23 April 2015
EMA/427491/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lumark

International non-proprietary name: lutetium, isotope of mass 177

Procedure No. EMEA/H/C/002749/0000

Note

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

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Administrative information

Name of the medicinal product:	Lumark
Applicant:	I.D.B. Radiopharmacy B.V. Weverstraat 17 5111 PV Baarle-Nassau NETHERLANDS
Active substance:	Lutetium (^{177}Lu)
International Nonproprietary Name/Common Name:	lutetium, isotope of mass 177
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication(s):	Lumark is a radiopharmaceutical precursor indicated in adults. It is not intended for direct use in patients. This medicinal must be used only for the radiolabelling of carrier molecules, which have been specifically developed for radiolabelling with this radionuclide.
Pharmaceutical form(s):	Radiopharmaceutical precursor, solution
Strength(s):	80 GBq/mL
Route(s) of administration:	Not applicable
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

BALB	Bagg Albinos
BED	Biologically Effective Dose
CHMP	Committee for Medicinal Products for Human Use
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DTPA	Diethylenetriaminepentaacetate
EDTA	Ethylenediaminetetraacetate
EDTMP	Ethylène Diamine TétraMéthylène Phosphonate
^{18}F	Fluorine-18 radionuclide
GBq	Gigabecquerel
GEP-NET	GastroEnteroPancreatic NeuroEndocrine Tumours
GCP	Good Clinical Practice
HAMA	Human Anti-Mouse Antibody
HER2	Human Epidermal Growth Factor Receptor
ICRP-60	International Commission on Radiological Protection
keV/kV	kilo electron volt/ kilovolt
^{177}Lu	lutetium-177 radionuclide
mCi	millicurie
MIRD	Medical Internal Radiation Dose
MRI	Magnetic Resonnance Imaging
MeV/ MV	Mega electron volt/ megavolt
MBq	MegaBecquerel
NET	Neuroendocrine Tumours
PET	Positron emission tomography
PFS	Progression-Free Survival
PRRT	Peptide Receptor Radionuclide Therapy
PSA	Prostate Serum Antigen
PSMA	Prostate-Specific Membrane Antigen
PSMF	Pharmacovigilance System Master File
QPPV	Qualified Person Responsible for Pharmacovigilance
Sv	Sievert
SPECT	Single photon emission computed tomography
SWOG	Southwest Oncology Group

1. Background information on the procedure

1.1. Submission of the dossier

The applicant I.D.B. Radiopharmacy B.V. submitted on 5 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lumark, 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 24 May 2012.

The applicant applied for the following indication "To be used only for the radiolabelling of carrier molecules which have been specifically developed for radiolabelling with this radionuclide".

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.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Not applicable.

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.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance lutetium, isotope of mass 177 contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

I.D.B. Radiopharmacy B.V.
Weverstraat 17
5111 PV Baarle-Nassau
NETHERLANDS

1.3. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings

Co-Rapporteur: Joseph Emmerich

- The application was received by the EMA on 5 December 2013.
- The procedure started on 26 February 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 May 2014.
- During the meeting on 26 June 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 June 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 December 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 February 2015.
- During the CHMP meeting on 26 February 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 05 March 2015.
- The Joint Assessment Report was circulated to all CHMP members on 31 March 2015. The second Joint Assessment Report was circulated to all CHMP members on 01 April 2015.
- During the meeting on 23 April 2015, 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 Lumark.

2. Scientific discussion

2.1. Introduction

Lutetium chemically belongs to one of two special groups of the Periodic Tables called Lanthanides. The other group – actinides - is more widely known as it contains the nuclear fuel elements uranium and plutonium. The Lanthanides series starts with lanthanum (La, Z = 57) and ends with Lutetium (Lu, Z = 71). All lanthanides commonly favour the (III) oxidation resulting in great similarity among these elements. Lutetium is not the only element from the series which is used for radiopharmaceutical purposes, but cerium (Ce), samarium (Sa), gadolinium (Gd), holmium (Ho) and ytterbium (Yb) likewise are currently under investigation for their suitability as radiopharmaceutical label. The lanthanides are often referred to as the rare earth elements with lutetium being the less abundant of these.

Lutetium (177Lu) chloride is produced by irradiation of 176Lu with neutrons. 177Lu is a medium-energy β-emitter with a maximum energy of 0.5 MeV and a maximal tissue penetration of 2 mm. 177Lu decays with a half-life (t1/2) of 6.647 days by beta decay to form the stable Hafnium nuclide, 177Hf. The maximum beta energy for the decay of 177Lu to 177Hf is 0.497 MeV. The average beta energy is approximately 0.13 MeV. Also low gamma energy is emitted, for instance at 113 keV (6.2%) and 208 keV (11%). The emission of gamma rays allows scintigraphy and subsequent dosimetry with the same therapeutic compound.

Lumark is a radiopharmaceutical precursor solution containing 80 GBq (becquerel) Lutetium (177-Lu) chloride per mL. It is packaged in colourless type I glass vial of 10 ml, closed with a bromobutyl rubber stopper and aluminium overseal. Each vial contains an activity ranging from 8 to 400 GBq which corresponds to an amount of 16 microgram to 800 micrograms Lutetium. The volume of one vial ranges from 0.1 – 5.0 ml solution.

Lumark is indicated in adults for the radiolabelling of carrier molecules which have been specifically developed for radiolabelling with this radionuclide. As Lumark is a radiopharmaceutical precursor, it is not designed to be given directly to patients.

In accordance with Article 10a of Directive 2001/83/EC, as amended the application relies on well-established medicinal use supported by bibliographic literature. According to Article 10a of Directive 2001/83/EC, as amended it is possible 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 Community 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 as follows:

a) Factors which have been taken into account by the CHMP in order to establish a well-established use

- Time over which the substance has been used

Lutetium has been used in the treatment of NETs since 2000 and it is the third generation of receptor targeted radionucleotide therapy. 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

A study between 2000 and 2006 showed 504 patients treated with 1772 administrations of study drug. The applicant's supply of lutetium in Becquerel from 2003-2013 shows over 500 patients treated in 2003, increasing year on year to nearly 3000 patients in 2013. Wide geographical use over the EU has been shown, with centres in the UK, France, Germany, Belgium and a number of others.

- The degree of scientific interest in the use of the substance (reflected in the published scientific literature)

There is continued scientific interest in lutetium, with publications spanning 15 years and at least 25 publications a year since 2005.

- Coherence of scientific assessments

The comprehensive body of data and discussion by the applicant fulfilled the requirements of the well-established use legal basis, not only in length of use but also quantity and extent.

b) The CHMP considers that the documentation submitted by the Applicant has covered all aspects of the quality, safety and efficacy and includes review of the relevant literature. The documentation, both favourable and unfavourable has been communicated.

c) The CHMP considers that adequate justifications and/or analyses have been provided by the applicant to complete any missing information, demonstrating that an acceptable level of safety and efficacy can be supported although some studies are lacking.

d) The Applicant explained the relevance of data submitted concerning the product reviewed in the literature being different from the product intended for marketing. A judgement has been made that the product studied in the literature, which are mostly related to studies with carriers radiolabelled with 177Lu, are considered relevant to the radioprecursor intended for marketing.

e) There is no post-marketing experience with this active substance as no product containing that active substance has not been authorised in the Union. Monitoring of adverse events, whilst not pro-active, has been described in the literature in a review article dated 2012 which is comprehensive in its description of the described adverse events and their frequency.

Lumark is presented as one mL of solution contains 80 GBq Lutetium (177Lu) chloride at activity reference time (ART), corresponding to at most a maximum of 160 microgram of Lutetium. The ART is defined as the end of production. Each vial contains a volume varying from 0.1 to 5 mL corresponding to an activity ranging from 8 to 400 GBq (at ART). The minimal specific activity is 500 GBq/mg Lutetium (177Lu) at the ART. The proposed indication is as follows:

Lumark is a radiopharmaceutical precursor. It is not intended for direct use in patients. This medicinal must be used only for the radiolabelling of carrier molecules, which have been specifically developed for radiolabelling with this radionuclide.

Lumark is only to be used by specialists experienced with in vitro radiolabelling.

Lumark is intended for in vitro radiolabelling of medicinal products, which are subsequently administered by the approved route.

Lumark should not be administered directly to the patient.

For instructions on extemporary preparation of the medicinal product before administration, see section 12 of the SmPC.

The radiopharmaceutical precursor solution is packaged in colourless type I glass vial of 10 mL, closed with a bromobutylrubber stopper and aluminium overseal.

Each vial contains a volume varying from 0.1 to 5 mL corresponding to an activity ranging from 8 to 400 GBq at the ART.

The vials are placed in a lead container for protective shielding and packed in a plastic jar.

Each pack contains one vial in a lead container.

2.2. Quality aspects

2.2.1. Introduction

Lumark is a radiopharmaceutical precursor solution. It is not intended for direct administration to patients. This medicinal product must be used only for the radiolabelling of carrier molecules which have been specifically developed for radiolabelling with this radionuclide.

