21 July 2022
EMA/689220/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ilLuzyce

International non-proprietary name: lutetium (177lu) chloride

Procedure No. EMEA/H/C/005859/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%ID	Percent injected dose (activity)
%ID/g	Percent injected dose (activity) per g tissue
$[^{177}Lu]LuCl_3$	Lutetium (^{177}Lu) chloride
Â	Time-integrated activity values
ALT	Alanine transaminase
API	Active Pharmaceutical Ingredient
ART	Activity Reference Time
AST	Aspartate transaminase
ASTM	formerly, American Society for Testing and Materials (currently, ASTM International)
ATC	Anatomical Therapeutic Chemical classification system
AX:	Anion exchange
BET:	Bacterial endotoxins
Bq	Becquerel
Bq (MBq, GBq)	Bequerel, mega-Bequerel, giga-Bequerel (Radioactivity unit)
BW, BWH, BWA	Body weight, body weight for humans, body weight for animals
Ca-DTPA	Trisodium calcium diethylene triamine pentaacetate
Ca-EDTA	Calcium disodium ethylene diamine tetraacetate
CC49	Code for a monoclonal antibody
ccRCC	Clear cell renal cell carcinoma
Cd^{2+}	Cadmium ion
Ci:	Curie (a non-SI unit of radioactivity)
CMPO:	n-Octyl(phenyl) N,N-diisobutylcarbamoylmethylphosphine oxide (one of the extractants in TK221 resin)
cps	Counts per second
CRW rats	Rat strain from Charles River
CT	Computed tomography
Cu^{2+}	Copper ion
CX:	Cation exchange
DAB4	Code for a lupus-associated monoclonal antibody
DART	Developmental and Reproductive Toxicology database
DGA:	One of the two alternative cation exchange resins proposed
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTANOC	$[DOTA^0\text{-}1\text{-}Nal^3]$octreotide
DOTATATE	Oxodotreotide, $[DOTA^0\text{-}Tyr^3]$octreotate
DOTATOC	Edotreotide, $[DOTA^0\text{-}Tyr^3]$octreotide
DPD	2,3-dicarboxypropane-1,1-diphosphonic acid
DTPA	Diethylene triaminepentaacetic acid
EANM	European Association of Nuclear Medicine
EC_{50}	Half-maximal effective dose
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines & Healthcare
EDTMP	Ethylene diamine tetra methylene phosphonic acid
ERPF	Effective renal plasma flow
ET	Extrathoracic region of the respiratory tract

ET1	Anterior nasal passages of the respiratory tract
ET2	Posterior nasal passages, naso-oropharynx, and larynx
eV	electron-volt
GABA	γ-aminobutyric acid
GBq	Radioactivity unit, giga-Becquerel
GEP-NET	Gastroenteropancreatic neuroendocrine tumour
GMP:	Good Manufacturing Practices
GOT	Aspartate transaminase, AST
GPT	Alanine transaminase, ALT
Gy	Radioactivity unit, Gray
HDEHP:	di(2-ethylhexyl) orthophosphoric acid
HED:	human equivalent dose
HEDP	1-hydroxyethane 1,1-diphosphonic acid
Hf	Hafnium
ICP-OES:	Inductively coupled plasma-optical emission spectrometry
ICRP 103	International Commission on Radiological Protection publication 103
IDAC	Internal dosimetry computer program
IDP	Imidodiphosphate tetrasodium salt
IV	Intravenous
J591	Monoclonal antibody against PSMA
KeV	Energy unit, kilo-electron volt
La^{3+}	Lanthanum ion
LD_{50}	Lethal dose for 50% of a tested group
LN2:	The resin in the separation chromatographic column
LOD:	Limit of detection
LOQ:	Limit of quantification
Lu	Lutetium
mCi	Radiation unit, milli-Curie
mCRPC	Metastatic castration-resistant prostate cancer
MeV	Energy unit, mega-electron volt
MIA:	Manufacturing/Importation Authorisation
MTD	Maximum tolerated dose
n.c.a.	Non carrier added
N.F.:	National Formulary
NET	Neuroendocrine tumour
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OH, OA	Organ mass for humans, organ mass for animals
PA-DOTA	1, 4, 7, 10-Tetraaza-N-(1-carboxy-3-(4-nitrophenyl)propyl)-N', N", N"'- tris(acetic acid) cyclododecane
PBS	Phosphate buffered saline
PCa	Prostate cancer
PCCs	Pheochromocytomas
PDE	Permitted daily exposure
PET	Positron emission tomography
PGLs	Paragangliomas
Ph.Eur.:	European Pharmacopoeia

ppm	part per million
ppt	parts per trillion
PRAC	Pharmacovigilance risk assessment committee
PRRT	Peptide receptor radionuclide therapy
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
QP:	Qualified person
rd	Rad (radioactivity unit)
RECIST	Response evaluation criteria in solid tumours
RIT	Radioimmunotherapy
RLT	Radioligand therapy
RMP	Risk management plan
RSD:	Relative Standard Deviation
Scisearch	Scientific literature database
SD	Standard deviation
SPE:	Solid Phase Extraction
SPECT	Single photon emission computed tomography
SSAs	Somatostatin analogues
SSTR	Somatostatin receptor
SSTRs	Somatostatin-receptors
SUV	Standard uptake volume
SWOG	Southwest oncology group
TAC	Time-activity curve
TACA	Organ TAC for animals
TACH	TAC equivalent for humans
TAG-72	Tumour-associated glycoprotein
TK221:	One of the two alternative cation exchange resins proposed
TO-DGA	tetra-octyldiglycolamide (the constituent extractant in DGA resin, also present in TK221 resin)
T-wave	Characteristic section of an ECG record
USP	United States Pharmacopoeia
WBC	White blood cell
X-ray	Form of electromagnetic radiation
Yb	Ytterbium
Zn^{2+}	Zinc ion

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Billev Pharma ApS submitted on 30 July 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for ilLuzyce, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 January 2021.

The applicant applied for the following indication: ilLuzyce 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

Not applicable.

1.6. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: Janet Koenig

The application was received by the EMA on	30 July 2021
The procedure started on	19 August 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2021

The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	19 November 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 November 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 December 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 March 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 May 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 June 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	06 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to ilLuzyce on	21 July 2022

2. Scientific discussion

2.1. Problem statement

The applicant is seeking marketing authorisation for the proposed medicinal product Lutetium (^{177}Lu) chloride non carrier added (n.c.a.), solution in accordance with Article 10a of Directive 2001/83/EC, as amended, based on the well-established medicinal use of the active substance lutetium-177 chloride as medicinal product for at least 10 years in the EU.

2.1.1. Disease or condition

The proposed medicinal product Lutetium (^{177}Lu) chloride n.c.a., solution is a radiopharmaceutical precursor, and not intended for direct use in patients. It is to be used only for radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.

Radionuclides have widely been used in medical applications such as diagnostic radiology for decades, with the first radiopharmaceuticals commercialised in 1950. For example, tumours as well as metastases can be localised by radionuclide-tracer-complexes specifically targeting tumour-tissue, such as prostate-specific membrane-antigen (PSMA) or somatostatin-analogues (Sgouros G, 2020).

Apart from being utilised for diagnostic imaging, radionuclide-tracer-complexes are also increasingly used in molecular radiotherapy.

2.2. About the product

Lutetium belongs to the group of lanthanides and is a rare earth metal. One of its isotopes is lutetium-177 emitting medium-energy β-particles with a maximum energy of 0.5 MeV (mean energy 47.66 to 149.35 KeV) and a maximum tissue penetration of 2 mm.

The proposed medicinal product Lutetium (^{177}Lu) chloride n.c.a., solution is a radiopharmaceutical precursor preparation of high purity intended only for the *in vitro* labelling of tracer molecules specifically developed for radiolabelling. Following radiolabelling of the radiopharmaceutical precursor, the tracer molecules (e.g., peptides or monoclonal antibodies) will be administered by the approved route for targeting a specific site (e.g. solid tumour) thereby allowing local irradiation. Lutetium (^{177}Lu) chloride n.c.a. is not intended for direct administration to patients.

Lutetium-177 has a half-life of approximately 6.7 days. Lutetium (^{177}Lu) chloride n.c.a. is produced by neutron irradiation of enriched ytterbium (^{176}Yb). Lutetium-177 decays by β-emission to stable hafnium (^{177}Hf), with the most abundant β-emission (79.3%) having a maximum energy of 497 keV. Also, low gamma energy is emitted, for instance at 113 keV (6.2%) and 208 keV (11%).

The pharmacodynamic properties of lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with ilLuzyce, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

The tracer molecule will direct the radionuclide Lutetium-177 to the tumour tissue where it will bind to surface molecules expressed specifically by tumour cells. Upon binding, the receptor-ligand complexes become internalised. Once intracellular, internalised ^{177}Lu-labelled radioligands accumulate in the perinuclear area allowing direct DNA damage by ionising radiation resulting in cell death. Lutetium (^{177}Lu) emits β-minus particles of moderate maximum energy (0.498 MeV) with a maximum tissue penetration of approximately 2 mm. Lutetium (^{177}Lu) also emits low-energy γ-rays which allow scintigraphic, biodistribution and dosimetry studies with the same lutetium (^{177}Lu)-labelled medicinal products.

The applied and recommended indication is as follows: ilLuzyce 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 section 4.1).

ilLuzyce is only to be used by specialists experienced with in vitro radiolabelling (see SmPC section 4.2).

The quantity of the proposed medicinal product required for radiolabelling and the quantity of lutetium (^{177}Lu)-labelled medicinal product subsequently administered will depend on the medicinal product radiolabelled and its intended use (see SmPC section 4.2).

2.3. Type of Application and aspects on development

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC, as amended – relating to applications relying on well-established medicinal use supported by bibliographic literature. According to Article 10a of Directive 2001/83/EC, and without prejudice to the law relating to the protection of industrial and commercial property, it is possible for an applicant to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substance of a medicinal product has been in well-established medicinal use within the Union for at least 10 years, with a recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply. The applicant has submitted a document to support the application as a well-established use where the fulfilment of the requirements of article 10a application are discussed.

It bears noting that, as applicable for all applications for marketing authorisation, the applicant declared that the data submitted are not subject to regulatory data exclusivity in the Union.

To determine if the application fulfils the requirements of Article 10a with regard to well-established medicinal use of lutetium (^{177}Lu) chloride non-carrier-added (n.c.a.), a radiopharmaceutical precursor not intended for direct use in patients, the CHMP took into account the following factors:

- ***Time over which the substance has been used:***

Lutetium has been used in the treatment of NETs since 2000. Due to its favourable radiochemical characteristics compared to other radionuclides such as yttrium- 90, lutetium-177 is widely established in clinical radiotherapy in conjunction with molecular tracers, mainly targeting somatostatin receptors (SSTRs) and prostate-specific membrane antigen (PSMA). Quantitatively, lutetium has been shown to be widely used in studies and also in supply data from the applicant.

- ***Quantitative aspects of use of the substance:***

According to the information provided in publicly available study data, at least about 4,000 patients have been treated with ^{177}Lu-labelled tracers in the course of published clinical trials so far. Considering a dose of 1-4 cycles per patient, about 4,000-16,000 doses of lutetium-177 have at least been applied in the course of published clinical trials only. Given the fact that several medicinal products containing the radionuclide lutetium-177 have been authorised during the past 7 years and are therefore considered established in clinical practice, and many patients are treated on a named-patient or compassionate use basis, a much higher number of patients treated with ^{177}Lu-labelled tracers must be assumed.

Altogether, the use of ^{177}Lu-labelled compounds in specific radiotherapy is widely distributed throughout the EU as well as worldwide as documented by various published clinical studies and current treatment guidelines. Furthermore, several medicinal products intended for radiolabelling containing the active substance $^{177}LuCl_3$ were authorised in and outside the EU during the past years. Clinical utility of the radiopharmaceutical precursor $^{177}LuCl_3$ can be considered well-established.

Table 1. Examples of ^{177}Lu-tracer-complexes used in radiotherapy

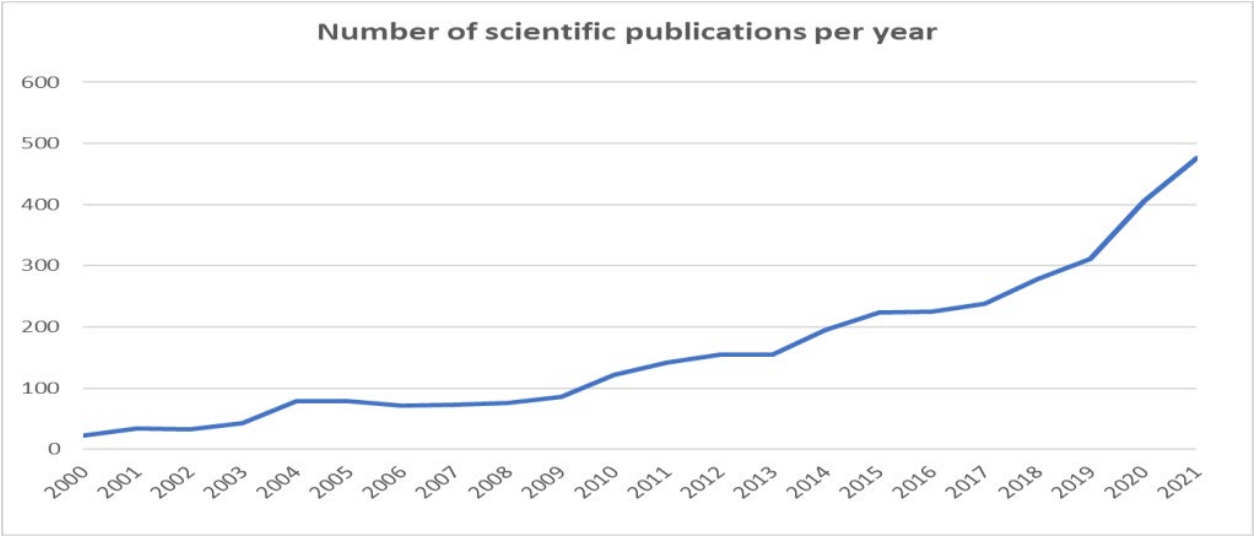
Tracer complex	Indication
^{177}Lu-DOTATOC	Radiotherapy of neuroendocrine tumours
^{177}Lu-DOTANOC	Radiotherapy of neuroendocrine tumours (only few reports)

Tracer complex	Indication
^{177}Lu-PSMA	Radiotherapy of prostate cancer
^{177}Lu-J591	Radiotherapy of prostate cancer
^{177}Lu-EDTMP	Palliative treatment of metastatic bone pain

- ***Degree of scientific interest in the use of the substance (reflected in the published scientific literature):***

An initial PubMed search in February 2021 using the terms "lutetium" OR "lutetium-177" OR "^{177}Lu" revealed about 3000 hits, including all articles without any limitation. After evaluation of all public sources, 178 references were included in the clinical overview presented by the applicant. There is continued scientific interest in lutetium, with continuous publications in the EU for about 20 years. The first clinical use of ^{177}Lu-labelled tracers in the EU was described for ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC in 2003 and 2005/2006, respectively. Since then, numerous publications have followed. There is continued scientific interest in the use of the active substance $^{177}LuCl_3$ documented by an increasing total number of publications listed in PubMed (including clinical trials, meta-analyses, systematic reviews, and reviews) during the last two decades as shown in the figure below.

Figure 1. Number of scientific publications per year



- ***Coherence of scientific assessments:***

As per Annex 1, Part III, point 2.2 of Directive 2001/83/EC as amended in Directive 2003/63/EC, Annex I:

"Clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes. However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented".

The efficacy and safety characteristics of lutetium (^{177}Lu) chloride n.c.a depend on the carrier molecule, which is radiolabelled with the proposed medicinal product. Therefore, no clinical studies investigating the efficacy and safety of the proposed medicinal product have been conducted by the applicant.

Therefore, according to the requirements to substantiate the well-established medicinal use of the active substance as medicinal product for at least 10 years in the Community as set out in Annex 1 Part III of Directive 2001/83/EC, as amended, the applicant presented comprehensive efficacy and safety data from published clinical trials, which have been conducted with ^{177}Lu-labelled tracer molecules, focussing mainly on the most established carriers used for radionuclide therapy targeting different types of carcinoid tumours such as neuroendocrine tumours (NETs) or prostate cancer (PCa).

The comprehensive body of data and discussion by the applicant fulfilled the requirements of the well-established use legal basis.

2.4. Quality aspects

2.4.1. Introduction

The finished product is a radiopharmaceutical precursor presented in sterile diluted hydrochloric acid. 1 mL of solution contains 51.8 GBq Lutetium(^{177}Lu) chloride on activity reference time (ART) corresponding to maximum 12.6 micrograms of Lutetium (^{177}Lu) (as chloride) as active substance.

The ART is defined as the end of production. The minimal specific activity is 3000 GBq/mg lutetium (^{177}Lu) at the ART.

Each 5 mL vial contains a volume varying from 0.1 mL to 4 mL corresponding to an activity ranging from 5.2 to 207.2 GBq at ART.

Each 10 mL vial contains a volume varying from 0.1 mL to 8 mL corresponding to an activity ranging from 5.2 to 414.4 GBq at ART.

The activity at the date and time ordered by the customer, indicated as CAL (calibration), is determined by the time elapsed from the ART and the half-life of Llutetium (^{177}Lu).

The other ingredient is hydrochloric acid, diluted

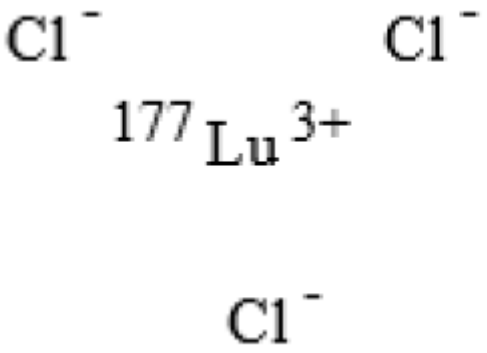
The product is available in 5 mL or 10 mL clear type I glass vial either conical or flat bottom, respectively, with a teflon coated chlorobutyl rubber stopper, closed with an aluminium cap as described in section 6.5 of the SmPC. The vials are placed into a lead container for protective shielding and packed into a polystyrene box and an outer carton

2.4.2. Active Substance

General information

The chemical name of active substance is lutetium-177($^{3+}$); trichloride corresponding to the molecular formula $LuCl_3$. It has a relative molecular mass of 283.3 g/mol and the following structure:

Figure 2. Active substance structure



Lu-177's gamma radiation is characterised by two main energies; 11% of Lu-177 decay is in the energy of 208 KeV and 6.4% is in the energy of 112 KeV. The measured spectrum of the active substance shows the presence of the two main 2 Gamma energies (112 and 208 keV) together with some other typical emission peaks known to be present, in lesser intensities, in Lu-177 gamma ray spectrum, thus the identity of the active substance is assured.

The active substance is presented as a clear colourless solution. The solubility of Lu3+ in aqueous solution is pH dependent. Lutetium chloride is very soluble in diluted hydrochloric acid solution.

Other properties relevant considering the radioactive nature of the active substance and its intended use are provided: decay mode and radiation emitted by the radionuclide and non carrier added (n.c.a.) qualification derived from the route of production that yields a high specific activity preparation. Lu-177 is a radioactive isotope that decays to Hf-177 with a half-life of 6.647 days and emits β-particles with maximum energies of 497 keV, 385 keV and 176 keV and low energy gamma photons of 113 keV and 208 keV. The moderate energy beta emission of ^{177}Lu is effective in destroying small tumours and metastatic lesions (typically less than 3 mm diameter) while sparing the surrounding normal tissue. The emission of low-energy gamma photons [Ec = 113 keV (6.6 %), 208 keV (11 %)] enable imaging and therapy with the same radiolabelled preparation and allow dosimetry to be performed before and during treatment.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

The manufacturing process covers all the operations that are required according to the guideline on radiopharmaceuticals. The active substance is synthesised in 3 main steps.

Natural ytterbium is enriched in Yb-176 by electromagnetic isotope separation, removed from the copper plate of the receiver, purified of unwanted chemical elements by precipitation and transformed into ytterbium oxide, the chemical form suitable for irradiation. The enriched ytterbium oxide is packed in sealed quartz tubes that are sent to a nuclear reactor for neutron irradiation. After irradiation, the target is cooled down to allow the Yb-177 decay to Lu-177. The nuclear reaction that occurs during irradiation in the nuclear reactor is:

$$^{176}\mathrm{Yb}\,(\mathrm{n},\gamma)\,^{177}\mathrm{Yb} \xrightarrow{\beta^-} {}^{177}\mathrm{Lu}$$

Afterwards, the purification and formulation of Lu-177 is done in a continuous automated process conducted in a synthesis module. In a chromatographic process, the accumulated Lutetium (177Lu) is separated chemically from the original target material and is dissolved in 0.04 M HCl.

