 and 4 % [25, 26, 27, 28, 29]. As the degree of hepatotoxicity is dependent on the radiolabelled carrier molecule, the overall frequency of such adverse events for Theralugand cannot be estimated.

Risk factors and risk groups:

Some studies with ^{177}Lu-DOTATATE postulated that high tumour burden with metastases in the liver could be a risk factor for radiation-induced hepatotoxicity [24, 30]. However, other investigations specifically looking into this aspect did not confirm this correlation [31, 32]. It is also suggested that prior radiotherapies to the liver, e.g., radioembolisation, could predispose patients to developing hepatotoxicity after ^{177}Lu-DOTATATE treatment [33]. Other risk factors generally associated with radiation-induced hepatotoxicity/RILD include high mean liver dose of radiation, primary liver cancer, male sex, chronic hepatic diseases such as cirrhosis and hepatitis B or C infections, prior transarterial chemoembolisation, and concurrent systemic therapy [19, 34, 35].

Preventability:

Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients. Therefore, laboratory tests should be performed before each administration of the medicinal product radiolabelled with Theralugand to re-assess patient's liver function and adapt the therapeutic protocol if necessary.

Impact on the risk-benefit balance of the product:

Whilst acute hepatotoxicity has been occasionally reported during the clinical use of (in particular) ^{177}Lu-DOTATATE, most reported cases were mild and transient. The included in the Theralugand's SmPC recommendations for continued monitoring of liver function throughout the treatment and, if required, dose reduction of the administered radiolabelled medicinal product mitigate the likelihood of serious outcome and overall maintain the positive risk-benefit balance of Theralugand.

Public health impact:

The impact to public health is expected to be minimal.

SVII.3.2 Presentation of the missing information

There are no missing information topics.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient • Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) • Myelodysplastic syndrome (MDS)/ Acute myeloid leukaemia (AML)
Important potential risks	• Osteosarcoma • Radiation-induced nephropathy • Radiation-induced hepatotoxicity

Summary of safety concerns	
Missing information	• None

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

III.1 Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Unlike with the other lutetium (^{177}Lu) chloride precursor solution authorised in the EU/EEA, Lutetium (^{177}Lu) chloride Billev 51.8 GBq/mL, the inclusion of targeted follow-up questionnaires for the important identified risk of MDS/AML and the potential risks of radiation-induced nephropathy has been forgone for Theralugand. As lutetium (^{177}Lu) chloride is not intended to be directly administered to patients but to be used only for radiolabelling of specific carrier molecules, the risk of adverse events will always depend on the pharmacological characteristics of the carrier molecule to be radiolabelled. Any AEs associated with the treatment using radiolabelled compounds will be initially reported to the marketing authorisation holders (MAHs) of these compounds, which is known from the experience of the applicant with other similar radiopharmaceutical precursor solutions. Consequently, the volume of spontaneous individual case safety reports (ICSRs) expected to be received by the applicant for Theralugand is predicted to be low, with the bulk of safety information rather derived from literature. Under these circumstances, the use of targeted follow-up questionnaires is not considered an effective pharmacovigilance measure.

III.2 Additional pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns. No additional pharmacovigilance activities are proposed.

III.3 Summary Table of additional pharmacovigilance activities

There are no on-going or planned additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

There are no planned or on-going imposed post-authorisation efficacy studies, i.e., imposed by the competent authority as a condition of marketing authorisation or which are specific obligations in the context of conditional marketing authorisation or marketing authorisation under exceptional circumstances.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

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**
Important identified risks	
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	Routine risk communication: • Relevant information related to radioactivity and proper handling of the product in SmPC sections 2, 4.1, 4.2, 4.4, 6.4, 6.6, and 12. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Information on radiation protection in SmPC section 4.4. • Instructions in case of accidental direct injection of lutetium (^{177}Lu) chloride in SmPC section 4.9. • Instructions / precautions for receipt, handling, and storage of the product in SmPC sections 6.4, 6.6, and 12. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	Routine risk communication: • Warning in SmPC section 4.4. • Listing as adverse reactions in SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 contains instruction to test blood count at baseline and to monitor it regularly during treatment.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Myelodysplastic syndrome (MDS)/ Acute myeloid leukaemia (AML)	Routine risk communication: • Warning in SmPC section 4.4. • Listing as adverse reactions in SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Important potential risks	
Osteosarcoma	Routine risk communication: • Information on indication / method (route) of administration in SmPC sections 4.1, 4.2, 4.4, and 6.6. • Information on osteosarcoma in SmPC section 5.3. • Dosimetry information in case of inadvertent direct injection of lutetium (^{177}Lu) chloride in SmPC section 11. • Warning related to bone accumulation of free lutetium (^{177}Lu) in SmPC section 12. • Information on method (route) of administration on the outer label of the product. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on administration of chelating agents after inadvertent direct injection of lutetium (^{177}Lu) chloride in SmPC section 4.9.