The radiopharmaceutical precursor can be prepared in a range of strengths to provide for changing hospital demands. These can vary according to the intended use of the product, number of patients to be treated and labelling agents to be used. As a result the composition is best described as following:

One mL of solution contains 80 GBq lutetium (^{177}Lu) chloride at activity reference time (ART), corresponding to at most a maximum of 160 mg of lutetium. The ART is defined as the end of production. Each vial contains a volume varying from 0.1 to 5 mL corresponding to an activity ranging from 8 to 400 GBq (at ART). The minimal specific activity is 500 GBq/mg lutetium (^{177}Lu) at the ART.

Lutetium (^{177}Lu) has a half-life of 6.647 days and is produced by neutron irradiation of enriched lutetium (^{176}Lu). Lutetium (^{177}Lu) decays by β^--emission to stable hafnium (^{177}Hf), with the most abundant β^- (79.3%) having a maximum energy of 0.497 MeV. Low gamma energy is also emitted, for instance at 113 keV (6.2%) and 208 keV (11%).

Other ingredients are hydrochloric acid (0.05 N) and water for injections.

The radiopharmaceutical precursor solution is packaged in colourless type I glass vials, closed with a bromobutylrubber stopper and aluminium overseal.

2.2.2. Active Substance

General information

The chemical name of active substance is lutetium (^{177}Lu) chloride solution (or trichloride). ^{177}Lu is a beta-emitter (e_{max}= 0,495 MeV) with a ã -component of two lines at 0.1134 and 0.208MeV. The active substance is a colourless or white monoclinic crystalline solid, soluble in water.

The active substance is not isolated during the manufacture and is dissolved in a solution of diluted hydrochloric acid. The general properties of the active substance therefore relate to the lutetium (^{177}Lu) chloride in diluted hydrochloric acid solution.

Manufacture, characterisation and process controls

The active substance ^{177}Lu is a synthetic isotope produced in a nuclear reactor. ^{177}Lu can be produced by two different routes:

i. directly by neutron bombardment of cold ^{176}Lu

ii. indirectly by neutron bombardment of ^{176}Yb to form ^{177}Yb which decays to ^{177}Lu;

The ^{177}Lu isotope is obtained by method (i) direct neutron activation of lutetium (^{176}Lu) as the nitrate salt.

The manufacturing process consists of three steps using commercially available a well-defined starting material with acceptable specifications: preparation of the target, irradiation of the target, dissolution in hydrochloric acid and measurement of activity.

Characterisation is mainly by emission spectrum. This technique shows the characteristics of the radionucleotides known to be present, i.e. ^{177}Lu, ^{177}mLu and ^{177}mHf. Analysis data of the starting material lutetium oxide using ICP-MS to determine the concentration of lutetium isotopes present was also provided. The isotopic composition in terms of ^{176}Lu (usually >80%) and the unwanted ^{175}Lu (usually <20%) is presented. The majority of the isotopes present in the starting material are likely to be present in the finished product as only a small amount will be converted to radioisotopes by bombardment.

Adequate in-process controls are applied during the synthesis.

Specification

Other than measuring activity no tests are performed on the active substance.

The active substance is not isolated during the manufacture and is dissolved in a solution of diluted hydrochloric acid. The activity of the solution is measured but apart from this no other controls are performed. The Guideline on radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) states that: "Where an active substance is not isolated during the production process, information on specification may presented in the Drug Product Specification(s)". Therefore the absence of testing in the specification for the active substance is acceptable.

Stability

The active substance is not isolated during the manufacture and is dissolved in a solution of diluted hydrochloric acid. The activity of the solution is measured but apart from this no other controls are performed. The Guideline on radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) states that "where an active substance is not isolated during the production process, information on specification may presented in the Drug Product Specification". Therefore the absence of testing in the specification for the active substance is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of pharmaceutical development was to produce a sterile finished product with a low content of metallic impurities, to ensure the intended performance of the product is of appropriate quality to deliver the intended radio-labelling capacity.

The active substance is a bulk solution of lutetium (^{177}Lu) solution supplied in 0.05 M HCl. This is diluted with 0.1 N HCl to obtain a radioactive concentration of 100 GBq/mL at the date of manufacture.

The excipients used are HCl and water for injections. HCl was chosen because of its use in the synthesis of the active substance and because ^{177}Lu is present in the ionic form of Lu^{+}, which has very high stability in aqueous solutions. HCl is a well known pharmaceutical ingredient 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.

The manufacturing process is a straightforward process starting with the bulk solution of the active substance and preparation to finished product in a shielded computer-assisted dispensing unit. The bulk solution is diluted to the required volume and dispensed into vials with each vial having its specific radioactivity and volume. The final step involves sterilisation and packaging into a shielded lead container.

The sterilisation process is primarily controlled parametrically and by the use of a microbiological indicator.

After radioactive decay, a test for sterility is performed with the same microbiological limit as would be applied to other parenteral dosage forms according to ICH guidelines. No process for removal of bacterial endotoxins is carried out before testing.

The radiopharmaceutical precursor solution is packaged in colourless type I 10 mL glass vials, closed with a bromobutylrubber stopper and aluminium overseal. 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.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: dilution, dispensing, sterilisation and packaging.

The finished product is prepared in a robotic dispensing line for vials with a computer-assisted unit. The dispensing line is placed in a clean room facility (Grade C) in which an isolator consisting of 3 hot cells, is positioned. These hot cells separately host the bulk manufacturing unit and a dispense & sterilization unit (Grade B), delivering the injection vials ready for packaging and shipment. A third unit is situated in between and serves as a transfer unit.

The dispensing unit is located in a radiation shielded laminar flow unit (class B at rest). The product is terminally sterilised according to an accelerated cycle shown to be at least equivalent to the standard sterilisation cycle of the Ph Eur.

Major steps of the manufacturing process have been validated by a number of studies. 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 pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, labelling, volumetric activity, specific activity, pH (potentiometry), radio nucleotide identification (identity ^{177}Lu, gamma spectroscopy), chloride test, radionuclidic impurities (gamma spectroscopy), radiochemical purity (TLC), and endotoxins (Ph Eur). Sterility (Ph Eur) is used as post release test and it will be determined after decay (10 weeks).

Batch analysis results are provided for six production batches 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 on three batches representative of that intended for routine production was provided. The product was packed in a container closure system that is identical to the intended commercial packaging and which includes vial (primary packaging), lead pot and plastic container. This was placed in an incubator set at 30 ^{o}C monitored using calibrated temperature sensors. No accelerated stability data is presented. This is accepted as given the nature of the product and its very short shelf-life, accelerated data would not be expected to yield any useful information. Samples were tested for appearance, pH-value (potentiometry), identity (^{177}Lu, gamma spectroscopy), chloride test, ^{177}mLu impurity, other radioisotope impurities, radiochemical impurities (TLC), endotoxins (Ph Eur) and sterility (Ph Eur). The analytical procedures used are stability indicating.

The shelf-life of the product is 8 days. The shelf-life is limited by radioactive decay and increase in radionuclide impurities relative to active ingredient nuclide.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

Adventitious agents

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

2.2.4. 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. In terms of posology, the quantity of Lumark required for radiolabelling and the quantity of the product to be radiolabelled with Lutetium(177Lu) that is subsequently administered will depend on the medicinal product to be radiolabelled and its intended use. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

2.2.5. 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.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical sections of the dossier have been compiled from published literature and the applicant has stated that administration of such a low quantity of an inorganic salt does not warrant further non-clinical testing. No new non-clinical studies have been presented in this submission.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacological properties of Lutetium was first described 60 years ago[1] . These studies demonstrated that there were no pharmacological effects with lutetium in cats dosed up to 10 mg/kg. At higher doses of 20 mg/kg and above, there were signs of transient hypotension of 10 to 15 mmHg with a concomitant decrease in peripheral blood flow. Complete cardiovascular collapse coupled with respiratory paralysis, was produced by 20 mg/kg in five animals and by 40 mg/kg in the other five. Respiration was not affected by the compound. Terminal electrocardiographic changes included inversion of the QRS-complex, ventricular fibrillation, heart block, and alterations in T-wave. Within the dosage range employed, lutetium chloride had no effect on the pharmacological responses to acetylcholine, histamine or vagal stimulation. Lutetium had no effect on transmission in the superior cervical ganglion or on contraction of the nictitating membrane. None of the above effects of lutetium chloride could be modified by atropinisation, and the cardiovascular collapse was not counteracted by adrenaline. In isolated rabbit ileum, concentrations ranging from 0.4 – 1.6 mg/ml lutetium trichloride were required to produce depression of the intestinal tonus and contractibility. This depressant effect counteracted the spasmogenic effect of both acetylcholine and nicotine. A similar depression also occurred with the Trendelenburg guinea pig enteric ganglia preparation, where blockade of the circular and longitudinal muscular contractions were observed with a similar concentration range. Although this would seem to indicate that lutetium trichloride had ganglionic blocking properties, considering the earlier findings described in cats, where lutetium was unable to block the cat superior cervical ganglion preparation, such activity is unlikely.