The manufacturing process is continuous and highly automated and there are no intermediates. Adequate in-process controls are performed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances and the guideline on radiopharmaceuticals.

Considering the production route of Lu-177 and the level of enrichment of ytterbium in the target, the only expected relevant radionuclidic impurity is Yb-175. The discussion on the control of potential metallic impurities is also provided and considered satisfactory.

Potential and actual impurities were well discussed with regards to their origin and characterisation.

The active substance is packaged in clear type I glass vials. The vial used to collect the bulk solution, is plugged with a teflon coated rubber stopper which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance is not isolated. The active substance bulk solution proceeds to filling and sterilising steps to produce the finished product. Considering the similarity between the active substance and the finished product and the continuous nature of the manufacturing process, and in

line with the guideline on radiopharmaceuticals, it is acceptable that the quality control testing is done mainly at the finished product stage.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

As mentioned above, the active substance is not isolated, so the stability of the active substance corresponds to the stability of the finished product. For stability studies and data, reference is made to the section on stability of the finished product. A re-test period for the active substance is not proposed. This is deemed acceptable because the manufacturing process is a continuous process starting from the beginning of the target processing and the active substance is not isolated or stored.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a clear colourless solution.

During the evaluation, the CHMP requested, as Major Objection (MO), that the activity per mL of the finished product at activity reference time should be fixed as required in the "Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007). The activity was fixed to 51.8 GBq/ml and it was considered satisfactory.

The aim of the pharmaceutical development was to develop a sterile finished product with a low content of metallic impurities according to current edition of the Ph. Eur. Lutetium (^{177}Lu) Solution for Radiolabelling.

The product is intended for use as a radioactive precursor in the preparation of several radio labelled peptides, used for radionuclide therapy. The finished product is not intended for direct use in patients.

The active substance is a synthetic radionuclide (^{177}Lu) produced by neutron bombardment of Ytterbium 176 (^{176}Yb). This radionuclide (^{177}Lu) is a non-fission product. The ^{177}Lu produced by this method is of high specific activity since the target material, enriched ^{176}Yb, is chemically different from the radioisotope produced and the sole source of stable Lu isotope is the decay of ^{175}Yb, produced during the neutron irradiation of the target material, to ^{175}Lu. An advantage of this process is avoiding production of the long-lived radionuclide impurity ^{177}mLu.

Hydrochloric acid solution is used as solvent for the active substance. The rationale for selection of this solvent is that dilute hydrochloric acid is used in the Ph. Eur monograph Lutetium (^{177}Lu) solution for radiolabelling and the pH requirement are pH 1.0 to 2.0. This excipient is well known pharmaceutical ingredients and its quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

An important parameter for the quality of the radiopharmaceutical product is the radiolabeling yield. To achieve a high yield of the subsequent labelling reactions even traces of metals should be avoided when choosing the excipients. Therefore, only excipients and reagents of high purity are used.

Manufacture is a continuous process from the irradiated starting material through to manufacture of the finished product.

The product (Lu-177 chloride solution) can be sterilised by steam sterilisation at a temperature ≥121°C for ≥15 minutes and therefore the finished product is terminally sterilised by autoclaving according to Ph. Eur 5.1.1

The primary packaging is a clear type I glass vial of 5 mL or 10 mL either conical or flat bottom, respectively, with a Teflon coated chlorobutyl rubber stopper, closed with an aluminium cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Regarding the primary packaging, the material of the container and closure system are commonly used for this type of products. Compatibility of the radiolabelled product with the container and closure is discussed, including the potential release of metallic impurities from the stopper. A self-sealing test of the rubber stopper has been conducted to support the eventual use of the finished product as a multi-dose product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 3 main steps: dispensing of bulk solution, steam sterilization and secondary packaging for shipment. The process is considered to be a non-standard manufacturing process.

The manufacture of the finished product consists in the filling of the finished product vials with the amount of bulk solution ordered by the clients, the terminal sterilisation in an autoclave, labelling and final secondary packaging. The dispensing process is done in a dispensing programmed robot for dispensing the calculated volumes into each vial; the activity of each vial is measured after vial closing before sterilisation and again after sterilisation just before final labelling of the lead shield. The sterilisation cycle is stated.

The validation of the manufacturing process covers the manufacture of both the active substance and the finished product and this is considered acceptable considering the nature of the process. The validation has been conducted on three batches representative of the proposed manufacturing process and includes suitable data: batch results of validation batches, results of in process controls, manufacturing parameters and additional validation tests.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product specifications include all the tests prescribed by the Ph. Eur. monograph #2798 on Lutetium (^{177}Lu) solution for radiolabelling and include additional limits for the content of ytterbium-176 and for specific activity. The finished product release specifications include appropriate tests for this kind of dosage form appearance (visual), pH (colorimetry), identification (Gamma spectroscopy, pH, iTLC), specific activity (ICP-OES), radioactive concentration of Lutetium (^{177}Lu) chloride (Dose calibrator), chemical purity (ICP-OES), radionuclidic purity (gamma spectrometry), radiochemical purity (iTLC), bacterial endotoxins (BET), and sterility (Ph. Eur.).

Regarding the characterisation of impurities, a discussion on metallic impurities on the limit for ytterbium content and on potential impurities originating from the resins have been provided and considered satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based

on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided representative of the proposed manufacturing process confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of three development batches and three routine production batches (upright and inverted position) of finished product stored for up to 11 days under long term conditions (25 ºC / 60% RH) as well as at accelerated temperature (40 ºC ± 2 ºC/ 75% RH ± 5%) according to the ICH guidelines were provided. The production batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: appearance, identification, pH, chemical purity, radionuclidic purity, radiochemical purity, bacterial endotoxins, and sterility. The analytical procedures used are stability indicating. All results are within specifications and significant trends are not seen

Sterility test is performed after decay which means after 10 to 12 weeks from time zero and it has thereby been shown that the results are within specification at end of shelf life.

Based on available stability data, the proposed shelf-life of up to 11 days from the date of manufacture and none storage conditions as stated in the SmPC (section 6.3) are acceptable.

From a microbiological point of view, unless the method of withdrawal from the vial or any insertion into the vial preclude the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

One issue was raised by CHMP as Major Objections (MO) related to the expression of activity of the finished product at activity reference time should be fixed. The issues were resolved satisfactorily by the applicant as discussed above.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Lutetium (^{177}Lu) chloride is not intended to be administered directly to the patient. As a precursor it should only be used for *in vitro* labelling of appropriate carrier molecules for targeted radiotherapy. Accordingly, it has no primary pharmacodynamic function and only very few data are available on the general pharmacodynamics of lutetium as a metal ion and as a free soluble radioactive metal salt.

The studies and data assessed in this application are based on scientific literature in accordance with the published legal basis.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

First reports on the medical use of ^{177}Lu were published in 1969, describing the use of this radioactive element for bone imaging in rabbits (O'Mara, 1969). Whereas ^{177}Lu is currently used as a targeted radiotherapeutic due to the emission of β-radiation with a range of only 2 mm compared to the range of 12 mm described for ^{90}Y, ^{177}Lu also emits γ-irradiation, enabling its use for radio-imaging purposes (Kam, 2012). ^{177}Lu was discussed to be advantageous for bone imaging, due to the medium energy gamma radiation emitted and the half-life of more than six days, giving a balance between practical considerations for handling and duration of radiation exposure (O'Mara, 1969).

Animal studies with the radioactive isotope of lutelium, ^{177}Lu, have shown that it has a high affinity with bone tissue and given its unique radioactive characteristics of emitting both beta and gamma energy, may be a useful product for imaging bone tissue. In addition, it has been shown that ^{177}Lu can have an immunosuppressive and growth suppressive effect supporting its suitability in the treatment of rheumatoid arthritis.

^{177}Lu decays to the more stable isotope ^{177}Hf, which is reported to be present in nature and can be taken up in food, drinking water or as inhaled dust. Its use for some medical applications has been also explored e.g. intravascular radiocontrast imaging, administration of hafnium oxide nanoparticles in cancer models or in medical devices for implantation in bone.

Hafnium alloys are being characterised for use in bone implants, such as hip replacement (Matsuno, 2001). Hafnium was well tolerated in rats where hafnium was implanted to allow contact with bone marrow and bone surface. No inflammatory response was observed around the implants, and all the implants were encapsulated with thin fibrous connective tissue. Histological examination of the hard tissue showed that the amount of new bone formation decreased slightly from the second to the fourth

week after implantation, and that the percentage of bone in contact with the implant increased markedly over the same period.

^{177}Lu: uses in radioimmunotherapy

The purpose of ^{177}Lu is to be linked to the selected protein or peptide to be used in radioimmunotherapy. This linking is achieved using specific chelators, i.e. molecules which complex $[^{177}Lu]^{3+}$ presented in an aqueous solution. The stability of the chelated complex is critical for the pharmacodynamics and for the pharmacokinetics of administered radioimmunotherapeutics since it determines whether the radiotracer reaches its intended target and whether ^{177}Lu may be released from the complex after administration. ^{177}Lu was found to form stable complexes with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and with DOTA-based complexing agents such as 1, 4, 7, 10-tetraaza-N-(1-carboxy-3-(4-nitrophenyl)propyl)-N', N", N"'-tris(acetic acid) cyclododecane (PA-DOTA). These chelators molecules could be rapidly filled with ^{177}Lu *in vitro*, resulting in stable complexes with high (>98%) rates of labelling, if optimised labelling conditions were selected (Breeman, 2003) (Li, 2001) (Stimmel, 1998). The complex with DOTA was found to be highly stable and mostly irreversible, with release of less than 5% of the label within 21 days of incubation *in vitro* (Brouwers, 2004).

2.5.2.2. Secondary pharmacodynamic studies

Lu^{3+} has been investigated as a membrane stabilizing agent, inhibiting transmembrane calcium permeation. Using a rat aorta preparation *in vitro*, lutetium and other rare earth metals were investigated for their effects on calcium distribution and transmembrane calcium movements, using the radioactive isotope Calcium-45. In addition, the effects of lutetium on aortic smooth muscle contractions were examined, since calcium entry is essential for contractions. At a concentration of 1.5 mM in the bath solution, Lu^{3+} reduced the calcium uptake in the preparation and had a relaxant property, interpreted as membrane stabilization (Weiss, 1975).

Ionic lutetium was also shown to interfere with inhibitory γ-aminobutyric acid (GABA) neurotransmission, resulting in enhancement of GABA currents. The effect of Lu^{3+} was investigated in rat septal neurons in culture by using the whole-cell voltage-clamp technique. GABA (10 μM) currents were moderately enhanced by about 40% upon application of a concentration of 100 μM Lu^{3+} (Kumamoto, 1996).

2.5.2.3. Safety pharmacology programme

Lutetium

The safety pharmacology of lutetium in its ionic form was evaluated using the isolated rabbit ileum, in anaesthetised cats and in non-anaesthetised rats.

In the isolated rabbit ileum preparation, lutetium chloride produced a concentration dependent relaxant effect, and at high concentrations (up to 40 mg) an irreversible paralysis was observed. If the rabbit ileum was pre-contracted with acetylcholine or nicotine, the contraction of these agents was antagonised with an antispasmodic EC_{50} of 0.6 and 0.5 mg/ml. In a different preparation, the cat superior ganglion preparation, lutetium had no ganglion blocking effect, indicating that the smooth muscle relaxant effect was due to a direct interaction with the muscle, in line with the reported calcium blocking activity of high concentrations of lutetium (Weiss, 1975) (Haley, 1964).

Cardiovascular effects of intravenously administered lutetium chloride were investigated in the anaesthetised cat. No pharmacological effects on respiration or on the cardiovascular system were observed in the dose range 1 to 10 mg/kg lutetium chloride, upon cumulative dosing. In this

publication, the intravenous LD_{50} for anaesthetized cats was established at 20 mg/Kg (12.5 mg/kg lutetium). However, even at this dose no QT-prolongation was reported. Within the dose range tested, lutetium chloride had no influence on the pharmacological response to acetylcholine, histamine, or electrical vagal stimulation (Haley, 1964).

Lutetium administration in non-anaesthetised rats had no effect on calcium accumulation at the dose level of 10 mg/kg i.v., but it resulted in increased concentration of calcium in various organs (liver, spleen, lungs and kidneys) at 20 mg/kg i.v. Lutetium (10 mg/kg) had no effect on hepatic metabolism, as indicated by a lack of change in hepatic cholesterol, triglycerides and phospholipids, serum lipids, and serum hepatic enzyme activity of aspartate transaminase (GOT or AST) and alanine transaminase (GPT or ALT) (Nakamura, 1997).

Hafnium

The safety pharmacology of hafnium chloride in its ionic form was evaluated using the guinea pig isolated ileum and in anaesthetised cats.

In the isolated guinea pig ileum preparation, hafnium chloride produced a concentration dependent relaxant effect, and at high concentrations (range tested: 10 to 200 mg, reference volume not given, most likely 10-200 mg/100 ml) an irreversible paralysis was obtained. If the rabbit ileum was pre-contracted with acetylcholine or nicotine, the contraction of these agents was antagonised with an antispasmodic EC_{50} of 128 and 99 mg, respectively (again, reference volume not given). In a different preparation, the cat superior ganglion preparation, hafnium had no ganglion blocking effect, indicating that the smooth muscle relaxant effect was due to a direct interaction with the muscle (Haley, 1962).

The cardiovascular effect of intravenously administered hafnium chloride was investigated in the anaesthetised cat. In cats, no pharmacological effects on respiration and cardiovascular function were observed up to a cumulative intravenous dose of 10 mg/kg Within the dose range tested, hafnium chloride had no influence on the pharmacological response to acetylcholine, histamine, or electrical vagal stimulation. (Haley, 1962).

2.5.2.4. Pharmacodynamic drug interactions

No studies were presented (see discussion on non-clinical aspects).

2.5.3. Pharmacokinetics

No specific studies were submitted with 177-lutetium. The characterization of absorption, distribution, metabolism and excretion (ADME) properties for lutetium is based on published data.

In the case of radiolabelled compound (^{177}Lu), gamma counting to quantify radioactivity was used. Non-labelled lutetium was quantified by using flame ionization detection. The referenced methods of analysis were obtained from the scientific publications provided in this section.

Distribution of ^{177}Lu

According to the general information provided in the review by ICRP (Paquet, 2019), in rats, lutetium is mainly distributed in the skeleton and liver, 60 and 10% respectively.

(Durbin, 1956)described the distribution of ^{177}Lu produced as no carrier added in rats. In this study, radioactivity was majorly found in skeleton (80%) and only 2-3% in liver after 24 post dosing. Significant levels were also found in kidney, as the primary route of excretion.

(O'Mara, 1969) investigated the distribution of [^{177}Lu]$LuCl_3$ in rabbits. In this study, effects of complexing agents were analysed. The authors concluded that the formation of a high stability constant complex (with DTPA), produced the rapid excretion in the urine without substantial reticuloendothelial or skeletal uptake. Complexes of low stability, "radiocolloid" formation and reticuloendothelial localization was observed, resulting in hepatic uptake. With hydroxyethyl ethylenediamine triacetic acid (HEDTA) as the complexing agent, complexes of intermediate stability were formed, and deposition in potential target organs was possible with no formation of 'radiocolloids'. With this complex, approximately 50% of the administered dose was taken up in the skeleton and then cleared by the kidneys.

(Muller, 1978) described a similar profile in terms of biodistribution in mice after intraperitoneal (ip) administration of lutetium oxide (solubilized in $KHSO_4$ and buffered with the complex forming agent citrate to a pH of 3.5). The highest levels of radioactivity were found in the skeleton (about 50%), followed by the liver, kidney and spleen, and with low exposure, the lung. The results of this study also showed the competition of radioactivity and non-radioactivity lutetium for bone uptake (when cold isotope dose was increased, deposition of radioactivity in bone was reduced).

Biodistribution of lutetium (^{177}Lu) chloride was investigated in rats using "cold" lutetium chloride among other chlorides of rare earth elements such as yttrium, cerium, praseodymium, europium, dysprosium, and ytterbium. The study results showed that rare earth elements are rapidly cleared from the systemic circulation upon IV administration, but there was significant and prolonged retention in the organs. The animals received either a low dose of 9 to 10 mg/kg body weight or a high dose of 18 to 20 mg/kg body weight of each rare earth metal. At 1 day after IV administration, more than 78% of the elements injected were distributed into liver, bone and spleen. With regard to lutetium, the major organs of accumulation at a dose of 10 and 20 mg/kg were the liver (64-67%), bone (11-15%) and spleen (5%), while only minor amounts (< 2%) could be detected in lungs and kidneys (Nakamura, 1997) (Pałasz A, 2000).

(Schmitt, 2003)conducted a biodistribution study in mice, after iv administration of radiolabelled lutetium. Again, liver, kidneys and bone (radioactivity was increasing with the time in the latter) showed the highest uptake values.

(Araujo, 2007) published a summarizing report with [^{177}Lu]$LuCl_3$ in mice. The results in Table 4 showed the primary target organs of exposure as the bone, blood, kidney and liver.

Table 2. Activity concentration of ^{177}Lu in different organs after administration of $[^{177}Lu]LuCl_3$ to Swiss mice expressed as % ID/g (Araujo, 2007)

Organ	1 h	4 h	24 h
Brain	0.22± 0.09	0.10 ±0.04	0.07 ± 0.02
Lungs	4.31 ± 1.12	2.74 ± 0.39	1.13 ± 0.34
Heart	2.14± 0.78	1.57 ± 0.40	0.63 ± 0.04
Spleen	2.32± 0.73	2.92 ±0.60	3.26± 0.73
Liver	5.65 ± 0.96	6.39 ± 0.34	5.83 ± 1.25
Stomach	5.59 ± 0.90	4.28 ±0.89	2.79± 0.63
Kidney	5.93 ± 1.50	10.52 ±4.43	7.13 ± 1.04
Small intestine	3.53 ± 0.43	1.96 ± 0.54	1.08 ± 0.44
Large intestine	1.53 ± 0.46	3.67 ± 1.06	0.77 ± 0.11
Adrenal glands[1]	1.64 ± 0.43	2.50 ± 0.31	0.84± 0.25
Pancreas	1.49 ± 0.30	0.95 ±0.30	0.32 ± 0.06
Muscle	0.84 ± 0.28	0.49 ± 0.09	0.16± 0.04
Blood	11.62 ± 7.47	5.87 ± 3.65	0.22± 0.10
Bone	11.41 ± 1.04	18.85 ± 5.77	12.32± 2.07

(Lungu, 2007) analysed the distribution of $[^{177}Lu]LuCl_3$ in tumour bearing Lewis rats (Table 5). The liver, kidney and bone were identified as the primary target organs for distribution, with a rapid clearance from blood. In bone, accumulation over 24 h followed by slow clearance was observed.

Table 3. Activity concentration of ^{177}Lu in different organs after administration of $[^{177}Lu]LuCl_3$ to Lewis rats expressed as % ID/g (Lungu, 2007)

	Time post-injection						
Region	30 min	1 h	4 h	24 h	48 h	120 h	168 h
Blood	7.90	6.21	3.84	0.84	0.10	0.03	0.00
Heart	2.80	2.14	1.82	0.65	0.04	0.03	0.00
Liver	4.10	4.80	5.34	4.73	2.22	1.09	0.35
Spleen	2.24	2.30	2.96	3.24	2.00	1.03	0.23
Kidneys	5.22	5.91	12.34	13.51	5.33	3.83	0.31
Stomach	2.04	3.04	4.53	2.87	2.37	0.61	1.12
Gastrointestinal tract	1.32	3.94	5.35	2.34	0.66	0.34	0.27
Bone	8.20	10.82	15.34	16.12	13.33	12.03	10.5
Muscle	0.16	0.48	0.52	0.26	0.26	0.17	0.08
Adrenal gland	0.53	0.84	1.84	1.41	0.54	0.36	0.16
Pancreas	1.62	1.53	1.13	0.82	0.53	0.30	0.21
Thyroid	0.56	0.67	0.58	0.32	0.16	0.10	0.08
Pituitary gland	0.03	0.09	0.12	0.19	0.02	0.00	—

Additional studies (Yousefnia, 2014) (Zolghadri, 2015) (Mirković, 2020) reported similar results as the ones from the previous distribution studies.