Safety concern	Routine risk minimisation activities
	• Recommendation to add chelating agents such as DTPA prior to administration of lutetium (^{177}Lu)-labelled medicinal products in SmPC section 12. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Radiation-induced nephropathy	Routine risk communication: • Information / warning in SmPC section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 contains recommendation to assess renal function including glomerular filtration rate (GFR) at baseline and during treatment, and to consider renal protection as applicable for radiolabelled medicinal product. Other routine risk minimisation measures beyond the product information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Radiation-induced hepatotoxicity	Routine risk communication: • Warning / precautions in SmPC section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 contains recommendation to monitor liver function during treatment and reduce the dose if required. Other routine risk minimisation measures beyond the product information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription.

Safety concern	Routine risk minimisation activities
	• Labelling: The symbol "radioactive" is placed on the labels.

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
Important Identified Risk:		
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	**Routine risk minimisation measures:** *SmPC sections 2, 4.1, 4.2, 4.4, 4.9, 6.4, 6.6, and 12* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	**Routine risk minimisation measures:** *SmPC sections 4.4 and 4.8* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*
Myelodysplastic syndrome (MDS)/ Acute myeloid leukaemia (AML)	**Routine risk minimisation measures**: *Restricted user group* *SmPC sections 4.4 and 4.8* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks:		
Osteosarcoma	**Routine risk minimisation measures:** *SmPC section 4.1, 4.2, 4.4, 4.9, 5.3, 6.6, 11, 12* *Product label* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*
Radiation-induced nephropathy	**Routine risk minimisation measures:** *SmPC section 4.4* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities:** *None*
Radiation-induced hepatotoxicity	**Routine risk minimisation measures:** *SmPC section 4.4* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities:** *None*

Part VI: Summary of the risk management plan

Summary of risk management plan for Theralugand (lutetium (^{177}Lu) chloride)

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

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

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

I. The medicine and what it is used for

Theralugand 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 (see SmPC for the full indication). When the active substance lutetium (^{177}Lu) chloride is combined with appropriate carrier molecules, the carrier molecules bind the radionuclide lutetium (^{177}Lu) and are afterwards used for different internal radiotherapy applications in accordance with their indications.

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

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

Measures to minimise the risks identified for the medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and is regularly analysed, including PSUR assessment so that immediate action can be taken if necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Theralugand 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 Theralugand. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

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

II.B Summary of important risks

Important identified risks:	
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	Studies investigating the occupational exposure as well as exposure to family members and the public from patients treated with ^{177}Lu-PSMA-617 or ^{177}Lu-DOTATATE report that cumulative radiation doses in close proximity to the patients could potentially exceed over time the ICRP-recommended annual limit of 1 mSv per year, in particular in the absence of contact restrictions.
Risk factors and risk groups	Health care professionals, carers, relatives, and all other individuals of prolonged close proximity to a treated patient.

Risk minimisation measures	Routine risk communication: • Information related to radioactivity and proper handling of the product in SmPC sections 2, 4.1, 4.2, 4.4, 6.4, 6.6 and 12. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Information on radiation protection in SmPC section 4.4. • Instructions in case of accidental direct injection of lutetium (^{177}Lu) chloride in SmPC section 4.9. • Instructions / precautions for receipt, handling and storage of the product in SmPC sections 6.4, 6.6 and 12. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	
Evidence for linking the risk to the medicine	Myelosuppression/ decreased blood cell counts may occur during therapy with lutetium (^{177}Lu)-labelled radiopharmaceuticals. Cases of anaemia, thrombocytopenia, leukopenia, lymphopenia, and less commonly neutropenia have been reported with radioligand therapy using ^{177}Lu-PSMA-617 and ^{177}Lu-DOTATATE. Most events are mild and transient, however treatment with blood and platelet transfusions may be required. More than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described.
Risk factors and risk groups	Previous chemotherapy and high bone tumour burden are reported in the literature as possible risk factors for decreased blood cell counts.
Risk minimisation measures	Routine risk communication: • Warning in SmPC section 4.4. • Listing as adverse reactions in SmPC section 4.8.