In another study[2] aortic smooth muscle strips, isolated from rabbit hearts, were incubated in the presence of 1.5 mM Lu^{3+}. These strips demonstrated changes in the maximal height of the tension response, changes in the area under the recorded tension curves as well as inhibition of the contractile response to noradrenaline. Increased time of exposure to Lu^{3+} before addition of noradrenaline resulted in a greater inhibition of the tension response. The uptake of ^{45}Ca in such aortic strips showed a marked decrease when 1.5 mM Lu^{3+} was present in the bathing medium. This concentration (approx. 0.4 mg/ml) compares well with the results presented above but these concentration are still well in excess of the usual concentration of lutetium trichloride in Lumark i.e. 20 µg/ml. These effects reducing calcium uptake are attributed to the competing affinity of lutetium ions for superficial calcium binding sites.

Cellular studies with lutetium have demonstrated that lutetium trichloride has some limited pharmacological activity at concentrations below those shown in the *ex vivo* studies above. Histamine release from rat peritoneal mast cells, caused by various releasing agents, was inhibited by concentrations as low as 10^{-6} M lutetium [3]. It is thought that the inhibition is mediated by antagonising the binding of calcium to superficial receptors on the mast cell membrane, presumably followed by internalisation of the lutetium ion. Different calcium-receptors and channels may be involved according to the nature of the secretagogue. It is also noted that the proposed

patient dose of 20 µg lutetium trichloride, considering a human distribution volume of 75 L, would represent 0.27 µg/L equal to a concentration of approximately 10^{-9} M, and a dose below the concentration that may cause a pharmacological effect.

On the biochemical level the Lu^{3+} ion has appeared to be a potent inhibitor of the $NAD(P)^+$-dependent human malic enzyme and the $NADP^+$-dependent malic enzyme from the pigeon liver[4] . These enzymes, which catalyse the reversible oxidative carboxylation of l-malate to yield CO_2 and pyruvate, with concomitant reduction of $NADP^+$ to NADPH, require the presence of divalent cations (magnesium, calcium and others). The lutetium ions compete with these divalent cations for their binding sites on the enzyme in a concentration above 10 µM (10^{-6} M). A similar competition with calcium ions underlies the main toxicological effect of lutetium trichloride.

In vivo animal tumour models

The shorter β-range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β-range of ^{90}Y which allows more uniform irradiation in large tumors that may show heterogeneous uptake. This was illustrated in an animal model, in which a combination of ^{90}Y- and ^{177}Lu-labelled somatostatin analogues demonstrated a better tumor response than the use of each radiolabelled analogue separately[5] .

Miao *et al* (2007)[6] examined the therapeutic efficacy of ^{177}Lu-DOTA-Re(Arg(11))CCMSH in the B16/F1 murine melanoma-bearing mouse model. Results revealed that ^{177}Lu-DOTA-Re(Arg(11))CCMSH yielded quantitative therapeutic effects in B16/F1 melanoma-bearing mice and appeared to be a promising radiolabelled peptide for the targeted radionuclide therapy of melanoma.

Treatment with radiolabelled somatostatin analogues is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumours. Symptomatic improvement may occur with ^{177}Lu-labelled somatostatin analogues that have been used for peptide receptor radionuclide therapy (PRRT). The results obtained with ^{177}Lu-[DOTA^0, Tyr^3]octreotate (DOTATATE) are very encouraging in terms of tumor regression[7].

Dalmo *et al* (2012)[8] evaluated the medullary thyroid carcinoma GOT2 animal model by analyzing the biodistribution of ^{177}Lu-octreotate and ^{111}In-minigastrin (MG0). BALB/c nude mice, subcutaneously transplanted with GOT2, were intravenously injected with either ^{177}Lu-octreotate or ^{111}In-MG0, with or without excess of unlabeled human minigastrin simultaneously with ^{111}In-MG0. For both radiopharmaceuticals the highest activity concentrations were found in the kidneys. The GOT2 animal model was considered as a valuable model for evaluation and optimization of diagnostic and therapeutic procedures using radiolabelled somatostatin, CCK2 and gastrin analogues prior to clinical studies.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted (see non-clinical discussion).

Safety pharmacology programme

No safety pharmacology studies have been submitted (see non-clinical discussion).

Pharmacodynamic drug interactions

No studies on drug interaction have been submitted (see non-clinical discussion).

2.3.3. Pharmacokinetics

The applicant has not submitted studies with Lumark. A literature review has been carried out to illustrate the pharmacokinetic behaviour of lutetium. The data reported concern both oral and parenteral administration and elucidate the characteristics of tissue distribution.

Absorption

Absorption of lutetium trichloride from the gastro-intestinal tract have been described from studies aimed at determining the feasibility of its use as non-absorbed marker for recovery, passage and indirect apparent digestibility studies[9]. Rats were starved overnight and then were fed rice containing 25 µg lutetium after which complete collections of faeces and urine by 24 hours periods were made for 7 days. The recovery of this marker fed as a single dose provided information on the time of passage through the alimentary tract, the quantity passed each day, the rate of passage and the total recovery. These experiments showed 78% of the lutetium to be recovered the first day and 99% cumulatively in the first 2 days. The missing 1% was indistinguishable from the background at the analytical limits of sensitivity. When incorporated into various diets at a concentration ranging from 0.11 – 0.14 µg/g diet, negligible diurnal variation in faecal concentration was noted with lutetium.

A similar negligible absorption, less than 0.1%, from the gastrointestinal tract had been demonstrated for some other lanthanides such as cerium, europium, terbium and thulium as citrate salt[10].

Distribution

Distribution studies have been performed to determine their affinity with particular tumour types. Some early work has been described in Yoshida sarcoma bearing rats in which 177Lutetium citrate was seen to be retained predominantly to the blood, liver, spleen, tumour and kidney. No data was presented for bone tissue in this study, however further work using Ehrlich's tumour bearing mice showed that lutetium was also retained to bone tissue[11], [12] . The retention values in various tissues, expressed as a per cent of the administered dose per gram tissue weight are shown in the table below.

Table 1: Lutetium retention in various tissues of Yoshida sarcoma-bearing rats expressed as % dosis /g tissue weight

Time	Blood	Tumor	Muscle	Liver	Kidney	Spleen
3 h	1.88	0.73	0.17	0.99	0.65	0.76
24 h	0.022	0.59	0.025	0.47	0.64	0.32
48 h	0.017	0.58	0.026	0.44	0.61	0.30

Table 2: Lutetium retention in various tissues of Ehrlich's tumour-bearing mice expressed as % dose/g tissue weight

Time	Tumor	Liver	Kidney	Spleen	Bone
28 h	1.94	15.22	3.04	12.84	2.4
48 h	6.69	5.58	3.63	5.76	3.75

Distribution to bone tissue has been described as a method of displacing or replacing calcium ions with lutetium ions in bone tissue[13] . Skeletal uptake also seems to be determined by whether lutetium is present with a carrier or not. Skeletal retention is higher without a carrier (55%) than with a carrier (25%), although this addition of carrier also leads to increased liver uptake. High skeletal uptake is also implied in increasing the incidence of osteosarcoma. Further distribution studies confirmed high distribution of lutetium to the liver, spleen and bone – in total around 80% - and this didn't vary with concentration of lutetium administered. Distribution of lutetium was 65% in the liver, 5.3% in the spleen and 13% in the bones 24 hours after administration, and in addition there is distribution to the blood – approximately 15% 2 hours after administration[14] .

In a distribution study in mice bearing small cell lung cancer, 177Lutetium trichloride was shown to accumulate in the bone over 7 days, as well as have high distribution to the liver and spleen and kidney.

A more detailed study of the biodistribution of ^{177}Lutetium trichloride in mice confirms the relatively high uptake in the liver, kidneys and bone marrow[15] . The results are presented in the table below.

Table 3: Activity concentration of 177Lu in different organs after administration of 177Lutetium trichloride to nude mice bearing small cell lung cancer expressed as percentage of injected activity per gram tissue corrected for decay

Time	Blood	Heart	Lungs	Liver	Pancreas	Spleen	Small intestine	Adrenals	Kidney	Muscle	Bone	Brain
24 h	0.03	0.72	0.93	2.80	0.31	0.91	0.85	0.32	3.72	0.16	1.41	0.10
3 d	0.02	0.49	1.00	1.82	0.33	0.93	0.37	0.42	2.50	0.20	3.52	0.09
7 d	0.01	0.57	1.04	1.40	0.32	1.16	0.33	0.39	1.78	0.16	5.28	0.18

Biodistribution

Four new biodistribution studies have been carried out after ICRP-30 data were published, covering the biodistribution of free (unlabelled) ^{177}Lu.