Previous biodistribution data obtained in mice were scaled up to humans and the applicant estimated scaled time integrated activity values as well as estimate absorbed doses for target organs. See 2.6.2.2. and Table 6 below:

Table 4 - Scaled time-integrated activity values (Â values) [MBq*h] for an injected activity of 1000 MBq in humans

Organ	(Schmitt, 2003)	(Repetto-Llamazares, 2013)	(Araujo, 2007)	(Yousefnia, 2014)	(Mirković, 2020)	Mean Scaled Average Human [MBq*h]
Blood	61	1050	1930	378	-	855
Brain	112	-	38	-	-	75
Cortical bone mineral surface	-	31700	6300	45700	126000	52425
Cortical bone mineral volume	-	31700	6300	45700	126000	52425
Heart Contents	104	-	48	120	720	248
Heart Wall	13	-	5	12	80	27
Kidneys	492	1490	702	-	1490	1044
Liver	2010	3170	9540	10300	13800	7764
Lungs	1050	1320	358	193	2830	1150
Muscle	2740	-	1190	108000	38100	37508
Pancreas	41	-	13	-	-	27
SI contents	357	-	263	4650	1300	1643
Spleen	127	121	489	313	1070	424
Stomach contents	-	-	133	165	519	272
Trabecular bone mineral surface	-	15600	3120	22500	62200	25855
Trabecular bone mineral volume	-	15600	3120	22500	62200	25855

Distribution of ^{177}Hf

(Hinerman, 1954) reported the distribution of hafnium after sc administration in rats. It was detected in the spleen, liver, bone, skin, adrenal glands, and in the gastrointestinal tract. There was no evidence of selective accumulation in adrenal glands. Hafnium was excreted both in faeces and urine.

Metabolism

The metabolism of free ^{177}Lu is described to decay to ^{177}Hf, which is a stable isotope. Renal and faecal route, as well as radioactive decay are described to contribute to the elimination of lutetium.

Excretion

(O'Mara, 1969) described the excretion of lutetium-177 via urine after iv administration in rabbits. (Durbin, 1956) reported also faecal excretion following intramuscular dosing in rats. Radioactive decay is also considered, especially from bone.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Lutetium: single dose toxicity

(Haley, 1964) reported the LD_{50} values in mice after a single dose (ip or po) of lutetium. Symptoms described were writhing, ataxia, laboured respiration, walking on toes with back arched, and sedation. Died animals were found within 24 hours. The intraperitoneal LD_{50} of lutetium chloride was 315 (267-372) mg/kg, corresponding to 197 mg lutetium/kg. The oral LD_{50} in mice was 7100 (6633-7590) mg/kg, corresponding to 4435 mg lutetium/kg. In this publication, also the intravenous LD_{50} for anaesthetized cats was established at 20 mg/Kg (12.5 mg/kg lutetium).

(Garrett, 1981) reported the subcutaneous LD_{50} in mouse (> 312 mg/kg lutetium). No lethality was induced, but calcification could be observed in the site of administration.

(BRUCE, 1963) defined the intraperitoneal LD_{50} values of lutetium nitrate in mice and rats. In mice, LD50 was established at 290 (259-325) mg/kgf or the salt, corresponding to a dose of the metal of 108 (97-121) mg/kg. In rats, an intraperitoneal LD_{50} of 335 mg/kg, corresponding to a dose of the metal of 125 (110-142) mg/kg, was determined.

Hafnium: single dose toxicity

(Haley, 1962) reported the toxicity of hafnium chloride (or hafnyl chloride, which is formed in water solution) in mice. Urination and lethargy were reported as acute toxicity symptoms, and deaths occurred within the 24 hours post dose. The intraperitoneal LD_{50} of hafnyl chloride was 112 (93.3-134.4) mg/kg, corresponding to an LD_{50} of 76 mg/kg for hafnium.

In the toxicity profile for lutetium published by (BIBRA toxicity profile, 1994), oral LD50 in rats was fixed at 2362 mg/kg for $HfCl_4$, whereas up to 10 g/kg of hafnium dioxide orally were tolerated in mice without lethality. For iv administration in rats, hafnium-sodium mandelate was used (improving solubility). The intravenous LD_{50} was 75 – 100 mg hafnium/kg (an exact LD50 could not be calculated, since the ratio of hafnium to sodium mandelate was not given in the report). In cats, the intravenous administration of 10 mg hafnium chloride/kg (corresponding to about 5.56 mg hafnium/kg) was lethal.

2.5.4.2. Repeat dose toxicity

Lutetium: repeat dose toxicity (90 days)

(Haley, 1964) reported the NOEL value for LuCl3 in rats at 1% in the diet (for 90 days), corresponding to about 1000 mg lutetium chloride/kg body weight or 625 mg lutetium/kg body weight.

Hafnium: repeat dose toxicity (up to 90 days)

In the toxicity profile for lutetium published by Bibra (1994), iv administration of hafnium dichloride (10 weeks at a dose of 14 mg/kg BW) in rats resulted in slower growth. No further signs of toxicity were reported.

(Haley, 1962) reported a NOEL value in rats after oral administration of hafnium chloride at 0.1% in the diet, corresponding to about 100 mg hafnium chloride/kg body weight or 55.5 mg hafnium/kg body weight (90 days of administration in the diet). No signs of toxicity were observed, but there was a dose dependent metabolic adaptation reaction seen in the liver, with perinuclear vacuolization and coarse granularity of the parenchymal cells. The findings were prominent in the 1% feeding group, but only sparse in the 0.1 and 0.01% feeding groups. The NOEL of orally administered hafnium chloride was considered to be 0.1% in the diet, corresponding to about 100 mg hafnium chloride/kg body weight or 55.5 mg hafnium/kg body weight.

In guinea pigs (BIBRA toxicity profile, 1994), a slightly increased liver weights and slightly reduced kidney and spleen weights were noted although they were not statistically significant. Histopathology revealed slight thickening of the alveolar walls in the lung and granularity in the cytoplasm of hepatocytes. No NOAEL was determined up to 2000 mg/kg daily for one month by oral administration of hafnium dioxide.

(Hinerman, 1954) described the effect of hafnium sodium mandelate (undefined amount of hafnium) following oral, subcutaneous or intramuscular administration in rats. The oral dose of 5-25 mg/rat for up to 16 days was well tolerated, and no signs of toxicity observed. The subcutaneous and intramuscular administration of up to 35 mg/rat for three weeks resulted in no overt systemic toxicity other than reduced body weight gain, but animals developed local abscesses related to the dosing site. Examination revealed that hafnium precipitated as insoluble material at the injection site and was taken up by mononuclear phagocytes. Histological evaluation revealed that the insoluble material was also carried to the reticuloendothelial cells of the spleen, liver, lymph nodes and occasionally also the kidneys.

2.5.4.3. Genotoxicity

No studies of mutagenicity with lutetium 177 were provided (see 2.5.6. Discussion on non-clinical aspects).

2.5.4.4. Carcinogenicity

(Muller, 1978) showed an increased rate of osteosarcoma formation in rats after a 12-month exposure period to 177Lu (estimated dose 2000-8000 rd, 20-80 Gy). It was comparable to the effect of the radiation from exposure to strontium-90.

(Shelley, 1973) reported the formation of dysplastic cartilage at the site of injection (intradermal) when hafnium oxychloride (3 mM, about 20 µg/mouse administered locally) was dosed to mice. It was observed 5 months after administration and was comparable to the effect observed for zirconium chloride. Other metal salts with known carcinogen potential including beryllium, cadmium, chromium,

cobalt, and nickel, did not induce this local reaction. No such local reactions were observed in humans after intradermal injection of hafnium oxychloride (Shelley, 1958).

2.5.4.5. Reproductive and developmental toxicity

No effect was reported on reproductive organs after a 90-day dosing period (food) for lutetium or hafnium chloride. The NOEL for lutetium and hafnium was 625 mg/kg body weight (Haley, 1964) and 55.5 mg/kg body weight (Haley, 1962), respectively.

No data for teratogenic potential were submitted (see 2.5.6. Discussion on nonclinical aspects).

No dedicated reproductive toxicity or juvenile animal studies were submitted (see 2.5.6. Discussion on nonclinical aspects)

2.5.4.6. Local Tolerance

Local tolerance of lutetium chloride

(Haley, 1964) reported the action of concentrated lutetium chloride (1:1 solution) to eyes, resulting in local irritation and delayed ulceration of the cornea, which healed completely within two weeks. When crystalline lutetium chloride (0.5 g) was applied to intact skin, no irritation was caused. While the crystalline compound in contact with abraded skin, produced a severe reaction. The irritated skin healed only after 35 days with formation of scar tissue.

Local irritation or necrosis were observed after intradermal administration (even at the lowest concentration tested 1:104 and 1:105 dilution in water). Formation of nodules (crystalline deposits of unknown composition, although probably they represent calcifications) was observed. Foreign body giant cells surrounded the crystals, and fibroblasts were found in the outer area.

(Garrett, 1981) described local calcifications in mice when lutetium chloride was administered (sc) at a concentration range of 500 to 10000 µg/0.2 ml. A dose of 200 µg/0.2 ml did not cause local calcification.

Local tolerance of hafnium chloride

(Haley, 1962) published that the application of a 1:1000 dilution of hafnyl chloride (pH 2.1) caused no damage of the cornea or iris or irritation of the conjunctiva. However, 1 mg of hafnium chloride (dry substance) in the eyes of rabbits caused an immediate increase in blinking rate and redness of the conjunctiva. It was completed reverted at 24 hours post dose.

In the skin, hafnium chloride produced a minor transient irritation. However, the direct application of crystals on abraded skin caused a strong local irritation, with ulceration observed at seven days and no healing at 14 days. The difference was attributed to the release of HCl from hafnium chloride.

Finally, intradermal injection of hafnyl chloride in guinea pigs (diluted solution 1:104 and 1:108) produced mild transient local irritation and complete remission to normal within seven days. At higher concentrations, stronger irritation was observed (probably for the acidic nature of the compound).

2.5.4.7. Other toxicity studies

See 2.5.6. Discussion on non-clinical aspects.

2.5.5. Ecotoxicity/environmental risk assessment

Phase I

PEC (Predicted Environmental Concentration) estimation was based on the maximum recommended dose of 0.002 mg, resulting in a PECsw value of 0.0000001096 μg/L. This value is below the action limit established in the guideline, so phase II was not considered necessary.

$$PEC_{surfacewater} = \frac{DOSE_{ai} \times F_{pen}}{WASTEW_{inhab} \times D \times 100}$$

$Dose_{ai}$	Maximum daily dose of active ingredient per inhabitant. According to the specific activity and the radiation dose limit of 6 GBq/dose, the highest foreseeable mass dose is 2 μg/patient, administered as up to 4 single doses (0.002 mg)
Fpen	Percentage of market penetration (default: 1%)
$WasteW_{inhab}$	Volume of waste water per capita and day (200 L x inh^{-1} x d^{-1})
D	Factor for dilution of waste water by surface water flow (default factor: 10)

As for potential risk for accumulation (highly lipophilic compounds with an experimentally determined log*Kow* (Log*P*) of >4.5), would require additional testing. In the case of lutetium chloride, it dissociates to [^{177}Lu]Lu^{3+} and chloride when in solution, and is therefore an electrolyte. According to the guideline, no ERA studies are required upon justification for electrolytes, as Lu^{3+} ^{as} due to their nature they are unlikely to result in a significant risk to the environment. Similar consideration is assumed for 177-Hafnium. In both cases, no accumulation is expected given they are electrolytes.

With regards to a potential hormone function or an endocrine disruptive function, no accumulation in reproductive organs has been reported and the applicant considers an interaction with endocrine system as unlikely.

The radiation related risk indicated that the final product prepared from Lu177 is intended to have a high affinity for the target issue and will be in the body for more time than the radioactive life-time (6.647 days). In addition, administration of LU177 will be performed in a hospital facility preventing the radioactive contamination of the general sewage system, so the radioactive environmental exposure will be limited to a minimum

Nevertheless, an environmental risk assessment should be carried out and submitted separately for any final radiolabelled product, which was prepared using lutetium (^{177}Lu) n.c.a.

Table 5. ERA Summary of main study results

Substance (INN/Invented Name): Lutetium-177			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		Electrolyte (no logK_{ow})	Potential PBT (**N**)
PBT-assessment			
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, refined (e.g. treatment regime)	0.0000001096	µg/L	> 0.01 threshold (**N**)
Other concerns	radioactive		(**Y**)

2.5.6. Discussion on non-clinical aspects

In accordance with the chosen legal basis, the information provided in this dossier is based on published literature. No dedicated nonclinical studies conducted with lutetium-177 have been submitted by the applicant. As non-clinical data have been derived from the published literature, the GLP status could not be verified from most of these publications, given that some of them were conducted and published prior to the GLP requirements came into force. However, the non-clinical data submitted were considered acceptable and it was not considered needed to repeat animal studies under GLP conditions, in the present case.

Lutetium (^{177}Lu) chloride non carrier added is a precursor to be used for radiolabelling purposes. The isotope will be linked to a disease-specific carrier for targeted radiotherapy.

Pharmacological actions are shown for lutetium as a free radioisotope according to the reports and publications on its medical use. Animal studies with the radioactive isotope of lutelium, ^{177}Lu, have shown that it has a high affinity with bone tissue and given its unique radioactive characteristics of emitting both beta and gamma energy, may be a useful product for imaging bone tissue.

^{177}Lu decays to the more stable isotope ^{177}Hf, which is reported to be present in nature and can be taken up in food, drinking water or as inhaled dust. Similarly, pharmacology actions of hafnium 177 are shown. Its use for some medical applications has also been explored e.g. intravascular radiocontrast imaging, administration of hafnium oxide nanoparticles in cancer models or in medical devices for implantation in bone.

In relation to secondary pharmacology, two studies were presented, one describing the effects of lutetium ions on calcium distribution (Weiss, 1975) and the other studying the effects of ionic lutetium on inhibitory GABA neurotransmission (Kumamoto, 1996). These effects were observed at concentrations far above those used in the intended clinical practice for ilLuzyce.

No novel actions from the already reported are described in terms of pharmacological effects.

Overall, toxicological data were also referred to scientific publications. The toxicity of non-radioactive lutetium chloride has been studied in different mammalian species and using different administration routes. Limited information after repeat dose of lutetium has been provided by the applicant. No studies after iv administration are presented. NOEL value was established at 1% (equivalent to 625 mg

lutetium/kg body weight) in rats after receiving a diet containing lutetium chloride for 90 days. The intraperitoneal LD50 in mice was found to be approximately 315 mg/kg. In cats, no pharmacological effects on respiration and cardiovascular function were observed up to a cumulative intravenous dose of 10 mg/kg. A high dose of 10 GBq of lutetium (^{177}Lu) chloride contains 2.4 µg lutetium, corresponding to a human dose of 0.034 µg/kg. This dose is approximately 7 orders of magnitude lower than the intraperitoneal LD50 in mice and more than 5 orders of magnitude lower than the NOEL observed in cats. Therefore, lutetium metal-ion toxicity of ilLuzyce (^{177}Lu)-labelled medicinal products can be excluded.In the case of hafnium, iv administration for 10 weeks resulted in slower growth of rats, with no symptoms of toxicity. When hafnium was orally dosed (diet), the NOEL was 55.5 mg/Kg body weight. In guinea pigs receiving hafnium (po), no NOAEL was set up to 2000 mg/Kg/day. An additional study, carried out in rats treated with hafnium sodium mandelate (no equivalent dose of hafnium was provided) showed findings in the spleen, liver, lymph nodes and kidneys, due to the presence of insoluble hafnium precipitated. Hafnium toxicity was also reviewed.

In addition, given that both lutetium and hafnium elicit no pharmacological effects at clinically relevant concentrations the lack of pharmacodynamic interaction studies is acceptable.

The pharmacokinetic profile of lutetium has been described based on scientific publications referencing standard methods of analysis (gamma counting and flame ionization detection) to quantify radiolabelled and non-radiolabelled molecules.

No absorption studies were conducted with animals. The applicant mentioned that following intravenous administration of [^{177}Lu]$LuCl_3$, ^{177}Lu is rapidly cleared from the blood. Other routes of administration, as oral route, indicate that the oral uptake of lutetium following oral ingestion is low, typically less than 0.5% (International Commission of Radiological Protection, ICRP, (Sowby, 1981)).

Distribution was reported to mainly occur in bone, liver, kidneys, red marrow and spleen. Short-term analysis indicated a distribution mainly in liver and kidney, while long-term uptake was shown in skeleton. It was also dependent on the complex formed after administration. Formation of stable complexes led to a rapid excretion, via urine with no accumulation. Low stability complexes caused radiocolloids, which were then localised in liver via reticuloendothelial system. Intermediate stability complexes localised in skeleton. Free lutetium administration was shown to result in hafnium-177 accumulation in bone (long-term uptake of lutetium-177), given radioactive decay. As for the calculation of the "scaled time-integrated activity values (Â) MBq*h] for injection activity of 1000 MBq in humans, it was based on published biodistribution data (See 2.6.2.2.).

Free ^{177}Lu is not metabolized, although it decays to ^{177}Hf, which is a stable isotope. No free ^{177}Lu is administered or released, so the metabolism of the final product will depend on the carrier molecule.

Given that since it is a precursor to be used for in vitro radiolabelling of carrier molecules and is not directly injected in patients, the absence of pharmacokinetic drug interactions and other pharmacokinetic studies is considered acceptable.

Extrapolation to humans from mammalian species, showed that although there is no accumulation of lutetium, low exposure to radiation may be expected for male and female reproductive organs.

The acute toxicity profile of lutetium and hafnium was described in mice, rats and cats. Correspondent LD_{50} values were established by using different routes of administrations (po, ip, iv). Signs of acute toxicity were ataxia, laboured respiration, or lethargy. Deaths occurred within 24 hours post dose, and peak was normally registered at 48 hours.

No genotoxicity studies were presented by the applicant. This is acceptable, considering the therapeutic dose levels intended.

According to Annex 1 Part I of Dir 2001/83/EC, carcinogenicity studies are required in case of long-term exposure. Radiopharmaceutical are used for a short period of time. Despite the known carcinogenic potential due to the radiation emitted during radioactive decay and described in rats after 12 months of exposure to lutetium 177 (estimated dose 2000-8000 rd, 20-80 Gy), the absence of carcinogenicity studies was considered acceptable, given the conditions for use of this product. Of note, the potential risk of osteosarcoma described in rats after 12 months exposure was comparable to the effect of the radiation from exposure to strontium-90 (See 2.5.4.4. and 2.6.9.).

No dedicated reproductive toxicity or juvenile animal studies with lutetium were presented. Effects of lutetium (^{177}Lu) chloride on male and female fertility have not been studied in animals. Low exposures could be demonstrated for male and female sexual organs. It cannot be excluded that ^{177}Lu-labelled medicinal products lead to reproductive toxicity including spermatogenetic damage in male testes or genetic damage in male testes or female ovaries (see SmPC section 4.6). Further information concerning the use of lutetium (^{177}Lu)-labelled medicinal products concerning fertility is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

Local tolerance effects observed with lutetium (and hafnium) can be attributed to the acidic character of the solution, which produces irritation or even necrosis of the tissues. However, lutetium chloride is not intended for direct administration in human.

The damage on tissues or necrosis (pH 1-2) caused by a paravenous injection or infusion into small or collapsed large veins were reported to be potentially irreversible (Braun Melsungen AG, 2006). In case of accidental administration of Lutetium (^{177}Lu) chloride n.c.a., solution to the patient, the catheter or affected area should be irrigated with isotonic saline solution.

A risk associated with inadvertent administration of ^{177}LuCl3 has been identified. (See 2.6.9.)

An environmental risk assessment conducted in accordance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2) for the chemical molecule, and not for the radiation produced as radiopharmaceutical was provided. Lutetium-177 PEC surfacewater value is below the action limit of 0.01 µg/L and therefore, lutetium (^{177}Lu) chloride is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical aspects of Lutetium-177 have been assessed and the information submitted is considered adequate. The main concern relates to the development of osteosarcoma and its latency observed in rats and mice studies after long-term exposure, however Lutetium-177 is only intended for short-term use. The risk has been addressed in the RMP as a potential safety concern and in the SmPC, which includes recommendations on the addition of DTPA prior to intravenous administration of ^{177}Lu labelled ligands.

No supplementary animal studies are needed because safety issues can adequately be evaluated from the literature.