	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 contains instruction to test blood count at baseline and to monitor it regularly during treatment. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Myelodysplastic syndrome (MDS)/ Acute myeloid leukaemia (AML)	
Evidence for linking the risk to the medicine	Occurrence of MDS and AML has been reported in several clinical studies that describe treatment of neuroendocrine tumours with peptide receptor radionuclide therapy utilising ^{177}Lu-DOTATATE.
Risk factors and risk groups	Risk factors include previous or concurrent chemotherapy (in particular with alkylating agents), prior radiation therapy, number of prior therapies, age above 70 years, impaired renal function, baseline cytopenias and presence of bone metastases.
Risk minimisation measures	Routine risk communication: • Warning in SmPC section 4.4. • Listing as adverse reactions in SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.

Important potential risks:	
Osteosarcoma	
Evidence for linking the risk to the medicine	Nonclinical data indicate that the injection of free lutetium (^{177}Lu) leads to profound accumulation of the radioisotope in the bones measurable over several weeks after injection. This can potentially trigger the development of osteosarcomas, main evidence for which was presented in a nonclinical study with more than 200 mice treated using a ^{177}Lu - $KHSO_4$ complex. There are however no available reports of osteosarcomas in humans caused by lutetium (^{177}Lu).
Risk factors and risk groups	Inadvertent direct injection of lutetium (^{177}Lu) chloride is considered as a particular risk factor.
Risk minimisation measures	Routine risk communication: • Information on indication / method (route) of administration in SmPC sections 4.1, 4.2, 4.4, and 6.6. • Information on osteosarcoma in SmPC section 5.3. • Dosimetry information in case of inadvertent direct injection of lutetium (^{177}Lu) chloride in SmPC section 11. • Warning related to bone accumulation of free lutetium (^{177}Lu) in SmPC section 12. • Information on method (route) of administration on the outer label of the product. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on administration of chelating agents after inadvertent direct injection of lutetium (^{177}Lu) chloride in SmPC section 4.9. • Recommendation to add a chelating agent such as DTPA prior to administration of lutetium (^{177}Lu)-labelled medicinal products in SmPC section 12. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.

Radiation-induced nephropathy	
Evidence for linking the risk to the medicine	Nephrotoxicity is reported in humans following administration of lutetium (^{177}Lu)-labelled radiopharmaceuticals ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 and is listed in the product information of corresponding marketing authorisations (for medicinal products Lutathera and Pluvicto, respectively). However, only Luthatera's product information explicitly describes nephropathy among known adverse reactions.
Risk factors and risk groups	Identified risk factors for nephrotoxicity following radionuclide therapies include hypertension, diabetes mellitus, advanced age (>60 years old), medical and surgical co-morbidities (nephrotic syndrome, congestive cardiac failure, renal insufficiency, sepsis, hypovolemia, prior nephrectomy, obstructive uropathy), nephrotoxic medications and thrombotic microangiopathy.
Risk minimisation measures	Routine risk communication: • Information / warning in SmPC section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 contains recommendation to assess renal function including glomerular filtration rate at baseline and during treatment, and to consider renal protection as applicable for radiolabelled medicinal product. Other routine risk minimisation measures beyond the product information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.
Radiation-induced hepatotoxicity	
Evidence for linking the risk to the medicine	Several published clinical studies, predominantly with lutetium (^{177}Lu)-labelled radiopharmaceutical ^{177}Lu-DOTATATE, report acute hepatoxicity of various - but mostly mild and moderate - severity grades. Hepatic adverse reactions are also included in the product information of the authorised ^{177}Lu-DOTATATE medical product Lutathera.
Risk factors and risk groups	Some studies with ^{177}Lu-DOTATATE postulated that high tumour burden with metastases in the liver could be a risk factor for radiation-induced hepatotoxicity. However, other investigations specifically looking into this aspect did not confirm this correlation. It is also assumed that prior radiotherapies to the liver, e.g., radioembolisation, could

	predispose patients to developing hepatotoxicity after ^{177}Lu-DOTATATE treatment. Other risk factors generally associated with radiation-induced hepatotoxicity (radiation-induced liver disease) include high mean liver dose of radiation, primary liver cancer, male gender, chronic hepatic diseases such as cirrhosis and hepatitis B or C infections, prior transarterial chemoembolisation, and concurrent systemic therapy.
Risk minimisation measures	Routine risk communication: • Warning / precautions in SmPC section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 contains recommendation to monitor liver function during treatment and reduce the dose if required. Other routine risk minimisation measures beyond the product information: • The product is a radiopharmaceutical precursor solution. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: Restricted medical prescription. • Labelling: The symbol "radioactive" is placed on the labels.

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 for Theralugand.

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

There are no studies required for Theralugand.

Part VII: Annexes

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable. There are no specific adverse event follow-up forms.

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

Not applicable. This medicinal product has no additional risk minimisation measures.