This new biodistribution data was used to make new radiation dose estimations (see dosimetry in clinical section). The applicant has used a staggered approach to address this concern, this includes:

1. Assessment of existing published literature to available on biodistribution of free Lu^{3+} or $LuCl_3$.

2. Estimation of biodistribution of free Lu^{3+} in mice/rats.

3. Calculation of absorbed dose per unit activity administered, based on biodistribution parameters.

4. Estimation of total effective dose.

The following publications have been used to estimate biodistribution of lutetium in mice and rats:

- Schmitt *et al*, 2003[15]

- V. Lungu *et al*.[16] – Labelling of Dotatate with 177Lu and 131I for diagnosis and Targeted Therapy: In Vitro and In Vivo Comparative Evaluation; IAEA Technical Report 458 (2007) 14:233-256
- A. Repetto-Llamazares *et al*.[17] – Biodistribution and Dosimetry of 177Lu-tetulomab, a New Radioimmunoconjugate for Treatment of Non-Hodgkin Lymphoma; Current Radiopharmaceuticals (2013) 6(1):20-27
- H. Yousefnia *et al*.[18]– Production, quality control, biodistribution assessment and preliminary dose evaluation of 177Lu-PDTMP as a possible bone palliative agent; Nuclear Medicines Communication (2014) 35:99-107

Information from all four articles has been used to construct a new dose estimation assessment and compare it with the original ICRP-30 data.

Estimation of biodistribution of free Lu3+ in mice/rats

An overview of the results of the Lu biodistribution studies was presented in the table below. The variability of reported biodistribution parameter values is most probably the result of the differences in study objects (mice or rats, tumour or non-tumour bearing) and by the difference in focus of the respective studies. Some commonalities can be seen from the data:

• Short-term uptake in liver and kidney

• Long-term uptake in bone tissue

Table 4: Biodistribution of Lu^{3+}: Overview of different biodistribution studies

	Schmitt - 2003			Lungu - 2007			Repetto - 2013			Yousefnia - 2013		
	Non-tumour bearing nude mice (7 w) %ID/g			Lewis tumour bearing rats (6-7 w) %ID/g			Non-tumour bearing nude mice (6 m) %ID/g			Wild-type rats (age unknown) %ID/g		
Organ	**24h**	**4 d**	**7 d**	**24h**	**5d**	**7 d**	**24h**	**2d**	**6 d**	**24h**	**2d**	**7 d**
Adrenals	0,32	0,42	0,39	1,41	0,36	0,16						
Blood	0,03	0,02	0,01	0,84	0,03	0,00	0,08	0,024	0,010	0,03	0,01	0,02
Bone				16,12	12,03	10,5				2,26	4,06	5,08
Bone marrow	1,14	3,52	5,28									
Brain	0,10	0,09	0,18									
Fat	0,27	0,31	0,32									
Femur							10	13	13			
Gastrointestinal tract				2,34	0,34	0,27						
Heart	0,72	0,49	0,57	0,65	0,03	0,00				0,11	0,11	0,06
Kidney	3,72	2,50	1,78	13,51	3,83	0,31	11,1	7,9	5,8			
Liver	2,80	1,82	1,40	4,73	1,09	0,35	3,8	3,3	2,18	1,81	3,07	0,16
Lungs	0,93	1,00	1,04				1,6	1,3	1,2	0,06	0,04	0,03
Lymph nodes							1,4	1,9	1,2			
Muscle	0,16	0,20	0,16	0,26	0,17	0,08				0,03	0,18	1,07
Pancreas	0,31	0,33	0,32	0,82	0,30	0,21						
Pituitary gland				0,19	0,00	ND						
Salivary glands	0,51	0,72	0,74									
Skin										0,11	0,08	0,08
Skull							26	32	32			
Small intestine	0,85	0,37	0,33							0,24	0,00	1,11
Spleen	0,91	0,93	1,16	3,24	1,03	0,23	1,2	0,9	1,02	0,37	1,01	0,20
Stomach				2,87	0,61	1,12				0,11	0,18	0,19
Thymus												
Thyroid				0,32	0,10	0,08						

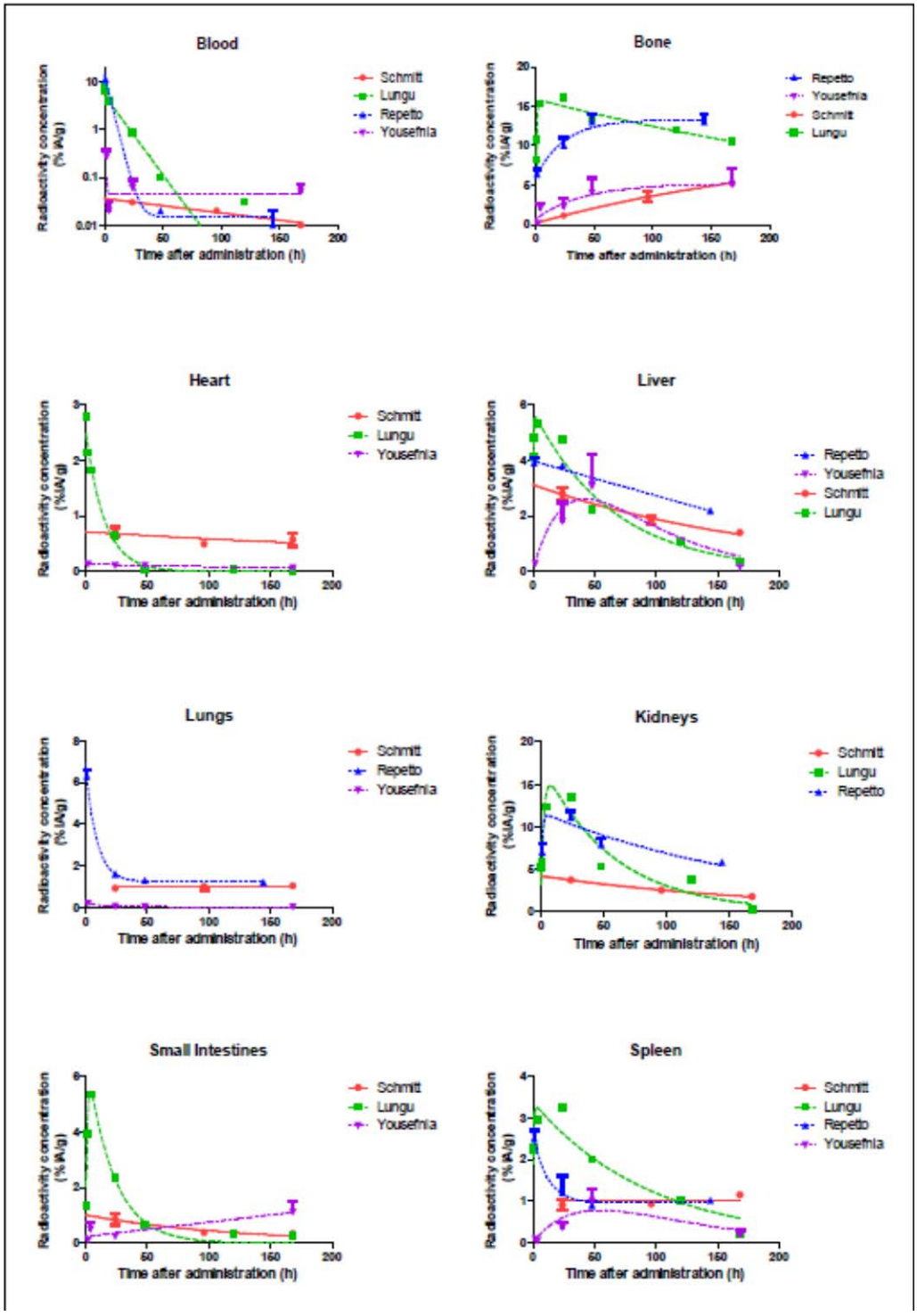
The biodistribution data is used to calculate the mean residence time of activity in organs, utilising the following sequence:

• For each organ with measured ^{177}Lu uptake, the radioactive concentration is plotted against time after injection. In Figure 1, the results of this exercise are shown for 8 of the most common organs.

• A function was fitted through these data points. This was either a one phase decay curve, a build-up curve (uptake and excretion curve), or a time independent curve, depending on whichever resulted in the best fit, as determined by the F-test.

• The area under the curve was calculated by taking the integral of the curve over time, to estimate the accumulated activity Ã per gram of tissue in the organ.

Figure 1: Biodistribution curves for free Lu in different organs



From the four literature sources cited, the article from Lungu *et al.* (2003)[16] has the most data points (13 organs, each with 7 time points). The curve-fitting for these data was considered to be more accurate than for the other data.

The accumulated activity Ã will be used to estimate radiation dose to the different (target) organs as a result of the activity in the different (source) organs. This was done using the standard MIRD (Medical Internal Radiation Dose) model, as described in ICRP-23 and ICRP-60:

$$D(r_k) = \sum_h \tilde{A}_h \times S(r_k \leftarrow r_h)$$

Where D(rk) is the absorbed dose of the target region rk, ÃS the accumulated activity in source region rh and S(rk←rh) called the S factor, is the mean absorbed dose to the target region rk per unit of accumulated activity in the source region rh.

The S-factor represents the physical decay characteristics of the radionuclide, the range of the emitted radiations and the organ size and configuration.