The toxicological properties of lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with ilLuzyce prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

For the purpose of an application for a radiopharmaceutical for radiolabelling, the non-clinical aspects of ilLuzyce have been adequately addressed.

2.6. Clinical aspects

2.6.1. Introduction

This is an application submitted under the legal basis of Article 10a of Directive 2001/83/EC, well-established use. The applicant has justified this with evidence of the first diagnostic and therapeutic use of ^{177}Lu being over a decade ago in Europe and provided further evidence to support an increase over the years in the use of this product as a radiolabel. ilLuzyce radiopharmaceutical precursor, which is intended for radiolabelling purposes and therefore not to be used directly in patients.

The applicant did not submit any clinical efficacy study, but in line with the Annex 1 Part III of Directive 2001/83/EC, as amended, on radiopharmaceutical precursors, relevant information on the clinical utility of the radiopharmaceutical precursor Lutetium (^{177}Lu) chloride when is attached to appropriate carrier molecules was provided.

A brief literature overview is presented on the various applications of ^{177}Lu-labelled tracer molecules.

Tracer molecules (see Table 1, in section 2.1.2- Epidemiology) were selected based on the experience in the field of radiopharmaceuticals, especially the tracer molecules DOTATATE, DOTATOC, DOTANOC as well as PSMA are widely known and can be considered well-established in this field. Thus, the applicant considered relevant clinical studies on the efficacy and safety of ^{177}Lu-labelled tracer molecules as well as ^{177}Lu-labelled tracer complexes, in and outside the EU. No restrictions were made in terms of the particular clinical indication.

An initial PubMed search in February 2021 using the terms "lutetium" OR "lutetium-177" OR "177Lu" revealed about 3000 hits, including all articles without any limitation. Focusing on the most important molecules regularly used in daily clinical practice for specific radiotherapies, the literature search was then narrowed down using the additional search terms "DOTATOC", "DOTATATE", "DOTANOC", "EDTMP", "PSMA", "antibody", and "safety".

Each article was evaluated for relevance based on title, abstract or the complete article. Full text articles were evaluated, including a check of the reference lists for further relevant articles.

GCP aspects

Not applicable as no clinical studies have been conducted with ilLuzyce.

2.6.2. Clinical pharmacology

The applicant has not provided any clinical studies referring to clinical pharmacology for Lutetium (^{177}Lu) chloride n.c.a (see 2.6.3. discussion on clinical pharmacology).

2.6.2.1. Pharmacokinetics

Lutetium (^{177}Lu) chloride n.c.a., solution is a radiopharmaceutical precursor which is only intended for use in in-vitro-labelling of medicinal products for diagnostic or therapeutic purposes. The pharmacokinetic properties of the proposed medicinal product depend on the particular tracer molecule labelled with radionuclide and its linker (chelator) which may affect the pharmacokinetics of the radionuclide (Forrer F, 2004), (Hijnen NM, 2012).

2.6.2.2. Dosimetry

Dosimetry of lutetium (^{177}Lu) chloride

The presented dosimetry data derived from literature in mice, rats and rabbits.

Dosimetry of the active substance Lutetium (^{177}Lu) chloride was investigated to evaluate the contribution of non-conjugated lutetium-177 to the radiation exposure following the administration of a ^{177}Lu-labelled tracer or resulting from an accidental injection of the precursor according to literature.

Following intravenous administration of lutetium (^{177}Lu) chloride, ^{177}Lu was rapidly cleared from the blood. Primary target organs were bone, liver and kidney.

Scientific studies published were used for the dosimetry calculations based on the fact that the studies were realised for $^{177}LuCl_3$. The studies used were the available literature for $^{177}LuCl_3$ and were also used in previous applications by other marketing authorisation holders. Reported biodistribution data for $^{177}LuCl_3$ in mice (Araujo, 2007), (Mirković, 2020), (Repetto-Llamazares, 2013), (Schmitt, 2003) and (Yousefnia, 2014) were scaled to humans using the following equation:

$$TAC_H = TAC_A \cdot \frac{O_H/BW_H}{O_A/BW_A}$$

where TAC_H is the time-activity curve (TAC) equivalent for humans, TAC_A is the organ TAC for animals (mice or rats) from the considered studies, O_H is the organ mass for humans, BW_H is the body weight for humans, O_A is the organ mass for animals and BW_A is the animal body weight. Body weight and organ masses for the animals were obtained from the animal biodistribution studies while the human body weight and organ masses were assumed to be for an average adult human (mean between adult male and female (Bolch, 2016)). Decay correction in TACs was revoked from the animal data when decay-corrected data was reported in the animal studies. When multiple bone structures were reported (e.g. femur and skull) the bone TAC was generated with the mean of the reported structures. (See 2.5.3.).

In order to provide dose calculation for paediatric phantoms as well, the mean human $\hat{A}$ have been scaled to the available Olinda/EXM 2.0 phantoms to determine model specific distribution data. The scaling between mean human and specific models was performed according to Eq.1.

The $\hat{A}$ values have been normalized to the injected activity of 1000 MBq to get the time integrated activity coefficient (TIAC) as required by Olinda/EXM 2. Olinda/EXM 2 models are based on ICRP 89 Publication.

All dose calculations were performed in Olinda/EXM 2 (Stabin, 2018) to have consistent dose results for all models (adults and paediatrics).

Dose calculations (absorbed doses for target organs [mGy/MBq] and effective doses [mSv/MBq]) were performed in Olinda/EXM 2 dose calculator using the mean $\hat{A}$ value (mean between the $\hat{A}$ values obtained from each considered animal study) for each source organ. Organ doses were reported for an adult male and female model as well as 15-year, 10-year, 5-year, 1- year and newborn male and female models (see Table 8 and Table 9 below), according to ICRP 89 (International Commission on Radiological Protection). The results show osteogenic cells, liver, kidneys, red marrow and spleen as the significant target organs for the biodistribution of lutetium (^{177}Lu) chloride.

Table 6. Estimated organ normalised absorbed doses [mGy/MBq] and effective normalized dose [mSv/MBq] in male models as calculated with the Olinda/EXM 2 dose calculator of ^{177}LuCl3.

Target organ	ICRP 89 Adult Male	ICRP 89 15 year old male	ICRP89 10 year old male	ICRP89 5 year old male	ICRP89 1 year old male	ICRP89 Newborn male
Adrenals	2.25E-02	2.78E-02	4.44E-02	6.60E-02	1.31E-01	2.31E-01
Brain	1.44E-02	7.41E-02	2.47E-02	3.69E-02	5.45E-02	1.30E-01
Esophagus	1.08E-02	1.23E-02	1.75E-02	2.55E-02	3.78E-02	7.87E-02
Eyes	1.00E-02	1.21E-02	1.48E-02	2.03E-02	2.30E-02	4.02E-02
Gallbladder wall	1.67E-02	1.98E-02	3.10E-02	4.90E-02	9.14E-02	2.22E-01
Left colon	9.62E-03	1.20E-02	1.94E-02	2.94E-02	4.99E-02	9.38E-02
Small intestine	1.95E-01	2.53E-01	5.01E-01	7.43E-01	9.47E-01	2.16E+00
Stomach wall	8.24E-02	1.07E-01	1.85E-01	3.08E-01	5.82E-01	1.62E+00
Right colon	8.16E-03	9.80E-03	1.60E-02	2.45E-02	4.11E-02	8.27E-02
Rectum	6.95E-03	8.37E-03	1.31E-02	1.96E-02	3.13E-02	5.59E-02
Heart wall	3.93E-02	5.05E-02	8.46E-02	1.39E-01	2.59E-01	7.14E-01
Kidneys	2.91E-01	3.78E-01	6.57E-01	1.10E+00	2.08E+00	5.86E+00
Liver	3.98E-01	5.16E-01	8.95E-01	1.50E+00	2.83E+00	7.98E+00
Lungs	9.22E-02	1.20E-01	2.06E-01	3.42E-01	6.47E-01	1.79E+00
Pancreas	2.83E-02	3.51E-02	5.85E-02	9.56E-02	1.79E-01	4.60E-01
Prostate	3.95E-03	5.24E-03	9.57E-03	1.21E-02	2.32E-02	4.01E-02
Salivary glands	6.43E-03	7.49E-03	9.02E-03	1.27E-02	1.69E-02	3.23E-02
Red marrow	2.70E-01	3.38E-01	6.98E-01	1.41E+00	3.44E+00	9.25E+00
Osteogenic cells	4.28E+00	5.35E+00	8.72E+00	1.36E+01	2.92E+01	7.83E+01
Spleen	2.45E-01	3.19E-01	5.53E-01	9.29E-01	1.76E+00	9.28E-02
Testes	3.40E-03	3.99E-03	5.59E-03	8.02E-03	1.41E-02	2.87E-02
Thymus	6.27E-03	7.74E-03	1.09E-02	1.75E-02	2.97E-02	6.92E-02
Thyroid	7.28E-03	8.04E-03	1.06E-02	1.51E-02	2.04E-02	4.22E-02
Urinary bladder wall	3.64E-03	4.78E-03	8.85E-03	1.10E-02	2.11E-02	3.57E-02
Total body	1.21E-01	1.53E-01	2.64E-01	4.20E-01	7.35E-01	1.84E+00
Effective dose [mSv/MBq]	1.22E-01	1.55E-01	2.76E-01	4.78E-01	1.02E+00	2.73E+00

Table 7. Estimated organ normalised absorbed doses [mGy/MBq] and effective normalized dose [mSv/MBq] in female models as calculated with the Olinda/EXM 2 dose calculator of ^{177}LuCl3.

Target organ	ICRP 89 Adult Female	ICRP 89 15 year old Female	ICRP 89 10 year old Female	ICRP 89 5 year old Female	ICRP 89 1 year old Female	ICRP 89 Newborn Female
Adrenals	2.66E-02	2.93E-02	4.65E-02	7.15E-02	1.36E-01	2.50E-01
Brain	1.59E-02	1.71E-02	2.47E-02	3.72E-02	5.49E-02	1.31E-01
Breasts	4.10E-03	4.31E-03	-	-	-	-
Esophagus	1.17E-02	1.24E-02	1.80E-02	2.67E-02	4.75E-02	1.25E-01
Eyes	1.06E-02	1.11E-02	1.48E-02	2.04E-02	2.30E-02	4.04E-02
Gallbladder wall	1.34E-02	1.45E-02	2.28E-02	3.31E-02	6.25E-02	1.21E-01
Left colon	9.92E-03	1.07E-02	1.71E-02	2.58E-02	4.27E-02	9.56E-02
Small intestine	2.59E-01	2.67E-01	5.01E-01	7.44E-01	9.50E-01	2.17E+00
Stomach wall	9.99E-02	1.12E-01	1.84E-01	3.07E-01	5.81E-01	1.63E+00
Right colon	8.06E-03	8.68E-03	1.41E-02	2.28E-02	4.30E-02	9.95E-02
Rectum	7.22E-03	7.73E-03	1.25E-02	1.85E-02	2.99E-02	5.16E-02
Heart wall	4.52E-02	5.05E-02	8.92E-02	1.35E-01	2.23E-01	6.98E-01
Kidneys	3.53E-01	3.99E-01	6.58E-01	1.10E+00	2.08E+00	5.87E+00
Liver	4.82E-01	5.45E-01	8.95E-01	1.50E+00	2.83E+00	7.99E+00
Lungs	1.11E-01	1.25E-01	2.05E-01	3.42E-01	6.46E-01	1.79E+00
Ovaries	7.16E-03	7.70E-03	1.15E-02	1.64E-02	2.76E-02	5.59E-02
Pancreas	3.55E-02	3.95E-02	6.28E-02	1.04E-01	1.87E-01	5.10E-01
Salivary glands	6.51E-03	6.66E-03	8.99E-03	1.26E-02	1.67E-02	3.23E-02
Red marrow	3.09E-01	3.50E-01	6.97E-01	1.41E+00	3.44E+00	9.25E+00
Osteogenic cells	3.79E+00	5.17E+00	8.72E+00	1.36E+01	2.92E+01	7.83E+01
Spleen	2.98E-01	3.37E-01	5.54E-01	9.32E-01	1.76E+00	4.96E+00
Thymus	7.49E-03	7.79E-03	1.16E-02	1.75E-02	2.86E-02	7.00E-02
Thyroid	7.37E-03	7.59E-03	1.04E-02	1.46E-02	1.97E-02	3.86E-02
Urinary bladder wall	4.40E-03	4.59E-03	8.53E-03	1.04E-02	2.02E-02	3.30E-02
Uterus	6.00E-03	6.43E-03	9.67E-03	1.42E-02	2.38E-02	5.36E-02
Total body	1.33E-01	1.55E-01	2.64E-01	4.20E-01	7.36E-01	1.85E+00
Effective dose [mSv/MBq]	1.32E-01	1.58E-01	2.76E-01	4.78E-01	1.02E+00	2.78E+00

2.6.2.3. Special populations

Impaired renal function

For PRRT, kidneys were usually the critical organs in terms of radiation toxicity due to non-specific or specific accumulation of radiolabelled peptide and renal excretion of radiolabelled peptides, and a range of 23-29 Gy was identified as renal maximum tolerated dose. Renal irradiation is mainly caused by reabsorption of radiolabelled peptides in the proximal tubules (Zhang J, 2018).

A study investigating the influence of renal function on kidney absorption and haematotoxicity upon administration of ^{177}Lu-DOTATATE to patients with advanced NETs was published by Svensson et al. in 2015. Fifty-one patients with advanced NETs received ^{177}Lu-DOTATATE at an average activity of 7.5 GBq (3.5-8.2 GBq) at intervals of 6 to 8 weeks on one to five occasions. A significant correlation could be found between inferior renal function before treatment and higher received renal absorbed dose per administered activity ($p<0.01$). Patients with inferior renal function also experienced a higher grade of haematotoxicity during treatment ($p=0.01$). The authors concluded that despite the general good tolerability of PRRT in patients with an advanced NETs– patients with inferior renal function are at risk of being exposed to higher absorbed doses to normal tissue on treatment (Svensson J, 2015).

Individualised treatment with ^{177}Lu-DOTATATE based on kidney dosimetry was investigated by Sundlöv and colleagues in 2017. Patients were treated with repeated cycles of 7.4 GBq ^{177}Lu-DOTATATE at 8-12-week intervals. Although GFR decreased in most patients after the completion of treatment, no grade 3-4 toxicity was observed. Patients with a reduced baseline GFR were considered to have an increased risk of GFR decline. It was concluded from the available data that individualised PRRT based on kidney dosimetry provides a safe and efficacious treatment approach (Sundlöv A, 2017).

Race

Data on diagnostic performance of radiolabelled PSMA-tracers in black South-African and white South-African prostate carcinoma patients were presented (Sathekge M, 2018). Maximum standardized uptake value (SUVmax) values were found to be significantly higher in black South-Africans than in white South-Africans. Moreover, SUVmax values correlated significantly with serum prostate-specific antigen (PSA) values, which were significantly higher in black South-Africans than in white South-Africans. The data suggested that PCa behaved more aggressive in black South-Africans compared to the white patient cohort and therefore, PSMA expression was much higher in tumour tissue of black patients. This was also reported in other studies where a two- to three-times higher mortality from prostate carcinoma in black African men compared to Caucasians was observed.

A study published in 2017 by Delpassand and colleagues enrolled 144 consecutive patients (84 men and 50 women; age range 11- 87 year; mean age 58.5) in the US with histologically confirmed NET which were mainly Caucasians (132 patients, 92.3% of total), but also Hispanics (5, 3.5%), African Americans (4, 2.8%), and Asians (2, 1.4%). No information on any differences in response to therapy or toxicity were provided by the authors (Hamiditabar M, 2017).

2.6.2.4. Pharmacokinetic interaction studies

The applicant has not performed any pharmacokinetics interactions studies.

In general, potential drug interactions depend on the medicinal product labelled with the proposed radioactive precursor.

In order to prevent nephrotoxicity secondary to treatment of NETs with ^{177}Lu-DOTATATE, an amino acid (AA) solution is co-infused resulting in decreased tubular renal reabsorption of ^{177}Lu-DOTATATE. A study published by Puszkiel and co-workers aimed to quantify the impact of AA co-infusion on ^{177}Lu-DOTATATE PK in cancer patients and to evaluate its relationship with toxicity during the first treatment cycle. Patients (n=42) received 7.4GBq of ^{177}Lu-DOTATATE over a 30 min IV infusion. Infusion of AA started 2 h before and continued for 6 h after the infusion of ^{177}Lu-DOTATATE. Indeed, AA co-infusion had a significant effect on ^{177}Lu-DOTATATE PK, with a mean value of 1.5-fold (95% CI 1.03-1.97) increase in the elimination rate constant (k_{10}) from 0.204 to 0.306 h^{-1}. However, this AA co-infusion effect was associated with a large inter-individual variability of 104% contributing to the variability in ^{177}Lu-DOTATATE plasma exposure. This in turn impacts the haematotoxicity of ^{177}Lu-DOTATATE as a clear association could be found between plasma AUC at day 15 and lymphocyte count (Puszkiel A, 2019).

2.6.2.5. Pharmacodynamics

The applicant has not submitted any pharmacodynamics-pharmacokinetics (PK/PD) studies.

2.6.3. Discussion on clinical pharmacology

Lutetium (^{177}Lu) chloride n.c.a., solution is a radiopharmaceutical precursor which is only intended for use in in-vitro-labelling of medicinal products for diagnostic or therapeutic purposes. The medicinal product intended for labelling with the precursor comprises a carrier molecule directing the radionuclide specifically to the site of disease (e.g. a solid tumour) as well as a linker molecule (chelator) suitable for radiolabelling. The pharmacokinetics of a radiopharmaceutical would be dependent on the carrier molecule labelled with ilLuzyce. As unstable linkage between the radionuclide and the tracer molecule would otherwise cause release of free ^{177}Lu from the complex, ilLuzyce should only be used with medicines intended for used in conjunction with radiolabelling. The bioavailability of lutetium (^{177}Lu)-labelled tracers used in radiotherapy can be considered 100% as they are usually administered via the intravenous route. As ^{177}LuCl3 is not intended for direct use in humans, preclinical data were utilised and the doses were extrapolated for humans. Biodistribution of ^{177}Lu3+ is consistent throughout the studies, showing bone, liver, kidneys, red marrow and spleen as the main target organs. The distribution of lutetium-177 throughout the body will strongly depend on the respective medicinal product intended for labelling with the radionuclide. Peptide receptor radionuclide therapy (PRRT) and radioligand therapy (RLT) are targeted therapy approaches directing the radionuclide specifically to the site of cancer.

Dose calculations (absorbed doses for target organs [mGy/MBq] and effective doses [mSv/MBq]) were performed in Olinda/EXM 2 dose calculator using the mean Â value (mean between the Â values obtained from each considered animal study) for each source organ. Organ doses were reported for an adult male and female model as well as 15-year, 10-year, 5-year, 1-year and newborn male and female models. The presented methodology is considered adequate. According to the data provided by the applicant, after accidental injection of Lutetium (^{177}Lu) chloride n.c.a., the total effective dose would be 0.132 mSv/MBq for adult female and 0.122 mSv/MBq for adult male. The effective dose for children varies between 1.02 mSv/MBq in 1-year-old and 0.158 mSv/MBq for 15-year-old model.

Inadvertent injection of non- labelled lutetium-177 as well the effects of the free radionuclide following administration of ^{177}Lu-labelled carriers should be discussed for radiopharmaceutical precursors. The applicant has provided enough information about the effects of free radionuclide in the dosimetry and clinical safety sections, considering published evidence and post-marketing experience from similar authorised medicinal products containing lutetium-177. See 2.6.2.2. Dosimetry.

Extrapolation of animal data to humans suggests that after accidental injection of Lutetium (^{177}Lu) chloride n.c.a., the highest absorbed dose is to be expected in osteogenic cells. Other organs which receive higher absorbed doses are liver, kidneys, red marrow and spleen.

Following intravenous administration of ^{177}LuCl3, ^{177}Lu is rapidly cleared from the blood. The primary target organs are the bone, the liver and the kidneys. Data from experiments on mice, rats and rabbits indicate that more than half the lutetium entering the systemic circulation is deposited in the skeleton with only small amounts going to the liver and kidneys. ^{177}Lu3+ shows high affinity to bone tissue with some retention in the skeleton. Its affinity to the bone can be explained by the fact that Lu3+, as a lanthanoid, has some chemical similarities with Ca2+, which is characterized by a high uptake in bone tissue. Therefore, lanthanoids were used for Ca2+ probes in biochemical and physiological studies (Hirano S, 1996). Lutetium-177 has a biological half-life of between 10 and 40 days in the soft tissue in mice and rats compared to a long biological half-life in the skeleton. However, these long half-life values are not of relevance for lutetium-177 non-carrier added (n.c.a.), since it completely decays with a half-life of 6.71 days following administration to form stable Hf, preventing any accumulation of lutetium-177 over time.

Appropriate information about ^{177}Lu3+ biodistribution and dosimetry have been included in the SmPC, sections 5.2 and 11.

Radiolabelled somatostatin analogues are excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using other radioisotopes. Renal function should be assessed at baseline and during treatment and renal protection should be considered, in accordance with clinical guidance.

No clear conclusions on the influence of race on the performance of ^{177}Lu-labelled tracers can be drawn from the presented literature data. Nevertheless, potential differences in SUV values dependent on the patient's race cannot be excluded.

No specific relationship on pharmacology and weight has been addressed.

From the published data, there is no evidence for significant differences between elderly and adult patients.

No data have been submitted for the paediatric population on grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. This is reflected under 5.1 in the SmPC and a cress reference is added in 4.2 to refer for more information concerning paediatric use of lutetium (^{177}Lu)-labelled medicinal products to the Summary of Product Characteristics/Package Leaflet of the medicinal product to be radiolabelled. No specific information about pharmacology on impaired hepatic function has been provided.

No specific information on gender-specificities has been provided. There is no evidence from pertinent literature that radionuclides show gender-specificities. Depending on the medicinal product to be labelled with the proposed radioactive precursor, gender-specific use of the final ^{177}Lu-labelled tracer might be of relevance, e.g., in case of PSMA-targeting ligands used in prostate cancer patients.

The applicant has not performed any pharmacokinetics interactions studies. In general, potential drug interactions depend on the medicinal product labelled with the proposed radioactive precursor.

Lutetium (^{177}Lu) chloride n.c.a. is not intended to be directly administered to the patient, therefore, no pharmacodynamic effect is sought for the unconjugated radionuclide. The pharmacodynamics of a radiopharmaceutical would also be dependent on the carrier molecule and on the method of

conjugation used to link it to the radioisotope. Thus, the lack of studies in pharmacology for this application is acceptable.

Skeletal uptake also seems to be determined by whether lutetium is present with a carrier or not. Although ^{177}Lu3+ emits beta-minus radiation with a low range of only 2 mm only, it can be assumed that the significant distribution of ^{177}Lu3+ to the skeleton may induce DNA damages and mutations in osteogenic cells as well as in the bone marrow. Clinically, this becomes visible by, on the one hand, a haematotoxic effect (myelosuppression) which is caused by the diminution of haematopoietic cells due to the induction of DNA double-strand breaks (followed by apoptosis). On the other hand, refractory cytopenia with multi-lineage dysplasia (so-called 'myelodysplastic syndrome') and acute myeloid leukaemia (AML) are possible adverse radiation effects. Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) and myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML) have been included in the RMP as important identified risks. In addition, special warnigns and precautions for use have been included in the SmPC. (See 2.6.9. Discussion on clinical safety).

In the bone tissue itself, radiation induced DNA damage/mutations may become apparent through the occurrence of osteosarcoma. An increased rate of osteosarcoma formation was observed in animals examined 12 months after an exposure to an estimated dose of 20 to 80 Gy. Of note, with lutetium-177 n.c.a, only the radioactive isotope ^{177}Lu is administered, which completely decays to stable hafnium. Therefore, any long-term uptake in bone does not translate in bone accumulation of lutetium over time, as the material decays. (See 2.5.4.4. and 2.5.6.)

The clinical pharmacology of ^{177}Lu-labelled medicinal products prepared by radiolabelling with Lutetium (^{177}Lu) chloride n.c.a. prior to administration will be dependent on the type of the medicinal product to be radiolabelled. Lutetium (^{177}Lu) chloride n.c.a. is not intended to be directly administered to the patient. Therefore, the lack of pharmacology studies is considered acceptable.

2.6.4. Conclusions on clinical pharmacology

Adequate information was provided about $^{177}Lu^{3+}$ biodistribution and dosimetry calculations, showing bone, liver, kidneys, red marrow and spleen as the main target organs.

The clinical pharmacology of ilLuzyce will be dependent on the carrier molecule and on the method of conjugation used to link it to the radionuclide. The relevant clinical pharmacology data with ilLuzyce will have to be submitted separately with the application for the different carrier molecules. Thus, the lack of studies in pharmacology for this application is acceptable. For the purpose of an application for a radiopharmaceutical for radiolabelling, the clinical pharmacology of ilLuzyce has been adequately addressed.

2.6.5. Clinical efficacy

The applicant did not submit any clinical efficacy study, but in line with the Annex 1 Part III of Directive 2001/83/EC, as amended, on radiopharmaceutical precursors, relevant information on the clinical utility of the radiopharmaceutical precursor Lutetium (^{177}Lu) chloride when is attached to appropriate carrier molecules was provided. (See 2.6.1. Introduction)

2.6.5.1. Dose response study(ies)

The applicant did not submit studies on dose response (see clinical efficacy discussion).

2.6.5.2. Clinical Utility

1. Efficacy of ^{177}Lu-oxodotreotide

The applicant submitted evidence from 7 phase I/II trials 11 studies and 1 meta-analysis (Kim SJ, 2015) investigating the efficacy and safety of ^{177}Lu-oxodotreotide in the radiotherapy of NETs.

The main studies are summarised as follows.

A meta-analysis was published by Kim and co-workers in 2015 aiming at the evaluation of efficacy of ^{177}Lu-labelled PRRT in patients with inoperable or metastatic NETs. Six studies with 473 patients (4 in RECIST criteria[1] group with 356 patients, 3 in SWOG criteria[2] group with 375 patients and 1 in both groups) were included. In the RECIST criteria group disease response rates ranged between 17.6 and 43.8% with a pooled effect of 29 % [95% CI 24-34%]. Disease control rates ranged from 71.8 to 100%. The random-effects model showed an average disease control rate of 81 % (95 % CI 71-91%). In the SWOG criteria group disease response rates ranged between 7.0 and 36.5 % with a pooled effect of 23 % (95% CI 11-38%). Disease control rates ranged from 73.9 to 89.1%. The random-effects model showed an average disease control rate of 82 % (95% CI 71-91%). The authors concluded from the meta-analysis that ^{177}Lu-labelled PRRT is an effective treatment option for patients with inoperable or metastatic NETs (Kim SJ, 2015).

Several phase I/II clinical trials comprising a significant number of patients showed efficacy and tolerability of PRRT using ^{177}Lu-oxodotreotide in the treatment of NETs, mainly of gastroenteropancreatic origin (GEP-NETs). However, promising results have also been achieved in patients with pancreatic NETs or BP-NETs.

Additionally, literature data about the therapeutic use of ^{177}Lu-oxodotreotide in other indications different than NETs were presented. Per the literature, ^{177}Lu-oxodotreotide PRRT was reported as a possible safe and effective treatment option in inoperable or metastatic paragangliomas (PGLs) and malignant pheochromocytomas (PCCs), which are rare tumours with only limited options for systemic treatment. In a study investigating the efficacy and safety of ^{177}Lu-oxodotreotide in 30 patients with PGL (n=27) or PCC (n=3), best tumour response was partial response in 7 (23%) and stable disease in 20 (67%), whereas 3 (10%) patients had progressive disease. In 20 patients with baseline disease progression, tumour control was observed in 17 (85%) (Zandee WT, 2019). A favourable efficacy and safety profile in the treatment of PGLs and PCCs was also reported in a systematic review and meta-analysis published in 2019 by Satapathy and co-workers. Overall, treatment with PRRT was reported to achieve an objective response rate of 25% and a disease control rate of 84%. Clinical and biochemical responses were seen in 61% and 64% of the patients, respectively. Among the PRRTs, similar tumour response rates were noted for ^{90}Y- and ^{177}Lu-based agents (Satapathy S, 2019).

2. Efficacy of ^{177}Lu-DOTATOC

Several studies were performed aiming at the efficacy and safety of PRRT using ^{177}Lu-DOTATOC in therapeutic management of SSTR-positive tumours, mainly NETs for which results are published.

A summary table was presented with 7 studies aimed to investigate efficacy and safety of PRRT using ^{177}Lu-DOTATOC in therapeutic management of SSTR-positive tumours, mainly NETs.

Improvement of symptoms as well as effects on disease progression were observed.

Effectiveness and toxicity of radiolabelled DOTATOC in patients with metastatic paraganglioma and pheochromocytoma has been investigated. To that end, patients (n=25) were treated with 200 mCi/m^2

[1] Response Evaluation Criteria in Solid Tumours 1.0 or 1.1 is a standard way to measure the response of a tumor to treatment (E.A. Eisenhauera, 2009)
[2] Southwest Oncology Group criteria for assessing tumour response, (S Green, 1992)

body surface ^{90}Y-DOTATOC and three patients were treated with cycle with 100 mCi/m^2 ^{90}Y-DOTATOC followed by 2 cycles of 200 mCi ^{177}Lu-DOTATOC. Two patients showed partial remission, five minor responses, 13 had stable disease, two showed mixed responses, and six patients remained progressive. Time to progression ranged from 3 to > 42 months. The treatment was well tolerated. The authors concluded that radiolabelled DOTATOC may exert a treatment option for surgically incurable paragangliomas because of low toxicity and long-lasting remissions (Forrer F, 2008).

3. Efficacy of ^{177}Lu-PSMA

During the past years, several clinical studies were conducted investigating the safety and efficacy of ^{177}Lu-PSMA RLT, mainly using ^{177}Lu-PSMA-617, in the treatment of mCRPC. Fourteen studies and 4 meta-analyses were.

Several systematic reviews and meta-analyses were published analysing the safety and efficacy of ^{177}Lu-PSMA RLT in treatment of patients with mCRPC. Yadav and co-workers concluded from their analyses that ^{177}Lu-PSMA RLT showed antitumor activity in the treatment of patients with mCRPC that has progressed after standard treatment. Due to its low toxicity, ^{177}Lu-PSMA RLT was reported as a potential therapeutic option for patients not tolerating docetaxel therapy or who have extensive bone marrow involvement.^{177}Lu-PSMA RLT was shown to reduce PSA levels and lengthen overall and progression-free survival with low and transient toxicity (Yadav MP, 2019).

As for patients with mCRPC, treatment with ^{177}Lu-PSMA-617 RLT and ^{177}Lu-PSMA I&T was reported to result in better efficacy and to causefewer adverse effects than third-line treatment with enzalutamide and cabazitaxel, which resulted in discontinuation of treatment for 10% to 23% of patients (von Eyben FE, 2018).

4. Efficacy of PSMA-targeting ^{177}Lu-J591 in radioimmunotherapy (RIT) of prostate cancer

J591 is a monoclonal murine anti-PSMA antibody targeting the extracellular domain of PSMA. Comparable with other PSMA-targeting tracer molecules, this antibody can be used to deliver radioisotopes to PCa cells. Five studies and 1 meta-analysis were summarised.

A phase I clinical trial was conducted by Bander and colleagues in 2005. A total of 35 subjects received treatment, of whom 16 received up to three doses. A total of 10 mg/m^2 of ^{177}Lu-J591 (ranging from 10 mCi/m^2-75 mCi/m^2) were administered per patient. While the majority of patients received sub-therapeutic doses in this dose-escalation phase I study, four (11.4%) patients experienced more than a 50% PSA decline that lasted three to eight months. Additionally, 16 (46 %) subjects experienced PSA stabilisation for a median of 60 days (1-21+ months). In this phase I trial acceptable toxicity was also reported (Bander NH, 2005).

The results of a phase II clinical trial were published in 2013 by Tagawa and co-workers. The study consisted of two cohorts of patients with mCRPC. The first cohort included 15 patients that received 65 mCi/m^2 ^{177}Lu-J591 and the second cohort included 17 patients who received 70 mCi/m^2 ^{177}Lu-J591. An expansion cohort of 15 patients received 70 mCi/m^2 to verify the response rate and examine biomarkers. Overall, 28 patients (59.6%) experienced a PSA decline with 17 patients (36.2%) experiencing more than 30% decline in PSA following a single dose of ^{177}Lu-J591. Twelve (25.53 %) patients had a measurable disease as defined by RECIST criteria. (Tagawa ST, 2013).

Further phase I/II clinical trials as well as pilot studies investigated dose fractionation of ^{177}Lu-J591 as potential effort to deliver a greater cumulative dose of ^{177}Lu with less toxicity. Fractionation of ^{177}Lu-J591 allowed for the administration of a greater cumulative dose (and, presumably, absorbed radiation dose) and resulted in improved PSA response and overall survival. This dose fractionation concept is also being studied with other radiotherapies for PCa, e.g. using ^{177}Lu-PSMA-617 RLT, with favourable results (Tagawa ST, 2019).

A meta-analysis comprising 10 studies on the efficacy of ^{177}Lu-J591, ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T was performed by Calopedos and colleagues in 2017. Overall, the meta-analysis showed that approximately two-thirds of patients had a biochemical response (Calopedos RJS, 2017).

5. Efficacy of ^{177}Lu-EDTMP in treatment of painful bone metastases

Bone metastases develop in multiple malignancies with a wide range of incidences. Skeletal metastases are considered a major cause of morbidity and mortality in 65%-75% of patients with advanced stages of breast and prostate cancer, as well as in 15%-30% cases of lung, colon, stomach, bladder, uterus, rectum, thyroid, and kidney malignancies, deteriorating quality of life (QoL) in all these groups of patients. Therefore, many therapeutic options, aiming to improve QoL of patients with metastatic bone involvement by pain reduction and prevention of further complications and morbidities have been focus of research interest.

Currently available palliative strategies include the administration of conventional analgesics, bisphosphonates, chemotherapy, external beam radiotherapy, and radionuclide therapy, showing variable degrees of success for bone pain palliation. Among them, radionuclide bone pain palliation is of particular interest due to low level of adverse reactions while imposing systemic effects *(Askari E, 2020)*.

Ethylene diamine tetra methylene phosphonic acid (EDTMP) forms stable complexes with various radiometals concentrating in the skeleton in proportion to osteoblastic activity *(Yuan J, 2013)*.

Seven clinical studies and 1 Meta-Analysis investigating the safety and efficacy of ^{177}Lu-EDTMP in the treatment of painful bone metastases were summarised.

In this meta-analysis (Askari E, 2020), treatment efficacy, safety profile, and toxicities of ^{177}Lu-EDTMP in patients with metastatic bone involvement was evaluated. Eight studies were included, comprising a total of 172 patients. This analysis revealed statistically significant effect of ^{177}Lu-EDTMP therapy on the visual analog score (4.84%, 95% CI: 3.88–5.81; $p < 0.001$), bone palliative pain response (84%, 95% CI: 75%–90%; $p < 0.001$), and Karnofsky performance status (21%, 95% CI: 18%–24%; $p < 0.001$) overall (as well as in the high-dose and low-dose subgroups). Complete palliative pain response to treatment was observed in 32% (95% CI: 16%–53%) of patients receiving ^{177}Lu-EDTMP. Anaemia was found to be the most common hematologic toxicity imposed by this therapeutic approach (grade I/II anaemia in 24% (95% CI: 14%–38%; $p < 0.001$) and grade III/IV anaemia in 19% (95% CI: 12%–28%; $p < 0.001$)). The authors concluded that ^{177}Lu-EDTMP seems to have comparable efficacy and safety profile as that of the frequently administered radiopharmaceuticals for bone palliation.

6. Efficacy of ^{177}Lu-labelled antibodies in RIT of other cancers

Antibody CC49

CC49 is a murine monoclonal antibody that recognises the tumour-associated glycoprotein 72. An initial Phase I study using ^{177}Lu-labelled CC49 in a small number of patients with previously treated advanced adenocarcinoma revealed no anti-tumour response *(Mulligan T, 1995)*.

In another early Phase I study, 12 ovarian cancer patients who failed previous chemotherapy received ^{177}Lu-CC49 antibody intraperitoneally with >50% of patients showing tumour reduction after therapy. The authors concluded that intraperitoneal RIT using ^{177}Lu-CC49 was well tolerated and appeared to be efficacious in chemotherapy-resistant ovarian cancer in the peritoneal cavity (Meredith RF, 1996).

A further phase I/II clinical trial of intraperitoneal ^{177}Lu-CC49 was conducted in 27 ovarian cancer patients who failed previous chemotherapy. One of 13 patients with gross disease showed >50% tumour reduction after therapy. Seven of 9 patients with 6 to 35 months. Bone marrow suppression was the dose-limiting toxic effect. MTD (maximum tolerated dose) was assessed at 1.67 GBq/m^2 (Alvarez RD, 1997).

In 2001, Meredith and co-workers investigated the feasibility of combining subcutaneous interferon and intraperitoneal Taxol (paclitaxel) with intraperitoneal ^{177}Lu-CC49 in a clinical phase I study. In total, 46 patients with recurrent or persistent ovarian cancer were enrolled. The MTD for ^{177}Lu-CC49 was 1.48 GBq/m^2 when given with interferon +100 mg/m^2 Taxol. Four of 17 patients with measurable disease had a partial response and 4 of 27 patients with non-measurable disease had progression-free intervals of 18+, 21+, 21+ and 37+ months. The authors concluded that the combination of intraperitoneal Taxol with ^{177}Lu-CC49 and interferon was well tolerated, with bone marrow suppression being the dose-limiting toxicity (Meredith RF, 2001). In 2012, the same working group analysed data from 92 patients >5 years after intraperitoneal radionuclide therapy with ^{90}Y- or ^{177}Lu-CC49 to determine prognostic factors. A statistically significant improvement in progression-free survival was noted for less bulky disease and younger age. Dose escalation of radionuclide did not change risk of progression. It was therefore concluded that this therapy may have therapeutic efficacy at modest dose levels (Meredith R, 2012).

Trastuzumab

Human epidermal growth factor receptor 2 (HER2/neu) is a protein that is over expressed in one fourth of the breast cancers. Among the various types of breast cancers, HER2-expressing breast cancers are considered to be associated with poor clinical outcome. Treatment strategies for those types of breast cancer include surgery, radiotherapy as well as chemotherapy and targeted therapy. Trastuzumab is an approved humanised monoclonal antibody that targets HER2/neu cancer cells and offers inhibitory effect on the growth of these cells. It was routinely used as targeted therapy for the treatment of HER2/neu overexpressing breast cancer in combination with other chemotherapy drugs (Bhusari P, 2017).

A preliminary pilot study was conducted on breast cancer patients (n=6 HER2-positive and n=4 HER-negative) to evaluate the ability of ^{177}Lu-trastuzumab for HER2-specific tumour targeting. The conjugates were efficiently labelled with ^{177}Lu with high radiochemical purity (up to 91%) and specific activity (6-13 µCi/µg). ^{177}Lu-trastuzumab was stable up to 12 h post-labelling. Studies in patients showed localisation of ^{177}Lu-trastuzumab at primary as well as metastatic sites (HER2-positive) in the planar and SPECT/CT images. No tracer uptake was observed in HER2-negative patients indicating specificity of ^{177}Lu-trastuzumab. The study showed that ^{177}Lu-trastuzumab had specific targeting ability for HER2-expressing lesions and may in future be considered as palliative treatment option in the form of targeted radionuclide therapy for disseminated HER2-positive breast cancer (Bhusari P, 2017).

Antibody cG250 (girentuximab)

The chimeric antibody cG250 (girentuximab) is reactive with carbonic anhydrase IX, a heat sensitive transmembranous glycoprotein which is ubiquitously expressed in clear cell renal cell carcinoma (ccRCC). Expression in normal tissues is restricted to the gastrointestinal mucosa and gastrointestinal-related structures with much lower expression levels than in ccRCC. Patients with metastatic ccRCC have a dismal prognosis. Results of a phase I RIT study with ^{177}Lu-cG250 in 23 patients with progressive metastasised ccRCC were published by Stillebroer and colleagues in 2013. Groups of 3 patients received ^{177}Lu-cG250, starting at a dose level of 1.11 GBq/m^2 with dose increments of 0.37 GBq/m^2 per group. Patients could receive a total of three treatment cycles. The MTD was assessed at 2.405 GBq/m^2 because higher doses resulted in dose-limiting myelotoxicity. Most patients (74%) demonstrated stable disease at 3 months after the first treatment, and 1 patient showed partial response lasting for 9 months. Mean growth of target tumour lesions was reduced from 40.4% during the last 3 months before study entry to 5.5% at 3 months after the first treatment cycle. It was concluded that RIT with ^{177}Lu-cG250 may stabilise previously progressive metastatic ccRCC (Stillebroer AB, 2013).