Table 5: Dose estimation for free Lu^{3+}: comparison between ICRP-30 results and new biodistribution results

	ICRP-30 data			New biodistribution data			LUNGU Lewis rats data
	Lu-177	Lu-177m (0,05%)	Total	Lu-177	Lu-177m (0,05%)	Total	Lu-177
Target Organ	**Organ dose (mGy/MBq)**			**Organ dose (mGy/MBq)**			**Organ dose (mGy/MBq)**
Adrenals	0,018	0,006	0,02	0,099	0,002	0,10	0,171
Brain	0,017	0,006	0,02	0,028	0,001	0,03	0,025
Breasts	0,005	0,002	0,01	0,028	0,001	0,03	0,025
Gallbladder Wall	0,012	0,003	0,02	0,038	0,002	0,04	0,041
LLI Wall	0,868	0,004	0,87	0,888	0,003	0,89	0,883
Small Intestine	0,069	0,003	0,07	0,092	0,002	0,09	0,089
Stomach Wall	0,038	0,002	0,04	0,115	0,002	0,12	0,177
ULI Wall	0,327	0,003	0,33	0,350	0,002	0,35	0,347
Heart Wall	0,009	0,003	0,01	0,049	0,001	0,05	0,086
Kidneys	0,210	0,004	0,21	0,700	0,002	0,70	1,580
Liver	0,220	0,009	0,23	0,319	0,001	0,32	0,620
Lungs	0,010	0,003	0,01	0,067	0,002	0,07	0,069
Muscle	0,012	0,004	0,02	0,030	0,001	0,03	0,027
Ovaries	0,015	0,003	0,02	0,036	0,002	0,04	0,032
Pancreas	0,012	0,004	0,02	0,109	0,003	0,11	0,196
Red Marrow	1,090	0,018	1,11	0,243	0,014	0,26	0,074
Osteogenic Cells	7,530	0,067	7,60	0,369	0,008	0,38	0,440
Skin	0,007	0,002	0,01	0,028	0,001	0,03	0,024
Spleen	0,008	0,002	0,01	0,190	0,002	0,19	0,476
Testes	0,006	0,002	0,01	0,029	0,001	0,03	0,025
Thymus	0,007	0,002	0,01	0,029	0,001	0,03	0,026
Thyroid	0,011	0,004	0,01	0,029	0,001	0,03	0,044
Urinary Bladder Wall	0,240	0,002	0,24	0,263	0,002	0,26	0,259
Uterus	0,011	0,002	0,01	0,034	0,002	0,04	0,030
Total Body	**0,185**	**0,008**	**0,19**	**0,056**	**0,002**	**0,06**	**0,064**
Effective Dose (mSv/MBq)	***0,35***	***0,006***	***0,35***	***0,21***	***0,003***	***0,21***	***0,25***

Metabolism

The applicant did not submit studies on metabolism of lutetium (see non-clinical discussion).

Excretion

After intramuscular administration, rare earth elements ions have been reported to be excreted both by the kidney and by the liver via the gastrointestinal tract. The relative importance of either excretion route for any given element of the series is dependent upon its position in the series[10]. More than 50% of the administered dose of the lighter lanthanides is accumulated by the liver, and is thereafter rapidly excreted in the faeces. The heavier elements, including lutetium, are excreted primarily by the kidney; for thulium the percentages were 25% via the urine and 8% through the faeces, 16 days after intramuscular injection in rats.

2.3.4. Toxicology

The applicant did not submit non-clinical studies in toxicology but a review of the literature of the toxicity of the inorganic active ingredient in mice, rats and dogs after administration of lutetium nitrates, oxides and salts. No data on chronic toxicity was submitted, however, long term effects of skeletal uptake of 177Lu have been described in publications.

Single dose toxicity

Acute toxicity of rare earth nitrates and oxides was first described in a series of experiments conducted in 1963 in mice and rats[19] . This included lutetium nitrate which revealed LD_{50} values of 290 mg/kg in mice and 335 mg/kg in rats. Most of the mice that were acutely poisoned became depressed within an hour after injection. Death usually occurred within the first 24 hours and post-mortem examination of randomly selected animals showed generalised peritonitis with adhesions and accumulation of some ascetic fluid. Very few of the rats that received lethal doses died during the first 8 days and the majority succumbed during the period from 10 to 25 days after injection. Almost all the rats that died during this period had grossly distended abdomens, and oedema of the limbs was observed in many of the animals that received the higher doses. Gross pathologic examination of the animals revealed an inflammatory condition in the peritoneal cavity with massive adhesions and accumulation of haemorrhagic ascetic fluid. This study also demonstrated the intraperitoneal toxicity of the various rare earth elements to be of the same magnitude.

Acute oral toxicity of the various rare earth elements in rats requires even higher doses up to approximately 3 g/kg but lutetium salt was not included in this series of experiments. Likewise the acute intravenous toxicity of a series of rare earth nitrates in rats showed LD_{50} – values to lie in the range of 30 – 60 mg/kg. These studies did suggest that the intravenous toxicity of the ionic compounds of the rare earth elements would decrease with atomic weight resulting lutetium being the least toxic of the series.

Similar high doses were required to induce toxicological effects in the anaesthetised dog[20]. 10 mg/kg of lutetium trichloride, or any other rare earth metal chloride, administered intravenously at ten-minute intervals for a total of ten doses, resulted in varying effects on the blood pressure ranging from no effect in some dogs to a transient decrease variable in amplitude (5 - 20 mmHg) from animal to animal. Likewise a decrease in heart rate was observed although in some occasional animals there was an increase. Electrocardiograms showed no irregularities in cardiac rhythm or conduction. Effects on respiration were slight and variable. Chlorides appeared more toxic than citrates or edetates, with 15 of 45 dogs treated with chlorides not surviving the three-hour experimental period, but no marked gross differentiating changes were found on necropsy and histopathological examination of the tissues demonstrated no evidence of acute damage resulting from the experimental procedure. This study showed a decreasing toxicity with increasing atomic weight.

Repeat dose toxicity

Various amounts of 177Lu as citrate were injected intraperitoneally in mice, containing 25 µg/kg stable lutetium per kg bodyweight as carrier in one series and 2 mg stable Lu per kg in the second series[21] . The percent of injected activity as present in the skeleton decreased from 60% to 34% with the higher dose carrier while the percent in the liver increased from 1.5% to 6%. Autoradiography experiments of the lumbar vertebra demonstrated pronounced activity along the bone surfaces of the spongiosa. The pattern of hepatic disposition showed diffuse small grains as well as hot spots.

No specific chronic toxicity studies are presented with lutetium. The only study data provided relate to the investigations of long term skeletal uptake of 177Lutetium in mice. This study was performed to examine the incidence of osteosarcomas thought to be related to extended accumulation of lutetium to the bone tissue. Five experimental groups and one control group each with about 50 animals were given increasing doses of ^{177}Lu (185 – 740 MBq/kg). The table below represents the data obtained.

Table 6: Incidences of osteosarcomas and latency periods in dependence on injected activities into mice

Activity dose MBq/kg)	Skeletal dose Gy	% Animals with osteosarcomas	Mean latency period (days)	% survivors at Day 251
0	0	0	-	96
185	28	13	645	92
370	56	36	570	98
740	112	38	534	96

A further increase of the dose to 1480 MBq/kg led to severe dental lesions, resulting in substantial underweight and subsequent elimination from the experiments leading to non-conclusive results for this dose level.

With respect to the location of the osteosarcoma's, most of the tumours appeared in the long bones and vertebrae (each 37%) with lower percentages in the pelvis (19%) and ribs (4%).

Genotoxicity

The applicant did not submit data on the mutagenicity and carcinogenicity of lutetium trichloride. There is no data directly described for genotoxicity with lutetium trichloride. Evidence was presented in which levels of naturally occurring lutetium in freshwater plants and invertebrates (10 µg/kg lutetium in freshwater invertebrates) exceed the anticipated tissue concentrations resulting from the quantity of lutetium obtained in a single dose of Lumark (0.25 µg/kg). Therefore, the therapeutic doses of Lumark do not result in any genotoxicity.

Carcinogenicity

The applicant did not submit data on carcinogenicity with lutetium trichloride. Carcinogenicity in the form of osteosarcomas associated with 177Lu administration has been presented in the repeat toxicity section above. The risk is related to excessive distribution and accumulation to bone tissue.

Reproduction Toxicity

The applicant did not submit data on reproduction toxicity (see non-clinical discussion).

Toxicokinetic data

The applicant did not submit data on toxicokinetics (see non-clinical discussion).

Local Tolerance

The applicant did not submit data on local tolerance (see non-clinical discussion).

Other toxicity studies

Studies on impurities

Possible related-impurities are present as elemental impurities or as radionuclidic impurities. The major impurities are silicon and calcium, which are consequently below the 0.2% (w/w) in the lutetium target solution. All other elemental impurities are below the 0.02% threshold level which is lower than the 0.05% reporting threshold following the guideline Q3A on Impurities in new drug substances.

Radiotoxicity

Some experimental data concerning the radiotoxicity of 177Lu in mice were reported by[22] . Overall data indicate that even large quantities of 177Lu-radioactivity can be safely administered, Lumark is contraindicated in established or suspected pregnancy or when pregnancy has not been excluded.

2.3.5. Ecotoxicity / environmental risk assessment

Screening for persistence, bioaccumulation and toxicity

This screening is required for substances with a logKow > 4.5. However, since lutetium trichloride, the active ingredient of Lumark, is an inorganic salt its logKow will by all means be negative.