Rituximab

Rituximab, a chimeric anti-human CD20 monoclonal antibody is authorised for the treatment of non-Hodgkin lymphoma. A phase I/II study using ^{177}Lu-DOTA-rituximab was conducted in 31 patients with

B-cell lymphomas. To evaluate the MTD, the dosage of the radiopharmaceutical was adjusted according to body surface area. The MTD was assessed at 1.67 GBq/m^2. Thrombocytopenia and leucopoenia were identified as dose-limiting toxicities. Clinical responses were observed at all dose levels and for all lymphoma entities with some of the responses showing notable duration. The authors concluded that ^{177}Lu-DOTA-rituximab treatment is a safe and feasible treatment option for the lymphomas investigated (Forrer F, 2013).

Lilotomab

Lilotomab is a murine monoclonal antibody against CD37, a glycoprotein expressed on the surface of mature human B cells. It is under development as a targeted radiopharmaceutical in which lilotomab is conjugated to the beta-minus radiation-emitting isotope lutetium-177 by means of a linker called satetraxetan, a derivative of DOTA. The resulting medicinal product is called ^{177}Lu-HH1 or lutetium (^{177}Lu) lilotomab satetraxetan (trade name Betalutin). Several international clinical studies with Betalutin in patients with **lymphoma** are ongoing, and promising animal and human data have been published.

2.6.6. Discussion on clinical efficacy

In accordance with the Annex 1 Part III of Directive 2001/83/EC, as amended, clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes. However, information demonstrating the clinical utility of the radiopharmaceutical precursor when attached to relevant carrier molecules shall be presented.

In support of the clinical utility of ^{177}Lu, the applicant performed a bibliographical search and presented comprehensive efficacy from published clinical trials, which have been conducted with ^{177}Lu-labelled tracer molecules during the past 20 years.

Clinical utility is considered demonstrated in treatment of patients with neuroendocrine tumours using ^{177}Lu-labelled somatostatin analogues.

Moreover, the applicant has presented enough evidence on the clinical utility of ^{177}Lu in the treatment of mCRPC based on literature data with ^{177}Lu-PSMA compounds, in particular when used in radioligand therapy. Although no ^{177}Lu-PSMA targeting radiopharmaceutical is currently authorised in the EU, many patients with mCRPC are treated on a named patient or compassionate use basis. The use of ^{177}Lu-PSMA radiopharmaceuticals mainly in RLT is also documented in clinical guidelines issued recently (Kratochwil C, 2019) and (Mottet N, 2021).

A recent meta-analysis (Askari E, 2020) reported ^{177}Lu-EDTMP as an effective and safe treatment for palliation of metastatic bone pain in patients with prostate or breast cancer. However, this meta-analysis is considered to have limitations which hamper interpretation of the results.

The evidence on the clinical utility of ^{177}Lu-labelled antibodies in RIT of other cancers like ovarian cancer (antibody CC49), breast cancer (trastuzumab), clear cell renal cell carcinoma (girentuximab), B-cell lymphomas (rituximab), lymphoma (lilotomab) is still considered preliminary.

2.6.7. Conclusions on the clinical efficacy

It is concluded that there is enough evidence to support the clinical utility of ^{177}Lu coupled to suitable carrier molecules in neuroendocrine tumours and prostate cancer. The evidence currently available to demonstrate clinical utility of ^{177}Lu in other areas is still limited or experimental.

2.6.8. Clinical safety

No original clinical safety studies were conducted by the applicant.

2.6.8.1. Patient exposure

Patient exposure information is based on published studies with ^{177}Lu-labelled tracers.

Numerous clinical studies have investigated the efficacy and/or safety of ^{177}Lu-labelled tracers such as SSTR2- or PSMA-targeting molecules for PRRT/RLT of NETs and PCa, respectively. Furthermore, some case reports could be identified reporting adverse events following administration of ^{177}Lu-labelled radiotracers, including those reporting safety findings upon accidental administration of lutetium-177. Reported adverse reactions associated with treatment using lutetium-177, as well as case reports on accidental administration of lutetium-177 chloride, are presented and summarised in tables, with the author of the study, posology, key safety findings, number and patients characteristics:

Annex I- Safety of ^{177}Lu-oxodotreotide: 26 studies and one case report on accidental administration of lutetium-177 chloride in 5 patients (Kang KW, 2020)

Annex II- Safety of ^{177}Lu-DOTATOC: 8 studies.

Annex III- Safety of ^{177}Lu-PSMA: 17 studies and a case report on accidental oral administration of ^{177}Lu-PSMA.

Annex IV- Safety of ^{177}Lu-J591: 5 studies.

Annex V- Safety of ^{177}Lu-EDTMP: 7 studies.

The main studies about safety with a specific ^{177}Lu-labelled compound are summarised as follows.

Safety of ^{177}Lu-oxodotreotide

During radiotherapy with ^{177}Lu-oxodotreotide, the most common minor side-effects were nausea (max. grade 2), asthenia, and mild alopecia in a study published in 2014 (Paganelli G, 2014). In another study comprising 468 patients, transient haematological toxicity of grade 1, grade 2, and grade 3 was found in 8 (1.7%), 1 (0.2%) and 1 patient (0.2%) respectively. Nephrotoxicity of grade 1, grade 2, grade 3, and grade 4 were seen in 16 (3.5%), 3 (0.6%), 2 (0.4%) and 1 patient (0.2%) respectively (Sitani K, 2021). In 2018, efficacy and safety of ^{177}Lu-oxodotreotide PRRT was analysed in a large cohort with NETs. Myelodysplastic syndrome or leukaemia developed in 22 patients (2.1%) and 5 patients required haemodialysis after treatment due renal toxicity; other adverse events were found to be rare (Baum RP, 2018).

Safety of ^{177}Lu-PSMA

Grade 3-4 haematotoxicity mostly occurred in less than 10% of patients, whilst the first prospective phase II trial published in 2018 by Hofman and colleagues reported slightly higher values. Low blood count levels at baseline and diffuse bone marrow involvement were linked to serious haematotoxicity in individual patients. The rate of grade 3-4 events was low for all other categories, including salivary gland function. A recent phase II trial reported grade 1 dry mouth in 87% patients, grade 1 or 2 transient nausea in 50%, and grade 1 or 2 fatigue in 50% of patients (Hofman MS, 2018). The most common toxic effects possibly related to ^{177}Lu-PSMA-617 were grade 3 lymphocytopenia in eleven (37%), grade 3 anaemia in four (13%), and grade 3 or 4 thrombocytopenia in four (13%) patients.

2.6.8.2. Adverse events

Adverse reactions known to be related to medicinal products containing the lutetium-177 were analysed for their frequency in EudraVigilance and are displayed in the table below:

Table 8. Frequency of adverse reactions reported with ^{177}Lu-labelled tracers as reported to EudraVigilance during the last 5 years (from 2016 to 27/03/2021)

System Organ Class	Adverse events	No of reports
Blood and lymphatic system disorders	Anaemia	44 (1/44 fatal)
	Thrombocytopenia	98 (1/98 fatal)
	Leukopoenia	28
	Lymphopenia	9
	Neutropenia	17
	Pancytopenia	9 (1/9 fatal)
Endocrine disorders	Carcinoid crisis	18 (1/18 fatal)
Metabolism and nutrition disorders	Tumour lysis syndrome	6
Gastrointestinal disorders	Nausea	49
	Vomiting	31 (1/31 fatal)
	Dry mouth	7
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Refractory cytopenia with multi-lineage dysplasia (Myelodysplastic syndrome)	31 (6/31 fatal)
	Acute myeloid leukaemia (AML)	8 (2/8 fatal)
Skin and subcutaneous tissue disorders	Alopecia	13

The following information on adverse reactions is provided in the SmPCs of authorised medicinal products containing the active substance lutetium (^{177}Lu) chloride (LutaPol, Lumark, EndolucinBeta). Adverse reactions are categorised according to the MedDRA convention frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 9. Adverse events provided in the SmPCs of authorised medicinal products containing the active substance lutetium (^{177}Lu) chloride

System Organ Class	Adverse events	Frequency
Blood and lymphatic system disorders	Anaemia, thrombocytopenia, leucopoenia, lymphopenia	very common
	Neutropenia	common
	Pancytopenia	not known
Endocrine disorders	Carcinoid crisis	not known
Metabolism and nutrition disorders	Tumour lysis syndrome	not known
Gastrointestinal disorders	Nausea, vomiting	very common
	Dry mouth	not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Refractory cytopenia with multi-lineage dysplasia (Myelodysplastic syndrome)	common
	Acute myeloid leukaemia	uncommon
Skin and subcutaneous tissue disorders	Alopecia	very common

Table 10. Tabulated list of adverse reactions in ilLuzyce SmPC

Adverse reactions are divided into groups according to the MedDRA convention frequencies: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA system organ class	Very common	Common	Uncommon	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (see section 4.4)	Acute myeloid leukaemia (see section 4.4)	
Blood and lymphatic system disorders	Anaemia Thrombo- cytopenia Leukopenia Lymphopenia	Neutropenia		Pancytopenia
Endocrine disorders				Carcinoid crisis
Metabolism and nutrition disorders				Tumour lysis syndrome
Gastrointestinal disorders	Nausea Vomiting			Dry mouth
Skin and subcutaneous tissue disorders	Alopecia			

Description of selected adverse reactions

Dry mouth
Dry mouth has been reported among patients with metastatic castration resistant prostate cancer receiving PSMA-targeted lutetium (^{177}Lu)-labelled radioligands and has been transient.

Alopecia
Alopecia, described as mild and temporary, has been observed among patients receiving lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.

Overdose

Accidental injection of ^{177}Lu chloride solution has been reported from Kang and co-workers (Kang KW, 2020). Activities of 7.7 to 8.1 GBq of unlabelled lutetium-177 chloride were accidentally injected to five patients (1 male and 4 female) with NETs from South Korea at a hospital in Malaysia. Radiation dose to

patients was estimated using biokinetic model of lutetium based on the animal experiments in ICRP Publication 30. Unfortunately, the accident was only noted the next day when post therapy scans showed only bone uptake rather than uptake by tumours. Rapid drop of white blood cell and platelet counts was noted. Even if repeated injections of G-CSF and platelet transfusion were done, severe pancytopenia continued for months. Unfortunately, one patient developed fever after 4 weeks and died from mid-brain haemorrhage related to disseminated intravascular coagulation at 5 weeks post-accident. One man died from disease progression 10 months later (Kang KW, 2020).

GENERAL SAFETY ASPECTS CONCERNING RADIATION EXPOSURE

Several studies have been published during the past years investigating the occupational radiation exposure of nuclear medicine personnel as well as patients' household members following administration of ^{177}Lu-labelled tracers for targeted tumour radiotherapy [(Abuqbeitah M, 2018)see Dosimetry of ^{177}Lu-labelled tracers in the Clinical Pharmacology section]. Additional studies are summarised hereafter.

In 2016, Demir and colleagues investigated the outpatient treatment protocol and radiation safety of ^{177}Lu-PSMA-617. The authors analysed the dose rate of 23 patients treated with 7.4 GBq ^{177}Lu-PSMA-617 at different distances (0, 0.25, 0.50, 1.0 and 2.0 m) and different time points (0, 1, 2, 4, 18, 24, 48 and 120 h) after the termination of infusion. The mean dose rate at 1 m after 4 h and 6 h was 23±6 µSv/h and 15±4 µSv/h respectively. The mean total dose to 23 caregivers was 202.3±42.7 µSv (range: 120-265 µSv). The radiation doses of the nurse and radiopharmacist were 6 and 4 µSv per patient, respectively, whereas the doses of the physicist and physician were 2µSv. The study showed that ^{177}Lu-PSMA-617 was a safe treatment modality to be applied as an outpatient protocol, since the dose rate decreased below the determined threshold of <30 µSv/h after approximately 5 h and was further reduced to 20 µSv/h after 6 h. (Demir M, 2016)

Exposure during radiolabelling was investigated by Arora and co-workers in 2017. The mean radiation doses recorded during labelling were found to be 0.023±0.01 mSv for ^{177}Lu-oxodotreotide/NOC, 0.01±0.002 mSv for ^{177}Lu-PSMA-617 and 0.002±0.0006 mSv for ^{177}Lu-EDTMP and the mean duration of labelling was 0.81, 0.65, and 0.58 h, respectively. The specific activity of ^{177}Lu was ~19-22 mCi/µg in all labelling procedures. The mean estimated radiation dose rate during the three labelling procedures was 0.03±0.01 mSv/h for ^{177}Lu-oxodotreotide/NOC, 0.01±0.003 mSv/h for ^{177}Lu-PSMA-617, and 0.003±0.001 mSv/h for ^{177}Lu-EDTMP. Overall, mean radiation dose was 0.014 mSv and duration was 0.72 h (Arora G, 2017).

In 2018, radiation exposure to the public caused by administration of ^{177}Lu-PSMA-617 was investigated by Kurth and co-workers. To that end, whole-body dose rates were measured at a distance of 2 m at various time points after application of 6.3 ± 0.5 GBq ^{177}Lu-PSMA-617. Unbound ^{177}Lu-PSMA-617 was found to be rapidly cleared from the body. After 4 h, approximately 50%, and after 12 h, approximately 70% of the administered activity were excreted, primarily via urine. The maximum dose to individual members of the public per treatment cycle was ~ 250±55 µSv when the patient was discharged from the clinic after 48 h and ~190±36 µSv when the patient was discharged after 72 h (Kurth J, 2018).

A further study was published in 2018 as well investigating the radiation exposure after ^{177}Lu-oxodotreotide and ^{177}Lu-PSMA-617 therapy. The authors found that radioactivity incorporated in patients treated with ^{177}Lu-PSMA-617 ligand seems to be eliminated from the body more slowly than in patients receiving ^{177}Lu-oxodotreotide. However, the inter-patient variation for ^{177}Lu-PSMA-617 was considered too large to provide a standardised and clinically reasonable discharge procedure. The tumour load of patients suffering from PCa varied considerably depending on the stage of the disease as well as the time radiotherapy was initialised.

Levart and co-workers reported mean dose-rates (in µSv/h) of 15.0 (5.0-25.0) at 1 m distance from the patient receiving therapy, comparable with those reported by Sulieman and colleagues, showing a mean dose rate (in µSv /h) at the same distance of 16.2 (8.0-23.0) (Levart D, 2019).

In 2020, Sulieman and colleagues reported decreased dose rates at 3 m compared to 0.3 m. With use of a bedside shield, the dose was found to drop below 0.1 µSv/h at 2 m distance (Sulieman A, 2020).

Results of a further study investigating the radiation exposure upon administration of ^{177}Lu-oxodotreotide were published in 2019 by Nelson and Sheetz. Data from a total of 77 treatment cycles involving 26 individual patients were analysed. Patient exposure upon release was found to be around 10 µGy h^{-1} at 1 m, after patients had eliminated approximately 50% of the administered dose. The authors concluded that radiotherapy with 177-lu oxodotreotide could be an outpatient procedure that could be performed safely in any hospital procedural room without the need for additional shielding (Nelson KL, 2019).

In 2019, a case was reported of radiation contamination following cremation of a deceased patient treated with 193.6 mCi of intravenous ^{177}Lu-oxodotreotide. The patient died from the underlying disease 2 days after treatment and was cremated 5 days post-treatment. Crematory equipment demonstrated a range of 5,000 to 25,000 counts per minute with a 7.5-mR maximum exposure rate per hour on direct contact with the Geiger-Mueller detector. The personal radiation detector identified that radioactivity was primarily from ^{177}Lu. Given the short range (1.5 mm) and half-life (approximately 6.7 days) of ^{177}Lu, the total effective dose equivalent annual limit of 1 mSv for members of the public was unlikely to have been exceeded (Yu NY, 2019).

2.6.8.3. Serious adverse event/deaths/other significant events

No data were submitted by the applicant.

2.6.8.4. Laboratory findings

No data were submitted by the applicant.

2.6.8.5. Safety in special populations

No data were submitted by the applicant. See 2.6.9. Discussion on clinical safety.

Pregnant and lactating women

According to the SmPCs of authorised medicinal products containing lutetium-177, those medicinal products are contraindicated in established or suspected pregnancy or when pregnancy has not been excluded.

Paediatric population

The proposed medicinal product is not intended for use in children and adolescents. As medicinal products containing ^{177}Lu are currently not authorised for use in the paediatric population, data on the safety of ^{177}Lu-labelled tracers in this vulnerable population are scarce.

Elderly

Due to the nature of the underlying diseases, a significant number of patients above the age of 65 years have been treated with ^{177}Lu-labelled tracers in the course of published clinical studies.

In a retrospective study, Leibowitz and co-workers evaluated the safety of ^{177}Lu-PSMA-617 RLT in patients below and above the age of 75 years. The authors found that fatigue was more prevalent in

the elderly patients compared with the younger patient cohort. The frequency of anaemia was also numerically higher in the elderly patients. The authors concluded that there were no new safety signals in elderly patients and that the safety profile observed in patients >75 years can be considered comparable to patients <75 years of age (Leibowitz R, 2020).

Renal impairment

Radiolabelled peptides are mainly excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using radioisotopes.

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

2.6.8.6. Immunological events

No data were submitted by the applicant.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No data were submitted by the applicant.

2.6.8.8. Discontinuation due to adverse events

No data were submitted by the applicant.

2.6.8.9. Post marketing experience

The applicant summarised the adverse events reported with medicinal products containing the radionuclide lutetium-177 based on EudraVigilance and the published information from Periodic Safety Update Single Assessments (PSUSAs) (refer to section on "adverse events").

2.6.9. Discussion on clinical safety

In accordance with the Annex 1 Part III of Directive 2001/83/EC, as amended, in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radiolabelling efficiency or in vivo dissociation of the radiolabelled conjugate, i.e. questions related to the effects produced in the patient by free radionuclide. These aspects have been adequately addressed in the

Dosimetry of ^{177}Lu chloride section (above), focusing on the accumulation of free lutetium-177 (^{177}Lu3+) in target organs (osteogenic cells). Furthermore, safety information from already authorised medicinal products containing the active substance lutetium (^{177}Lu) chloride was evaluated, including a query in EudraVigilance. After evaluation of all public sources, 189 references were included in the clinical overview presented by the applicant.

In general, adverse reactions following the administration of a ^{177}Lu-labelled medicinal product prepared by radiolabelling with the proposed medicinal product will be mainly dependent on the specific medicinal product being used. Such information will be supplied in the SmPC/package leaflet of the medicinal product to be radiolabelled.

Exposure to ionising radiation is known to induce cancer and is potentially mutagenic. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. As a general rule, it is necessary to ensure that the risks of the radiation are lower than from the disease itself and therefore, the radiation exposure by treatment with ^{177}Lu labelled tracers should be always carefully considered.

The presence of free ^{177}Lu chloride in the body after an inadvertent administration of the lutetium (^{177}Lu) chloride proposed medicinal product can be considered to result in increased bone marrow toxicity and haematopoietic stem cell damage. Therefore, in case of an inadvertent administration of ilLuzyce, the radiotoxicity for the patient must be reduced by immediate (i.e. within 1 hour) administration of preparations containing chelators like Ca-DTPA or Ca-EDTA in order to increase the elimination of the radionuclide from the body. The following preparations must be available in medical institutions, which use ilLuzyce for labelling of carrier molecules for therapeutic purposes: Ca-DTPA (trisodium calcium diethylenetriaminepentaacetate) or Ca-EDTA (calcium disodium ethylenediaminetetraacetate).

These chelating agents help with the elimination of lutetium (^{177}Lu) radiotoxicity by an exchange between the calcium ion in the complex and the lutetium (^{177}Lu) ion. Due to the capacity of the chelating ligands (DTPA, EDTA) of forming water soluble complexes, the complexes and bound lutetium (^{177}Lu) are rapidly eliminated by the kidneys. One gram of the chelating agents should be administered by slow intravenous injection over 3 – 4 minutes or by infusion (1 g in 100 – 250 mL of glucose, or sodium chloride 9 mg/mL (0.9%) solution for injection). The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of chelator with reduced efficiency. Intravenous administration should not be protracted over more than 2 hours. In any case, the blood parameters of the patient have to be monitored and the appropriate actions immediately taken if there is evidence of radiotoxicity. The toxicity of free lutetium (^{177}Lu) due to in-vivo release from the labelled biomolecule in the body during therapy could be reduced by post-administration of chelating agents.

Although no dedicated carcinogenicity studies were submitted, the potential risk for osteosarcoma was described in rats after 12 months of exposure to lutetium 177 (estimated dose 2000-8000 rd, 20-80 Gy). It was comparable to the effect of the radiation from exposure to strontium-90. See 2.5.4.4. Carcinogenicity in the form of osteosarcomas has been included as an important potential risk in the RMP and instructions to handle the risk have been included in the SmPC as instructions to prepare radiopharmaceuticals: Free lutetium (^{177}Lu) is taken up and accumulates in the bones. This could potentially result in osteosarcomas. It is recommended to add a binding agent such as DTPA prior to intravenous administration of lutetium (177Lu)-labelled conjugates in order to form a complex with free lutetium (^{177}Lu), if present, leading to a rapid renal clearance of lutetium (^{177}Lu).

Due to the myelosuppressive effect of ^{177}Lu-labelled tracers as frequently reported in PRRT and RLT, concomitant chemotherapy and treatment with radioactive bone seekers can be considered critical as

additive effects may occur. Therefore, current guidelines recommend discontinuing the treatment with those medicinal products for at least four weeks during radiotherapy with ^{177}Lu-labelled tracers (Kratochwil C, 2019).

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been observed after treatment with lutetium (177Lu) peptide receptor radionuclide therapy for neuroendocrine tumours (see section 4.8). This Recommendation to take this should be taken into account when considering the benefit/risk, especially in patients with possible risk factors like prior exposure to chemotherapeutic agents (such as alkylating agents) has been included in the SmPC. Anaemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with lutetium (^{177}Lu). Most events are mild and transient, but in some cases patients have required blood and platelet transfusions. In some patients more than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described. A blood count should be taken at baseline and monitored regularly during treatment, in accordance with clinical guidance.

Radiolabelled somatostatin analogues are excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using other radioisotopes. Renal function should be assessed at baseline and during treatment and renal protection should be considered, in accordance with clinical guidance. Generally, careful consideration of the benefit-risk-ratio is deemed required in these patients due to potentially increased renal radiation exposure as shown in clinical studies. It was shown that patients with inferior renal function also experienced higher grades of haematotoxicity during treatment (p=0.01) (Svensson J, 2015). Individual radiation dosimetry assessments of specific organs which may not be the target organ of therapy might be of relevance. It is advisable to assess renal function at baseline and during treatment. This is also in line with recommendations given in the SmPCs of already authorised medicinal products containing the radionuclide lutetium-177. Furthermore, renal protection should be considered according to the SmPC of the medicinal product intended for labelling with lutetium-177. In order to prevent nephrotoxicity secondary to treatment of NETs with ^{177}Lu-oxodotreotide, co-infusion of amino acids is administered resulting in decreased tubular renal reabsorption of the radiolabelled peptide.

Altogether, radiation exposure of radiopharmacists during labelling and exposure of medical personnel during treatment as well as of the general public was found to be acceptable and within the limits as defined by the International Commission on Radiological Protection (ICRP). However, radiation exposure varies between patients and different radiopharmaceuticals and therefore, additional inpatient and outpatient regulations should be taken into account as well. Considering the Table 8 and Table 9 data presented under Dosimetry, an accidental injection of 2GBq (^{177}Lu)LuCl3 (each 5 ml vial delivered contains an activity ranging from 5.2 to 207.2 GBq at activity reference time (ART) in a volume of 0.1 to 4 ml), would be a total effective dose of 0.244 Sv for a male adult and 0.264 Sv for a female adult (associated with first clinical signs of radiation toxicity, such as nausea and fatigue (U.S.EPA., 2020)), while in a five-year-old and lower, would cause severe radiation toxicity. From the dosimetry tables it is clear that even the lowest dose contained in one vial, if administered accidentally, would result in radiation toxicity to individual organs.

Procedural guidelines for the management of radiotherapy, including regulations on patients' discharge, have been developed and should be strictly followed to avoid unnecessary radiation exposure. Information related to occupational hazards and radiation exposure to hospital staff and to the environment is properly addressed and captured in the product information for ilLuzyce (see sections 4.4, 6.6 and 12 of the SmPC).

Before use, packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber. Lutetium (^{177}Lu) is a beta(-)/gamma emitter. Activity measurements using an

ionization chamber are very sensitive to geometric factors and therefore should be performed only under geometric conditions which have been appropriately validated. Usual precautions regarding sterility and radioactivity should be respected. Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system. If the integrity of this vial is compromised, the medicinal product should not be used. The complexing agent and other reagents should be added to the vial with lutetium (^{177}Lu) chloride. Adequate quality control of the radiochemical purity of ready to use radiopharmaceuticals gained after radiolabelling with ilLuzyce should be assured. Limits for radiochemical impurities should be set recognising the radiotoxicological potential of lutetium (^{177}Lu). Free non-bound lutetium (^{177}Lu) should be consequently minimised.

After therapy with ^{177}Lu-labelled peptides, haematological toxicity, myelodysplastic syndrome, renal toxicity and liver toxicity have been reported. Haematotoxicity and dry mouth have been reported with ^{177}Lu-labelled PSMA-ligands in radioligand therapy for metastatic castration-resistant prostate cancer. In patients with protaste cancer, Tagawa et al. described myelosuppression was the most prominent toxicity with 22 (47%) patients developing grade 4 thrombocytopenia. Nearly all patients (97.9%) reported a complete recovery in platelet count. Overall, ^{177}Lu-J591 was well-tolerated with reversible myelosuppression (Tagawa ST, 2013).

Beside the numerous publications where the safety profile has been well established, clinical guidelines regarding efficacy and safety of medicinal products containing lutetium-177 have been recently issued (Zaknun JJ, 2013) (Kratochwil C, 2019) and (Mottet N, 2021).

Furthermore, post-marketing experience, information from Periodic Safety Update Single Assessments and PRAC scientific conclusions from the approved medicinal products containing lutetium-177 have depicted a well-known safety profile for these medicinal products and the product information (PI) has been updated accordingly.

Information on adverse events reported to the EudraVigilance database (by 27/03/2021) during ^{177}Lu PRRT by age group has been presented by the applicant. Unfortunately, the patients' age was not reported for all cases. From the information available, it cannot be concluded that highly frequent adverse reactions, e.g., those concerning the blood and lymphatic system, are significantly more pronounced in patients above 65 years of age (elderly). However, as elderly patients are considered to be more vulnerable to immunosuppression, the risk of significant haematotoxicity due to radiotherapy should be taken into consideration in this special population.

A case of cardiomyopathy was described upon administration of ^{177}Lu-oxodotreotide in a patient with cardiac metastases. Caution was advised in those patients who may be receiving PRRT, and cardiac evaluation before and after therapy was recommended (Hendifar AE, 2018). However, more data are deemed required to assess this particular risk factor accordingly.

Cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with ^{177}Lu-PRRT for NETs. Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients. Before each administration and during the treatment, biological tests are required to re-assess the patient's condition and adapt the therapeutic protocol if necessary.

2.6.10. Conclusions on the clinical safety

For the purpose of an application for a radiopharmaceutical precursor for radiolabelling, the safety of ilLuzyce has been adequately characterised and adequate measures have been set up to manage the risks associated with ilLuzyce.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient 2. Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) 4. Myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)
Important potential risks	2. Osteosarcoma 3. Radiation nephropathy 4. Radiation-induced hepatotoxicity
Missing information	NA

2.7.2. Pharmacovigilance plan

Not applicable since there are no additional pharmacovigilance activities proposed.

2.7.3. Risk minimisation measures

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

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	Routine risk communication: Warning about exposure to radioactivity in SmPC section 4.4. and PL section 1. Adverse reactions including induction of certain risk of cancer and development of hereditary effects included in SmPC section 4.8 and PL section 4.	Routine pharmacovigilance activities.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Contains a general warning on radiation protection in SmPC section 4.4. Recommendation to administer the smallest quantity to the patient to achieve the appropriate outcome included in PL section 3. Contains information about precautions to be taken during the receipt, handling and storage of the radiopharmaceutical in SmPC sections 6.4, 6.6 and 12 and PL sections 3 and 5. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: The symbol "radioactive" is given on the labelling.	
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	Routine risk communication: Warning concerning haematological side effects and myelosuppression included in SmPC section 4.4 and PL section 2. Anaemia, thrombocytopenia, leukopenia and lymphopenia are listed as adverse reactions	Routine pharmacovigilance activities.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Instruction to perform blood count test at baseline and monitor the blood count regularly during treatment included in SmPC section 4.4 and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	
Myelodysplastic syndrome/Acute myeloid leukaemia	Routine risk communication: Warning about MDS and AML in SmPC section 4.4 and PL section 2. MDS is listed as common and AML as uncommon adverse reactions in SmPC section 4.8 and PL section 4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaires for adverse reaction reports of myelodysplastic syndrome / acute myeloid leukaemia.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• The symbol "radioactive" is given on the labelling.	
Osteosarcoma	Routine risk communications: Warning in SmPC section 12 concerning the uptake and accumulation of free Lutetium ^{177}Lu in the bones, which could potentially result in osteosarcomas. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to use a binding agent such as DTPA prior to intravenous administration of ^{177}Lu labelled conjugates in SmPC section 12. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	Routine pharmacovigilance activities.
Radiation nephropathy	Routine risk communication: Warning concerning the excretion of radiolabelled somatostatin analogues by the kidneys in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaires for adverse reaction reports of radiation nephropathy.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Recommendation for assessment of the renal functions at baseline and during treatment in SmPC section 4.4 and PL section 2. Recommendation to consider renal protection in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	
Radiation-induced hepatotoxicity	Routine risk communication: Warning about hepatotoxicity in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to monitor the liver function regularly during treatment in SmPC section 4.4 and PL section 2. Recommendation to consider dose reduction in affected patients in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaires for adverse reaction reports of radiation-induced hepatoxicity.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.	

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to EndolucinBeta. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, ilLuzyce (lutetium (^{177}lu) chloride) is not included in the additional monitoring list.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed medicinal product ilLuzyce (lutetium (^{177}Lu) chloride n.c.a) is a radiopharmaceutical precursor not intended for direct use in patients. It is to be used only for radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.

3.1.2. Available therapies and unmet medical need

There are other available therapies based on Lutetium-177, but due to its radioactive characteristics (decay), granting a new marketing authorisation would improve the availability of these therapies.

3.1.3. Main clinical studies

In line with the Annex 1 Part III of Directive 2001/83/EC, as amended, on radiopharmaceutical precursors, relevant information on the clinical utility of the radiopharmaceutical precursor Lutetium (^{177}Lu) chloride when is attached to appropriate carrier molecules has been provided.

An appropriate number of published articles and meta-analyses have been presented documenting a well established use of ^{177}Lu-tracer-complex, mainly in neuroendocrine gastro-entero-pancreatic tumours and in prostate cancer.

3.2. Favourable effects

Clinical utility has been shown in the treatment of patients with neuroendocrine tumours using ^{177}Lu-labelled somatostatin analogues. In this regard, the use of ^{177}Lu-oxodotreotide for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults, is considered established, as ^{177}Lu-oxodotreotide is already authorised in this clinical setting.

Moreover, there is sufficient evidence to support clinical utility of lutetium (^{177}Lu) chloride when coupled to a carrier molecule in the treatment of mCRPC based on available efficacy data on ^{177}Lu-PSMA compounds, in particular in Radioligand therapy RLT supported with the most robust data.

3.3. Uncertainties and limitations about favourable effects

The applicant has presented evidence on efficacy and safety of ^{177}Lu-EDTMP on bone pain in patients with breast and prostate cancer and of ^{177}Lu-labelled antibodies in radioimmunotherapy (RIT) of other cancers like ovarian cancer (antibody CC49), breast cancer (trastuzumab), clear cell renal cell carcinoma (girentuximab), B-cell lymphomas (rituximab), lymphoma (lilotomab). The evidence currently available to demonstrate clinical utility of ^{177}Lu in these areas is still limited or experimental.

3.4. Unfavourable effects

Unfavourable effects are mainly related to the radioactivity of ^{177}Lu. Exposure to ionising radiation is known to induce cancer and is potentially mutagenic.

After therapy with ^{177}Lu-labelled peptides, haematological toxicity, myelodysplastic syndrome, renal toxicity and liver toxicity have been reported. Haematotoxicity and dry mouth have been reported with ^{177}Lu-labelled PSMA-ligands in radioligand therapy for metastatic castration-resistant prostate cancer.

Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) and Myelodysplastic syndrome/Acute myeloid leukaemia as well Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient are included in the RMP as important identified risks. In addition, osteosarcoma, radiation nephropathy and radiation-induced hepatotoxicity are considered as important potential risks in the RMP. Moreover, corresponding special warnings and precautions for use are included in the SmPC accordingly.

3.5. Uncertainties and limitations about unfavourable effects

Unfavourable effects will depend on the specific ^{177}Lu-labelled medicinal product prepared by radiolabelling with the proposed medicinal product. After administration of ^{177}Lu-labelled medicinal product, in-vivo release of free lutetium ($^{177}Lu^{3+}$) from the labelled biomolecule could occur. The degree of in-vivo release and free lutetium ($^{177}Lu^{3+}$) toxicity are unclear.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor intended to be used for radiolabelling of suitable carrier molecules (peptides, antibodies) which have been specifically developed and authorised for radiolabelling with lutetium-177. Therefore, clinical utility must be demonstrated. As required, the applicant has reviewed the literature in order to document the clinical utility of lutetium-177.

When coupled to a carrier molecule, clinical utility of ^{177}Lu in neuroendocrine tumours and prostate cancer has been demonstrated. The use of ^{177}Lu-labelled somatostatin analogues in treatment of patients with neuroendocrine tumours has been consolidated after having been granted with a marketing authorisation in the EU.

Unfavourable effects are mainly related to the radioactivity of ^{177}Lu. Adverse reactions following the administration of a ^{177}Lu-labelled medicinal product prepared by radiolabelling with the proposed medicinal product will be mainly dependent on the specific medicinal product being used. Therapy with these medicinal products is well tolerated and toxicity is manageable if protective recommendations and dose limits are followed, which have been adequately reflected in the product information.

3.7.2. Balance of benefits and risks

The proposed medicine is a radiopharmaceutical precursor intended solely for radiolabelling purposes.

The clinical utility of ^{177}Lu has been demonstrated and is considered to outweigh the risks associated with Lutetium (^{177}Lu) chloride.

The benefits and risks of ^{177}Lu-labelled medicinal product(s) will depend on the specific ^{177}Lu-labelled medicinal product(s) in the intended indications and therefore be evaluated independently.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of ilLuzyce is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of ilLuzyce is favourable in the following indication(s):

ilLuzyce (lutetium (^{177}Lu) chloride n.c.a.) 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

References

Abou Jokh Casas E Pubul Núñez V, Anido-Herranz U, Del Carmen Mallón Araujo M, Del Carmen Pombo Pasín M, Garrido Pumar M, et al. Evaluation of (177)Lu-Dotatate treatment in patients with metastatic neuroendocrine tumors and prognostic factors [Journal] // World journal of gastroenterology. - 2020. - pp. 26(13):1513-1524.

Abuqbeitah M Demir M, Uslu-Beşli L, Yeyin N, Sönmezoğlu K. Blood clearance and occupational exposure for (177)Lu-DOTATATE compared to (177)Lu-PSMA radionuclide therapy [Journal] // Radiation and environmental biophysics. . - 2018. - pp. 57(1):55-61..

Alvarez RD Partridge EE, Khazaeli MB, Plott G, Austin M, Kilgore L, et al. Intraperitoneal radioimmunotherapy of ovarian cancer with 177Lu-CC49: a phase I/II study [Journal] // Gynecologic oncology. - 1997. - pp. 65(1):94-101.

Araujo E., et al. Development of somatostatin based radiopharmaceuticals for receptor mediated radionuclide therapy. In: Comparative evaluation of radiotherapeutic radiopharmaceuticals. [Journal] // International Atomic Energy Agency (IAEA). - Vienna : [s.n.], 2007. - p. Chapter 3.

Arora G Mishra R, Kumar P, Yadav M, Ballal S, Bal C, et al. Estimation of Whole Body Radiation Exposure to Nuclear Medicine Personnel During Synthesis of (177)Lutetium-labeled Radiopharmaceuticals [Journal] // Indian journal of nuclear medicine : IJNM : the official journal of the Society of Nuclear Medicine, India.. - 2017. - pp. 32(2):89-92.

Askari E Harsini S, Vahidfar N, Divband G, Sadeghi R. (177)Lu-EDTMP for Metastatic Bone Pain Palliation: A Systematic Review and Meta-analysis. [Journal] // Cancer biotherapy & radiopharmaceuticals. - 2020.

Bander NH Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ., Phase I trial of 177lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. [Journal] // Journal of clinical oncology : official journal of the American Society of Clinical Oncology.. - 2005. - pp. 23(21): 4591-4601.

Baum RP Kulkarni HR, Singh A, Kaemmerer D, Mueller D, Prasad V, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with (90)Yttrium and (177)Lutetium in 1048 patients with neuroendocrine neoplasms. [Journal] // Oncotarget. - 2018. - pp. 9(24):16932-17050.

Baum RP Kulkarni HR, Singh A, Kaemmerer D, Mueller D, Prasad V, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with(90)Yttrium and (177)Lutetium in 1048 patients with neuroendocrine neoplasms [Journal] // Oncotarget. - 2018. - pp. 9(24):16932-50.

Bhusari P Vatsa R, Singh G, Parmar M, Bal A, Dhawan DK, et al. Development of Lu-177-trastuzumab for radioimmunotherapy of HER2 expressing breast cancer and its feasibility assessment in breast cancer patients [Journal] // International journal of cancer. - 2017. - pp. 140(4):938-947.

BIBRA toxicity profile Anonymous Toxicity Profile, Hafnium & its compounds [Journal] // Bibra, Cantium House, Railway Approach, Wallington, Surrey, SM60DZ, UK. Study report. - 1994. - pp. BIBRA Report no. T.2090: p. 1-7..

Bodei L Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study [Journal] // European journal of nuclear medicine and molecular imaging. - 2011. - pp. 38(12):2125-2135.

Bolch W., et al. ICRP publication 133: The ICRP computational framework for internal dose assessment for reference adults: specific absorbed fractions [Journal] // Annals of the ICRP. - 2016. - pp. 45(2): 5-73.

Braun Melsungen AG Salzsäure 7,25 %. Braun- Melsungen Fachinformation [Journal]. - 2006.

Breeman W.A., et al.. Optimising conditions for radiolabelling of DOTA-peptides with 90Y, 111In and 177Lu at high specific activities. [Journal] // Breeman, W.A., et al., Optimising conditions for radiolabellEur. J Nucl. Med. Mol. Imaging. - 2003. - pp. 30(6): 917-920.

Brouwers A.H., et al. Optimization of radioimmunotherapy of renal cell carcinoma: labeling of monoclonal antibody cG250 with 131I, 90Y, 177Lu, or 186Re. [Journal] // J Nucl. Med. . - 2004. - pp. 45(2): 327-337.

BRUCE D.W., B.E. HIETBRINK, and K.P. DUBOIS THE ACUTE MAMMALIAN TOXICITY OF RARE EARTH NITRATES AND OXIDES [Journal] // Toxicol. Appl. Pharmacol.. - 1963. - pp. 5:750-579.

Calopedos RJS Chalasani V, Asher R, Emmett L, Woo HH. Lutetium-177-labelled anti-prostate-specific membrane antigen antibody and ligands for the treatment of metastatic castrate-resistant prostate cancer: a systematic review and meta-analysis [Journal] // Prostate cancer and prostatic diseases. - 2017. - pp. 20(3):352-60.

Delpassand ES Samarghandi A, Zamanian S, Wolin EM, Hamiditabar M, Espenan GD, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE for patients with somatostatin receptor-expressing neuroendocrine tumors: the first US phase 2 experience [Journal] // Pancreas. - 2014. - pp. 43(4):518-525.