Therefore no screening for persistence, bioaccumulation and toxicity for Lumark will be necessary.

Predicted Environmental Calculation

The predicted environmental concentration for a given medicinal product needs to be calculated using the following formula:

$$PEC_{SURFACEWATER} = \frac{DOSEai * Fpen}{WASTEWinhab * DILUTION}$$

Where the various parameters stand for the following:

DOSEai	Maximum daily dose per inhabitant (mg/inh/day)
Fpen	Fraction of market penetration (default value = 0.01)
WASTEWinhab	Amount of wastewater per inhabitant per day (200 l)
Dilution factor	10

The maximum dose of Lumark i.e. lutetium trichloride will amount to 20 µg and such a dose will be given with a few weeks intervals. Using this value a PECsurfacewater is calculated to be 0.1 ng/l, falling below the action limit of 0.01 µg/l. A Phase II assessment is therefore not deemed necessary.

The Expert has stated that concentrations of lutetium in surface waters worldwide have previously been reviewed (Weltje, 2003) with figures varying from 0.25 pmol/l to 5.5 pmol/l. This would correspond to lutetium chloride concentrations equal to 70 – 1545 pg/l based on its molecular weight of 281. The predicted environmental concentration of lutetium resulting from the administration of Lumark is of a similar magnitude as the concentration already present in the environment.

Concerns for radiation waste management

Lumark is indicated for use in hospital patients only. This means that administration and the related patient care will take place within nuclear medicine departments that are equipped with the infrastructure to contain the presence of radioactive substances as well as to protect health care professionals and the environment against any radiation damage resulting from such presence.

Table 7: Summary of main study results

Substance (INN / Invented Name): Ravicti			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	None		Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		not B
	BCF		not B
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.0001	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate – none needed			

2.3.6. Discussion on non-clinical aspects

The applicant submitted an application under Art. 10a – well established use. The applicant submitted literature data on the pharmacology, pharmacokinetics and toxicity of lutetium, which is acceptable under the proposed legal basis. A number of pharmacology studies from the literature have been presented that demonstrate a limited pharmacological effect of lutetium trichloride. Studies include a number of ex vivo studies with isolated organs – rabbit ileum and rabbit heart, in vivo study in cats, and a number of in vitro studies.

The inorganic nature in general and the trivalent nature of the lutetium ion in particular governed the pharmacokinetic characteristics of lutetium trichloride. This nature predicts a low absorption after oral administration as well as the absence of metabolic pathways. There is only limited absorption data with lutetium. When lutetium was administered in feed to rats, 99% was recovered over 48 hours. This finding of negligible absorption via the gastro intestinal tract was confirmed in a second study with other similar lanthanides. The information on metabolism of lutetium was limited to literature that indicated that transport of inorganic salt ions were mainly taken up by the liver before biliary excretion.

Pharmacokinetics of Lutetium (^{177}Lu) was investigated in rats and mice. The distribution and mineral concentrations in the organs were investigated at low (9-10 mg/kg) and high (19-20 mg/kg) doses administered intravenously to rats. It appeared that more than 78% of the doses was distributed into liver, bone and spleen. For Lutetium (^{177}Lu) the different dose levels did not result in significantly different uptake with 65% appearing in the liver, 5.3% in the spleen and 13% in the bones at one day after administration.

With respect to the distribution pattern in blood it appeared that 2 h after administration 15% of the Lutetium as being present in blood, had entered the blood cells with the remaining 85% still being present in the serum.

A more detailed study of the biodistribution of Lutetium (^{177}Lu) chloride in mice confirms the relatively high uptake in the liver, kidneys and bone marrow The results indicated that lutetium (^{177}Lu) chloride is accumulated in the bone marrow and emphasizes the importance of all Lutetium (^{177}Lu) to be peptide-bound at injection, as well as the in-vivo stability of the radionuclide-chelate-complex during therapy.Distribution studies were performed in Yoshida sarcoma bearing rats in which ^{177}Lutetium citrate was seen to be retained predominantly to the blood, liver, spleen, tumour and kidney. No data was presented for bone tissue, however further work using Ehrlich's tumour bearing mice showed that lutetium was also retained to bone tissue. Lutetium retention in bone was found to be lower when it was added to a carrier (25%) than without a carrier (55%). In a distribution study in mice bearing small cell lung cancer, ^{177}Lutetium trichloride was shown to accumulate in the bone over 7 days, as well as have high distribution to the liver and spleen and kidney. The increasing incidence of osteosarcoma implies a high skeletal uptake. Distribution of lutetium was 65% in the liver, 5.3% in the spleen

and 13% in the bones 24 hours after administration, and in addition there is distribution to the blood – approximately 15% 2 hours after administration. The excretion of lutetium appears to be mainly via the kidney (25%), followed by faecal excretion (8%).

The multitude of animal biodistribution data available in the literature forms the basis of the applicant's justification for dosimetry.

There are no literature data submitted to describe pharmacokinetic drug interactions. This is acceptable Lumark is a precursor to be used for in vitro radiolabelling of carrier molecules and is not directly injected in patients.

At the concentration present in Lumark, lutetium trichloride appears to have no pharmacological action. Therefore, it is acceptable not to submit additional pharmacodynamic data.

With respect to the intrinsic toxicity of lutetium trichloride, as Lumark is intended for use as a single dose of 10-20 µg (approx. 0.25 µg/kg), the levels of intake are below the threshold stated in the 'Guideline on the limits of genotoxic impurities' (EMA/CHMP/SWP431994/2007 Rev. 3), in which the Threshold of Toxicological Concern (TTC) for an exposure of 3 months is a maximum allowable daily intake of 20 µg per day, i.e. a total intake of 1800 µg during this period.

No data on animal toxicity studies were submitted with Lumark. The toxicity of Lutetium (^{177}Lu) chloride has been studied in different mammals and using different administration routes. Intraperitoneal administration resulted in generalized peritonitis with adhesion and accumulation of some ascetic fluid. By intraperitoneal route, the LD50 is approximately 300 mg/kg in mice and rats. By intravenous route, the LD50 in rats and mice ranges between 30 and 60 mg/kg. Intravenously administrated doses resulted in varying effects on the blood pressure and a decreased heart rate. Electrocardiograms showed no irregularities in cardiac rhythm or conduction. Effects of the respiration were slight and variable. No gross differentiating changes were found of the tissues demonstrating no evidence of acute damage resulting from the experiment. The studies suggest that the intravenous toxicity of the ionic compounds of the rare earth elements would decrease with atomic weight resulting in Lutetium (^{177}Lu) being the least toxic of the series. Its main risk derives from the emission of energy β radiations.

No data on chronic toxicity studies were submitted with Lumark. The only study data provided relate to the investigations of long term skeletal uptake of ^{177}Lu in mice. This study was performed to examine the incidence of osteosarcomas thought to be related to extended accumulation of lutetium to the bone tissue. The data showed that the level of skeletal uptake increased with increasing dose of ^{177}Lu and latency period also seemed to decrease with increasing dose. To further combat this feature of lutetium toxicity, further investigations designed to chelate small molecules to radioactive lutetium have been presented. The evidence suggests that when combined with diethylene triaminepentetate (DTPA), the extent of skeletal uptake is greatly diminished, so much so that in rats un-chelated $^{177}LuCl_3$ demonstrated skeletal retention of 80%, but when 0.5 µg DTPA was added to the injection the body retention was reduced to 4%. Further retention work using rat femur demonstrated a similar reduction in skeletal uptake. It has been explained that the formation of the ^{177}Lu- DTPA complex may initiate rapid renal clearance of free ^{177}Lu3+, therefore reducing the potential for accumulation. Therefore, information on the risk of osteosarcoma and precautions to use DTPA prior to intravenous administration of ^{177}Lu-labeled conjugates are included in the RMP as a potential safety concern and have been addressed in the SmPC section 4.9 and 12. A statement is included in the SmPC (section 12) that the amount of free Lu-ions should be maintained as low as possible to avoid unnecessary accumulation of ^{177}Lu in the bone:

"Free $^{177}LuCl_3$ 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 ^{177}Lu-labeled conjugates in order to form a complex with free ^{177}Lu, if present, leading to a rapid renal clearance of ^{177}Lu. "

The risk of genotoxicity is considered low at therapeutic doses of Lumark and it is assumed that is does not result in any genotoxicity. Carcinogenicity in the form of osteosarcomas associated with ^{177}Lu administration was discussed – the risk is related to excessive distribution and accumulation to bone tissue has been identified as a potential safety concern in the RMP. Therefore, the lack of further genotoxicity and carcinogenicity data is acceptable.

The applicant has not submitted data from the literature for reproductive toxicity with lutetium. The lack of reproductive toxicity data was acceptable, given the known concerns over the exposure of the foetus to ionising radiation. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. Therefore, the use of Lumark during pregnancy is contraindicated, and patients are advised to not breastfeed should they be administered Lumark.

The applicant did not submit data in juvenile animals. This is acceptable as ^{177}Lu-labelled medicinal products should not be used in children and adolescents up to 18 years.

No data has been provided to support any conclusions on female or male fertility. This has been reflected in section 4.6 of the SmPC.

The applicant did not submit data on local tolerance. This was acceptable given the single use of Lumark.

The Environmental Risk Assessment (ERA) report stated that the active substance in Lumark, lutetium trichloride, would provide a negative value for Logkow and so an assessment for persistence, bioaccumulation and toxicity (PBT) was unnecessary. The CHMP agrees with this assessment and that no further examination of PBT was necessary. The PECsurfacewater based upon a maximum daily dose of 20 µg, gives a value that is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. With respect to the radioactive environmental impact of Lumark, it is important to highlight that ^{177}Lutetium is a radioisotope with a relatively short half-life (6.7 days) which contribute significantly to a relative short-lasting environmental impact of the product. Therefore lutetium trichloride is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

There is no general concern over the toxicity of the lutetium in this preparation, as the amount of ^{177}lutetium is below the threshold of the maximum allowable daily intake of 20 µg per day and therefore is unlikely to be toxic.

The main concern related to the development of osteosarcoma and its latency observed in mice studies. 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 and considering that single and repeated dose toxicity studies will be provided for the carrier medicinal products using the ^{177} Lutetium radiolabel.

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

2.4. Clinical aspects

2.4.1. 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. Lumark is not intended for direct administration to patients. The solution is intended for the labelling of peptides or proteins which subsequently are administered to patients. A brief literature overview is presented on the various applications of different peptides and monoclonals, labelled with ^{177}Lu.

GCP

Not applicable as no clinical studies have been submitted with Lumark.

- Tabular overview of clinical studies

Table 8: Human studies with 177Lu -labelled radiopharmaceuticals

Study reference and type	Radiopharmaceutical	Aim of the study	Target disease	Number of patients	Efficacy results	Tolerance results
Neuro-endocrine tumors						
Teunissen et al (2011) Endocr Rel Cancer Review 2003 - 2011	^{177}Lu -dotatate	Definition of the therapeutic value of ^{177}Lu -dotatate for neuroendocrine tumors	Neuroendocrine tumors	310 for clinical efficacy 504 for adverse effects	2% complete remission 28% partial remission	Mild and transient haematological toxicity with grade 3 or 4 in 10% Nausea 25% Vomiting 10% Abdominal pain 10%
Dobson & Vinjamuri (2013)	^{177}Lu -dotatate	Case report	Orbital metastase of neuroendocrine tumor	1	Complete remission	Not specified
Delpassand (2014)	^{177}Lu -dotatate	Phase II study	Neuroendocrine tumors	32	28% partial response 3% minimal response 41% stable disease 28% progressive disease	Hematological toxicity Nausea and vomiting during infusion

Claringbold et al (2013)	^{177}Lu –dotatate + capecitabine and temozolomide	Phase I – II study	Safety and efficacy	35	15% complete response 38% partial response 38% stable disease	Transient nausea 18% Thrombocytopenia 24% Leukopenia 6%
Prostate cancer						
David et al (2006) Clinic Genour Cancer Review 2001 - 2006	^{177}Lu –Antibody J591	Definition of the therapeutic value of ^{177}Lu –Antibody J591 for prostate cancer	Prostate cancer	35	60 % response: 11% > 50% PSA ↓ 44% PSA stabilization	
Simone and Hahn, 2013 Clin Cancer Res Review up tp 2013	^{177}Lu –Antibody J591	Therapeutic value Relative value compared to other modalities	Prostate cancer	47	11% > 50% PSA decline 36% > 30% PSA decline ^{177}Lu better than ^{90}Y	
Bone metastases						
Liu et al (2011) Nucl Med Comm Imaging study	^{177}Lu -EMPD	Whole body imaging of bone metastases in combination with pain palliation	Bone metastases	11	Femur-muscle ratio = 13 Lesion-bone ratio = 8	Not studied
Yuan et al (2013)	^{177}Lu -EMPD	Efficacy and toxicity	Bone metastases	16	Complete response in 55/80% in low/high dose	Hemaotological toxicity
Miscelleanous indications						
Forrer et al (2012) Q J Nucl Med Mol Imag Phase 1 Study	^{177}Lu –dotatate-rituximab	Clinical response and maximum dose in indolent lymphomas	Indolent B-cell lymphoma	31	20% complete response 28% stable disease	Haematological toxicity Fatigue and nausea
Stillebroer et al (2013)	^{177}Lu -girentuximab	Maximum tolerated dose	Renal cell carcinoma	23	MTD = 2405 MBq/m^2	Hematological toxicity

European Urology Phase 1 Study	and potential therapeutic efficacy	74% stable disease

2.4.2. Pharmacokinetics

No clinical pharmacology studies were submitted with this application (see clinical pharmacology discussion).

2.4.3. Pharmacodynamics

No clinical pharmacology studies were submitted with this application (see clinical pharmacology discussion).

2.4.4. Discussion on clinical pharmacology

The lack of clinical pharmacology studies is considered acceptable. The pharmacokinetics of a radiopharmaceutical would be dependent on the carrier molecule labelled with Lumark. 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.

The applicant provided a discussion on the event of a failed labelling or a complete dissociation. The resulting amount of free 177Lutetium circulating in the body will be extremely low and equivalent to approximately 0.25 µg/kg. No pharmacological or toxicological effects will result from such a low quantity as has been demonstrated in animal experiments. The applicant provided evidence that when attached to a ligand that the conjugate is stable over many hours.

The applicant has provided a discussion to justify the low likelihood of the presence of free 177lutetium in the body, following administration of a 177lutetium labelled radiopharmaceutical. This is based on the administration of an extremely low quantity (approximately 0.25µg/kg) of an inorganic salt such as lutetium trichloride, which is considered to have negligible effect on PK and PD parameters.

No interaction studies of Lutetium (^{177}Lu) with other medicinal products have been performed. The possible use of chelating therapies could interfere with the use of Lutetium(^{177}Lu)-labeled medicinal products.

For information concerning interactions associated with the use of Lutetium (^{177}Lu)-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the radiolabelled medicinal product.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of Lumark 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 Lumark 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 Lumark has been adequately addressed.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

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

2.5.1. Clinical Utility

The applicant submitted clinical data from the literature to support the clinical utility of Lumark or 177Lu trichloride radionuclide in treatment of neuroendocrine tumours, breast cancer, bone metastases, glioblastoma and in the management of advanced prostate cancer.

^{177}Lu as a radiopharmaceutical for neuroendocrine tumors

The applicant states that the most widely investigated application and also the oldest use of ^{177}Lu is in neuroendocrine tumour therapy. In a review article of nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours by[23] , it states that preclinical experiments with ^{177}Lu coupled to dotatate were started in 2002 and demonstrated the highest tumour uptake together with excellent tumour-to-kidney ratios compared with ^{111}In – labelled octreotide or ^{177}Y – labelled dotatate[24] .

In the same review article, it further states that the first reports on the results of the clinical use of ^{177}Lu – Dotatate published by Kwekkeboom *et al* (2003) [25] were promising with 30% of the patients with gastroenteropancreatic neuroendocrine tumours (GEP-NET) showing partial or complete remission, 40 % of the patients showing stable disease and only 12% of the patients showing minimal response. A more recent analysis by Kwekkeboom et al. (2008)[26] confirmed these results in a group of 310 GEP-NET patients. These patients were treated up to a total administered activity of 28 – 30GBq, usually in four treatment cycles, with treatment intervals of 6 – 10 weeks. Complete and partial tumour remissions occurred in 2% and 28% of patients respectively. Median time-to-progression in the treated GEP-NET patients who did not have progressive disease was 40 months from start of the first cycle. Median overall survival was 46 months and median disease-related survival was > 48 months. Some patients benefit from an additional salvage therapy i.e. two additional cycles of 7.4 GBq; in particular patients with metastasised bronchial GEP-NET's or who had clear tumour responses or remissions. Published reports from other clinical centres are in line with the results obtained in this group of 310 patients.

As compared with (historical data of) conventional therapy for this disease (somatostatin analogues like octreotide), the consistent difference is at least suggestive for a better survival after ^{177}Lu-dotatate therapy.

A publication by Amir Sabet *et al* (2014)[27] showed that PRRT with 177Lu-octreotate in the re-treatment setting is safe and effective in patients with metastatic GEP-NET. They retrospectively analysed a consecutive cohort of 33 patients with metastatic GEP-NET who underwent salvage peptide receptor radionuclide therapy (PRRT). All patients had progressive NET prior to salvage treatment and had shown an initial response to PRRT. The mean cumulative activity was 44.3 GBq (30.0–83.7 GBq). Response was assessed using CT and/or MRI according to modified SWOG criteria. Toxicity was evaluated using laboratory data, including complete blood counts and renal function tests using CTCAE 3.0. Radiographic responses showed complete response in 1 patient (3.0 %), partial response in 6 patients (18.2 %), minor response in 1 patient (3.0 %), stable disease in 14 patients (42.4

%), and progressive disease in 11 patients (33.3 %). Median progression-free survival from the start of salvage therapy was 13 months (95 % CI 9–18) and patients with a history of a durable PFS after initial PRRT tended to have long-lasting PFS after salvage treatment (p =0.04). None of the patients developed severe nephrotoxicity (grade 3/4) or a myelodysplastic syndrome during follow-up. Relevant albeit reversible haematotoxicity (grade 3/4) occurred in 7 patients (21.2 %). The cumulative administered activity was not associated with an increased incidence of haematotoxicity.