Demir M Abuqbeitah M, Uslu-Beşli L, Yıldırım Ö, Yeyin N, Çavdar İ, et al. Evaluation of radiation safety in (177)Lu-PSMA therapy and development of outpatient treatment protocol [Journal] // Journal of radiological protection : official journal of the Society for Radiological Protection. - 2016. - pp. 36(2):269-278.
Durbin P.W., et al., Metabolism of the lanthanons in the rat. [Journal] // Proc. Soc. Exp. Biol. Med.. - 1956. - pp. 91(1): 78-85.
E.A. Eisenhauera P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) [Journal] // EUROPEAN JOURNAL OF CANCER. - 2009. - pp. 45: 228-247.
Forrer F Oechslin-Oberholzer C, Campana B, Herrmann R, Maecke HR, Mueller-Brand J, et al. Radioimmunotherapy with 177Lu-DOTA-rituximab: final results of a phase I/II Study in 31 patients with relapsing follicular, mantle cell, and other indolent B-cell lymphomas. [Journal] // Journal of nuclear medicine : official publication, Society of Nuclear Medicine. - 2013. - pp. 54(7):1045-1052.
Forrer F Riedweg I, Maecke HR, Mueller-Brand J. Radiolabeled DOTATOC in patients with advanced paraganglioma and pheochromocytoma [Journal] // The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR). - 2008. - pp. 52(4): 334-340.
Forrer F Uusijärvi H, Waldherr C, Cremonesi M, Bernhardt P, Mueller-Brand J, et al. A comparison of (111)In-DOTATOC and (111)In-DOTATATE: biodistribution and dosimetry in the same patients with metastatic neuroendocrine tumours [Journal] // Journal of nuclear medicine: official publication, Society of Nuclear Medicine. - 2005. - pp. 46(8):1310-1316.
Forrer F Uusijärvi H, Waldherr C, Cremonesi M, Bernhardt P, Mueller-Brand J, et al. A comparison of (111)In-DOTATOC and (111)In-DOTATATE: biodistribution and dosimetry in the same patients with metastatic neuroendocrine tumours [Journal] // European journal of nuclear medicine and molecular imaging. - 2004. - pp. 31(9):1257-1262.
Garrett I.R. and J. McClure Lanthanide-induced calcergy [Journal] // J Pathol. - 1981. - pp. 135(4): 267-275..
Haley T.J., et al. Pharmacology and toxicology of lutetium chloride [Journal] // J Pharm. Sci.. - 1964. - pp. 53:1186-8.: 1186-1188..
Haley T.J., et al. The toxicologic and pharmacologic effects of hafnium salts. [Journal] // Toxicol. Appl. Pharmacol.. - 1962. - pp. 4:238-246.
Hamiditabar M Ali M, Roys J, Wolin EM, O'Dorisio TM, Ranganathan D, et al. Peptide Receptor Radionuclide Therapy With 177Lu-Octreotate in Patients With Somatostatin Receptor Expressing Neuroendocrine Tumors: Six Years' Assessment. [Journal] // Clinical nuclear medicine. - 2017. - pp. 42(6):436-443.
Hendifar AE Delpassand ES, Kittleson MM, Tuli R. Cardiac Toxicity in a Patient Receiving Peptide Receptor Radionuclide Therapy [Journal] // Pancreas. - 2018. - pp. 47(8):e55-e56..
Hijnen NM de Vries A, Nicolay K, Grüll H. Dual-isotope 111In/177Lu SPECT imaging as a tool in molecular imaging tracer design [Journal] // Contrast media & molecular imaging. - 2012 . - pp. 7(2):214-222.
Hinerman D.L., R.C. Hendrix, and C.V. Weller, Toxicity, distribution, excretion and morphologic effects of hafnium sodium mandelate in rats [Journal] // Am J Clin. Pathol.. - 1954. - pp. 24(2): 150-152..
Hirano S Suzuki KT. Exposure, metabolism, and toxicity of rare earths and related compounds [Journal] // Environmental health perspectives. - 1996. - pp. 104 Suppl 1(Suppl 1):85-95.
Hofman MS Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. [Journal] // The Lancet Oncology. - 2018. - pp. 19(6):825-833.
Kam B.L., et al., Lutetium-labelled peptides for therapy of neuroendocrine tumours. [Journal] // Eur. J Nucl. Med. Mol. Imaging. - 2012. - pp. 39 Suppl 1:S103-12.
Kang KW Song YS, Kwon TE, Ha WH, Jin YW. Accidental Injection of Unlabeled Lu-177 Caused Catastrophic Consequences in Patients with Neuroendocrine Tumor. [Journal] // Abstract #2838. 17th Annual ENETS Conference 2020.. - 2020.
Kim SJ Pak K, Koo PJ, Kwak JJ, Chang S. The efficacy of (177)Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis [Journal] // European journal of nuclear medicine and molecular imaging. - 2015. - pp. 42(13): 1964-1970.
Kratochwil C Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with (177)Lu-labelled PSMA-ligands ((177)Lu-PSMA-RLT) [Journal] // European journal of nuclear medicine and molecular imaging. - 2019. - pp. 46(12):2536-2544.

Kratochwil C Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with (177)Lu-labelled PSMA-ligands ((177)Lu-PSMA-RLT). [Journal] // European journal of nuclear medicine and molecular imaging. . - 2019. - p. 46(12):2536.
Kumamoto E. and Y. Murata. Lack of correlation between the molecular size and the efficacy of lanthanides for potentiating GABAA currents in rat septal cholinergic neurons in culture. [Journal] // Brain Res.. - 1996. - pp. 723(1-2): 235-237..
Kunikowska J Królicki L, Hubalewska-Dydejczyk A, Mikołajczak R, Sowa-Staszczak A, Pawlak D. Clinical results of radionuclide therapy of neuroendocrine tumours with 90Y-DOTATATE and tandem 90Y/177Lu-DOTATATE: which is a better therapy option? [Journal] // European journal of nuclear medicine and molecular imaging. - 2011. - pp. 38(10):1788-1797.
Kurth J Krause BJ, Schwarzenböck SM, Stegger L, Schäfers M, Rahbar K. External radiation exposure, excretion, and effective half-life in (177)Lu-PSMA-targeted therapies [Journal] // EJNMMI research . - 2018. - p. 8(1):32..
Leibowitz R Davidson T, Gadot M, Aharon M, Malki A, Levartovsky M, et al. A Retrospective Analysis of the Safety and Activity of Lutetium-177-Prostate-Specific Membrane Antigen Radionuclide Treatment in Older Patients with Metastatic Castration-Resistant Prostate Cancer [Journal] // The oncologist. - 2020. - pp. 25(9):787-792.
Levart D Kalogianni E, Corcoran B, Mulholland N, Vivian G. Radiation precautions for inpatient and outpatient (177)Lu-DOTATATE peptide receptor radionuclide therapy of neuroendocrine tumours [Journal] // EJNMMI physics. - 2019. - p. 6(1):7.
Li W.P., et al. Development of an in vitro model for assessing the in vivo stability of lanthanide chelates. [Journal] // Nucl. Med. Biol.. - 2001. - pp. 28(2): 145-154.
Lungu V., et al. Labelling of Dotatate with 177 Lu and 131 I for diagnosis and targeted therapy: In vitro and In vivo comparative evaluation [Journal] // Comparative evaluation of therapeutic radiopharmaceuticals.. - 2007.
Mair C Warwitz B, Fink K, Scarpa L, Nilica B, Maffey-Steffan J, et al. Radiation exposure after (177)Lu-DOTATATE and (177)Lu-PSMA-617 therapy [Journal] // Annals of nuclear medicine. - 2018. - pp. 32(7):499-502.
Matsuno H., et al. Biocompatibility and osteogenesis of refractory metal implants, titanium, hafnium, niobium, tantalum and rhenium [Journal] // Biomaterials. - 2001. - pp. 22(11): 1253-1262.
Meredith R You Z, Alvarez R, Partridge E, Grizzle W, LoBuglio A. Predictors of long-term outcome from intraperitoneal radioimmunotherapy for ovarian cancer [Journal] // Cancer biotherapy & radiopharmaceuticals. - 2012. - pp. 27(1):36-40.
Meredith RF Alvarez RD, Partridge EE, Khazaeli MB, Lin CY, Macey DJ, et al. Intraperitoneal radioimmunochemotherapy of ovarian cancer: a phase I study. [Journal] // Cancer biotherapy & radiopharmaceuticals. - 2001. - pp. 16(4):305-315.
Meredith RF Partridge EE, Alvarez RD, Khazaeli MB, Plott G, Russell CD, et al. Intraperitoneal radioimmunotherapy of ovarian cancer with lutetium-177-CC49. [Journal] // Journal of nuclear medicine : official publication, Society of Nuclear Medicine. - 1996. - pp. 37(9):1491-1496.
Mirković M., et al. Investigation of 177Lu-labeled HEDP, DPD, and IDP as potential bone pain palliation agents [Journal] // Journal of Radiation Research and Applied Sciences. - 2020. - pp. 13(1): 27-36..
Mottet N Brier E, De Santis M, Gillesen S, Grummet J. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. [Journal] // EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021.. - 2021.
Muller W.A., U. Linzner, and E.H. Schaffer Organ distribution studies of lutetium-177 in mouse. [Journal] // Int. J Nucl. Med. Biol.. - 1978. - pp. 5(1): 29-31..
Mulligan T Carrasquillo JA, Chung Y, Milenic DE, Schlom J, Feuerstein I, et al. Phase I study of intravenous Lu-labeled CC49 murine monoclonal antibody in patients with advanced adenocarcinoma [Journal] // Clinical cancer research : an official journal of the American Association for Cancer Research. - 1995. - pp. 1(12):1447-1454.
Nakamura Y., et al. Differences in behavior among the chlorides of seven rare earth elements administered intravenously to rats. [Journal] // Fundam. Appl. Toxicol.. - 1997. - pp. 37(2): 106-116.
Nelson KL Sheetz MA. Radiation Safety Observations Associated with 177Lu Dotatate Patients. [Journal] // Health physics. . - 2019. - pp. 117(6):680-687..
O'Mara R.E., J.G. McAfee, and G. Subramanian. Rare earth nuclides as potential agents for skeletal imaging. [Journal] // J Nucl. Med. - 1969. - pp. 10(1):49-51.
Paganelli G Sansovini M, Ambrosetti A, Severi S, Monti M, Scarpi E, et al. 177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study [Journal] // European journal of nuclear medicine and molecular imaging. - 2014. - pp. 41(10):1845-1851.
Paganelli G Sansovini M, Ambrosetti A, Severi S, Monti M, Scarpi E, et al. 177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a

phase II study. [Journal] // European journal of nuclear medicine and molecular imaging. - 2014. - pp. 41(10):1845-1851.
Pałasz A Czekaj P. Toxicological and cytophysiological aspects of lanthanides action. [Journal] // Acta biochimica Polonica. - 2000. - pp. 47(4):1107-14..
Paquet F., et al. ICRP Publication 141: Occupational Intakes of Radionuclides: Part 4 [Journal] // Annals of the ICRP. - 2019. - pp. 48(2-3): 9-501..
Puszkiel A Bauriaud-Mallet M, Bourgeois R, Dierickx L, Courbon F, Chatelut E. Evaluation of the Interaction of Amino Acid Infusion on (177)Lu-Dotatate Pharmacokinetics in Patients with Gastroenteropancreatic Neuroendocrine Tumors [Journal] // Clinical pharmacokinetics. - 2019. - pp. 58(2): 213-222.
Ranade R Basu S. 177Lu-DOTATATE PRRT in Patients with Metastatic Neuroendocrine Tumor and a Single Functioning Kidney: Tolerability and Effect on Renal Function. [Journal] // Journal of nuclear medicine technology. . - 2016. - pp. 44(2):65-9..
Repetto-Llamazares A., et al. Biodistribution and dosimetry of 177Lu-tetulomab, a new radioimmunoconjugate for treatment of non-Hodgkin lymphoma [Journal] // Current radiopharmaceuticals. - 2013. - pp. 6(1): 20-27.
S Green G R Weiss Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria [Journal] // Investig. New Drugs. - 1992. - pp. 10:239–253.
Sansovini M Severi S, Ambrosetti A, Monti M, Nanni O, Sarnelli A, et al. Treatment with the radiolabelled somatostatin analog Lu-DOTATATE for advanced pancreatic neuroendocrine tumors [Journal] // Neuroendocrinology. - 2013. - pp. 97(4):347-354.
Satapathy S Mittal BR, Bhansali A. Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: A systematic review and meta-analysis [Journal] // Clinical endocrinology. - 2019. - pp. 91(6):718-727.
Sathekge M Lengana T, Maes A, Vorster M, Zeevaart J, Lawal I, et al. (68)Ga-PSMA-11 PET/CT in primary staging of prostate carcinoma: preliminary results on differences between black and white South-Africans. [Journal] // European journal of nuclear medicine and molecular imaging. - 2018. - pp. 45(2):226-234.
Schmitt A., et al. Biodistribution and dosimetry of 177Lu-labeled [DOTA0, Tyr3] octreotate in male nude mice with human small cell lung cancer [Journal] // Cancer Biotherapy and Radiopharmaceuticals. - 2003. - pp. 18(4): 593-599.
Schmitt A., et al. Biodistribution and dosimetry of 177Lu-labeled [DOTA0, Tyr3] octreotate in male nude mice with human small cell lung cancer. [Journal] // Cancer Biotherapy and Radiopharmaceuticals. - 2003. - pp. 18(4): 593-599..
Sgouros G Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges [Journal] // Nature Reviews Drug Discovery. - 2020. - pp. 19(9):589-608.
Shelley W.B. Chondral dysplasia induced by zirconium and hafnium [Journal] // Cancer Res.. - 1973. - pp. 33(2): 287-292..
Shelley W.B., et al. Intradermal tests with metals and other inorganic elements in sarcoidosis and anthraco-silicosis [Journal] // J Invest Dermatol. - 1958. - pp. 31(6): 301-303..
Sitani K Parghane RV, Talole S, Basu S. Long-term outcome of indigenous (177)Lu-DOTATATE PRRT in patients with Metastatic Advanced Neuroendocrine Tumours: a single institutional observation in a large tertiary care setting [Journal] // The British journal of radiology. - 2021. - p. 94(1117):20201041.
Sitani K Parghane RV, Talole S, Basu S. Long-term outcome of indigenous (177)Lu-DOTATATE PRRT in patients with Metastatic Advanced Neuroendocrine Tumours: a single institutional observation in a large tertiary care setting. [Journal] // The British journal of radiology.. - 2021. - p. 94(1117):20201041..
Sowby F.D. ICRP Radiation Protection. Limits for intakes of radionuclides by workers. Metabolic data for lutetium [Journal] // ICRP publication 30 Part 3. Including addendum to parts 1 and 2. International Commission on Radiological Protection 1977-1981. Annals of the ICRP. - 1981. - pp. 6(No. 2-3): 85-87.
Stabin M. G., & Siegel, J. A. RADAR dose estimate report: a compendium of radiopharmaceutical dose estimates based on OLINDA/EXM version 2.0. [Journal] // Journal of Nuclear Medicine. - 2018. - pp. 59(1): 154-160.
Stillebroer AB Boerman OC, Desar IM, Boers-Sonderen MJ, van Herpen CM, Langenhuijsen JF, et al. Phase 1 radioimmunotherapy study with lutetium 177-labeled anti-carbonic anhydrase IX monoclonal antibody girentuximab in patients with advanced renal cell carcinoma [Journal] // European urology. - 2013. - pp. 64(3):478-485.
Stimmel J.B. and F.C. Kull, Jr. Samarium-153 and lutetium-177 chelation properties of selected macrocyclic and acyclic ligands. [Journal] // Nucl. Med. Biol. . - 1998. - pp. 25(2): 117-125..
Sulieman A Mayhoub FH, Salah H, Al-Mohammed HI, Alkhorayef M, Moftah B, et al. Occupational and ambient radiation exposures from Lu-177 DOTATATE during targeted therapy.

Applied radiation and isotopes : including data, instrumentation and methods for use in agriculture, industry and medicine [Journal]. - 2020. - p. 164:109240..
Sundlöv A Sjögreen-Gleisner K, Svensson J, Ljungberg M, Olsson T, Bernhardt P, et al. Individualised (177)Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry. [Journal] // European journal of nuclear medicine and molecular imaging. - 2017. - p. 44(9):14.
Svensson J Berg G, Wängberg B, Larsson M, Forssell-Aronsson E, Bernhardt P. Renal function affects absorbed dose to the kidneys and haematological toxicity during ^{177}Lu-DOTATATE treatment. [Journal] // European journal of nuclear medicine and molecular imaging.. - 2015.
Tagawa ST Milowsky MI, Morris M, Vallabhajosula S, Christos P, Akhtar NH, et al. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. [Journal] // Clinical cancer research : an official journal of the American Association for Cancer Research. - 2013. - pp. 19(18):5182-5191..
Tagawa ST Milowsky MI, Morris M, Vallabhajosula S, Christos P, Akhtar NH, et al. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. [Journal] // Clinical cancer research : an official journal of the American Association for Cancer Research.. - 2013. - pp. 19(18):5182-5191.
Tagawa ST Vallabhajosula S, Christos PJ, Jhanwar YS, Batra JS, Lam L, et al. Phase 1/2 study of fractionated dose lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 ((177) Lu-J591) for metastatic castration-resistant prostate cancer. [Journal] // Cancer. - 2019. - pp. 125(15):2561-2569..
Teunissen JJ Kwekkeboom DJ, Krenning EP. Quality of life in patients with gastroenteropancreatic tumors treated with [177Lu-DOTA0,Tyr3]octreotate [Journal] // Journal of clinical oncology : official journal of the American Society of Clinical Oncology. - 2004. - pp. 22(13):2724-2729.
U.S.EPA. Radiation Health Effects [Journal] // https://www.epa.gov/radiation/radiation-health-effects / ed. (EPA) United Sates Environmental Protection Agency. - 2020.
von Eyben FE Roviello G, Kiljunen T, Uprimny C, Virgolini I, Kairemo K, et al. Third-line treatment and (177)Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review [Journal] // European journal of nuclear medicine and molecular imaging. - 2018. - pp. 45(3): 496-508.
Weiss G.B. and F.R. Goodman. Interactions between several rare earth ions and calcium ion in vascular smooth muscle. [Journal] // J Pharmacol. Exp. Ther. . - 1975. - pp. 195(3): 557-564.
Yadav MP Ballal S, Sahoo RK, Dwivedi SN, Bal C. Radioligand Therapy With (177)Lu-PSMA for Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis [Journal] // AJR American journal of roentgenology. - 2019. - pp. 213(2): 275-285.
Yousefnia H., et al. Production, quality control, biodistribution assessment and preliminary dose evaluation of 177Lu-PDTMP as a possible bone palliative agent. [Journal] // Nuclear medicine communications,. - 2014. - pp. 35(1): 99-107..
Yu NY Rule WG, Sio TT, Ashman JB, Nelson KL. Radiation Contamination Following Cremation of a Deceased Patient Treated With a Radiopharmaceutical. Radiation Contamination Following Cremation of a Deceased Patient Treated With a Radiopharmaceutical. [Journal] // Jama. - 2019. - pp. 321(8):803-804..
Yuan J Liu C, Liu X, Wang Y, Kuai D, Zhang G, et al. Efficacy and safety of 177Lu-EDTMP in bone metastatic pain palliation in breast cancer and hormone refractory prostate cancer: a phase II study. [Journal] // Clinical nuclear medicine. - 2013. - pp. 8(2):88-92.
Zaknun JJ Bodei L, Mueller-Brand J, Pavel ME, Baum RP, Hörsch D, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. [Journal] // European journal of nuclear medicine and molecular imaging.. - 2013. - pp. 40(5):800-816.
Zandee WT Brabander T, Blažević A, Kam BLR, Teunissen JJM, Feelders RA, et al. Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors. [Journal] // The Journal of clinical endocrinology and metabolism.
Zandee WT Feelders RA, Smit Duijzentkunst DA, Hofland J, Metselaar RM, Oldenburg RA, et al. Treatment of inoperable or metastatic paragangliomas and pheochromocytomas with peptide receptor radionuclide therapy using 177Lu-DOTATATE. [Journal] // European journal of endocrinology. - 2019. - pp. 181(1):45-53.
Zhang J Wang H, Jacobson O, Cheng Y, Niu G, Li F, et al Safety, Pharmacokinetics, and Dosimetry of a Long-Acting Radiolabeled Somatostatin Analog (177)Lu-DOTA-EB-TATE in Patients with Advanced Metastatic Neuroendocrine Tumors. [Journal] // Journal of nuclear medicine : official publication, Society of Nuclear Medicine. - 2018. - pp. 59(11):1699-705.
Zolghadri S., et al. Production, quality control, biodistribution assessment and preliminary dose evaluation of [177Lu]-tetra phenyl porphyrin complex as a possible therapeutic agent. [Journal] // Brazilian Journal of Pharmaceutical Sciences. - 2015. - pp. 51(2): 339-348.