A publication from Romer *et al.* (2014)[28] compared the benefits and harms of the β-emitting radionuclides 90Y or 177Lu. Patients with advanced neuroendocrine tumours underwent repeated cycles of (90Y-DOTA)- TOC or (177Lu-DOTA)-TOC in a comparative cohort study until progression of disease or permanent adverse events. Overall, 910 patients underwent 1,804 cycles of (90Y-DOTA)-TOC and 141 patients underwent 259 cycles of (177Lu-DOTA)-TOC. The median survival after (177Lu-DOTA)-TOC and after (90Y-DOTA)-TOC was comparable (45.5 months versus 35.9 months, hazard ratio 0.91, 95 % confidence interval 0.63–1.30, p =0.49). Subgroup analyses revealed a significantly longer survival for (177Lu- DOTA)-TOC over (90Y-DOTA)-TOC in patients with low tumour uptake, solitary lesions and extra-hepatic lesions. The rate of severe transient haematologic toxicities was lower after (177Lu-DOTA)-TOC treatment (1.4 vs 10.1 %, p =0.001), while the rate of severe permanent renal toxicities was similar in both treatment groups (9.2 vs 7.8 %, p =0.32). This study showed no difference in median overall survival after (177Lu-DOTA)-TOC and (90Y-DOTA)-TOC. Furthermore, (177Lu-DOTA)-TOC was less haematotoxic than (90Y-DOTA)-TOC.

A publication from E. Seregni *et al*. (2014)[29] evaluated in a phase II study the feasibility of combined PPRT with a high-energy beta emitter 90Y and a medium energy beta/gamma emitter 177Lu. Patients with metastatic NET refractory to conventional therapy received treatment with tandem (90Y-DOTA)-TATE and (177Lu-DOTA)-TATE A group of 26 patients with metastatic NET were treated with four therapeutic cycles of alternating (177Lu-DOTA)-TATE (5.55 GBq) and (90Y-DOTA)-TATE (2.6 GBq). A dosimetric evaluation was carried out after administration of (177Lu-DOTA)-TATE to calculate the absorbed doses in healthy organs. Administration of tandem (90Y-DOTA)-TATE and (177Lu-DOTA)-TATE induced objective responses in 42.3 % of patients with metastatic NET with a median progression free survival longer than 24 months. Of patients with pretreatment carcinoid syndrome, 90 % showed a symptomatic response or a reduction in tumour-associated pain. The cumulative biologically effective doses (BED) were below the toxicity limit in the majority of patients, in the absence of renal function impairment.

^{177}Lu as a radiopharmaceutical for prostate cancer

Yao *et al.* (2002)[30], described the potential of using monoclonal antibodies to prostate-specific antigens, in particular prostate-specific membrane antigen (PSMA), as therapeutic tool in the management of advanced prostate cancer. One of these antibodies, J591 (IgG1) can be deimmunised eliminating the human anti-mouse antibody (HAMA) response while maintaining the binding specificity and affinity for PSMA. Then, using as a chelator for both this antibody and 177Lutetium, the resulting complex can be used as an imaging agent for radioimmunoscintigraphy to diagnose prostate cancer. They report that this complex has shown excellent targeting of prostate cancer not only in soft tissue but in bone as well, without patients developing human anti-humanised antibodies.

The use of radiolabeled J591 antibodies in patients with prostate cancer was reviewed by David *et al.* (2006)[31] and both ^{90}Yt as well as ^{177}Lu has been used as radiolabel for this purpose in Phase 1 trials. ^{177}Lu -labeled J591 antibodies were evaluated in 35 patients with androgen-independent prostate cancer with dose levels varying from 10mCi/m^2 - 75 mCi/m^2 and retreatment occurring at 6 – 12 weeks intervals up to a maximum of 4 treatments. Targeting of all known sites of prostate cancer metastases in soft tissue and bone was seen in all

30 patients. With regard to antitumor activity, none of the 7 patients with measurable disease had an objective tumor response but with respect to PSA criteria, 21 patients demonstrated evidence of some response, with 4 patients showing a > 50% PSA decrease lasting between 3 months and 8 months before returning to baseline. Sixteen patients have PSA stabilisations for a median of 60 days, defined as a PSA increase of < 25% from baseline.

No human anti-humanised antibodies developed in these patients and the pattern of neutrophil decrease was not consistent. Non-haematological toxicity appeared not dose limiting but some dose limiting myelosuppression occurred with repeat dosing at 45-60 mCi/m^2.

^{177}Lu as a radiopharmaceutical for breast cancer

The application of 177Lu in this therapeutic area is based on early work in the preclinical phase. The applicant has presented two publications in which it is used in this setting:

Salouti *et al.* 2011[32]: PR81 is a monoclonal antibody which binds with high affinity to MUC1 antigen that is over expressed in 80% of breast cancers. In this study, a method for indirect labelling of PR81 with ^{177}Lu was developed. Biodistribution and scintigraphy studies in BALB/c mice with breast tumour of ^{177}Lu coupled to the PR81 monoclonal antibody resulted in accumulation of the complex at the site of tumours with high sensitivity and specificity. The authors concluded that PR81 coupled with ^{177}Lu may be considered as a potential radiopharmaceutical for therapy of human breast cancer, which needs further investigations.

D'Huyvetter *et al.* 2012[33]: In this study, a different approach has been followed while targeting the HER2 antigen which is overexpressed in 20-30% of breast cancers often associated with higher recurrence rates. Such targeting can be obtained using nanobodies, the smallest natural antigen-binding fragments occurring from heavy-chain-only Camelidae antibodies, labelled with ^{177}Lu with the use of bifunctional chelators. This approach showed high specific tumour uptake combined with the lowest background while no specific binding was observed in a HER2-negative model.

The applicant concludes that in breast cancer, these therapies need extensive additional clinical investigation to validate these early results and to demonstrate comparative results in patients.

^{177}Lu as a radiopharmaceutical for bone metastases

^{177}Lutetium-EDTMP (methylene phosphonic acid) is a beta-emitting, bone-seeking therapeutic radiopharmaceutical, being assessed as an agent for palliation of bone pain for disseminated skeletal metastases in patients with breast and prostate cancer. It can emit suitable gamma-photons for scintigraphy. Liu *et al.* 2012[34], sought to characterise the optimal condition for ^{177}Lutetium-EDTMP for whole-body gamma camera imaging in patients. It was found to have optimal characteristics for imaging bone metabolism in humans using a gamma camera. Optimal results were obtained 24 hours after administration while using a medium-energy collimator.

^{177}Lu as a radiopharmaceutical for brain tumours

Bulte *et al.* 2011[35]: This therapeutic application of ^{177}Lu is still in its early developmental phase and includes the incorporation of ^{177}Lu in a C80 fullerene (a hollow sphere molecule composed entirely of carbon atoms). These fullerenes can be infused intratumourally in glioblastoma (a highly invasive brain tumour with poor prognosis)

and phase I, II and III trials including fullerenes loaded with cytotoxins or iodine-131-labelled monoclonal antibodies already have been performed but with only small gains in overall survival. It is postulated that the path length of ^{177}Lu (0.04 – 1.8 mm) is particularly useful for this therapy as the extracellular metallofullerenes present in the interstitial fluid are still effective for eradicating tumour cells from a distance.

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant did not submit analyses performed across trials.

2.5.2. Discussion on clinical efficacy

177Lu is intended to be used as a radiolabel for diagnostic and therapeutic purposes. There is strong evidence which support the use of 177Lu in gastroenteropancreatic neuroendocrine tumours (GEP-NET) and some evidence in prostate cancer. PRRT with ^{177}Lu radiolabelled somatostatin analogues has been widely used in numerous publications.

The evidence currently available to demonstrate clinical utility of ^{177}Lu in bone imaging, breast cancer and brain tumours is still experimental.

For the purpose of this application, it is sufficient that clinical utility in neuroendocrine tumours is well-established. As expected with this radiopharmaceutical precursor, no indication is claimed with this application. It is intended for radiolabelling of suitable carrier molecules (peptides, antibodies) which have been specifically developed and authorised for radiolabelling with this radionuclide.

2.5.3. Conclusions on the clinical efficacy

It is the view of the CHMP that clinical utility of Lumark attached to the relevant molecular carrier has been demonstrated for the treatment of neuroendocrine tumours. According to Directive 2001/83/EC, as amended, Annex I Part III, this is considered sufficient for the purposes of applications for radiopharmaceuticals for radiolabelling. Further efficacy and safety data in particular indications will be assessed during the marketing authorisation application for carrier molecules proposing to use Lumark as a radiolabel.

2.6. Clinical safety

The applicant did not submit safety data in humans with Lumark since Lumark is not intended to be administered directly to patients.

The safety of Lumark has been considered from two perspectives: safety relating to lutetium itself and safety relating to radioactivity.

Patient exposure

Lumark is a precursor for radiopharmaceuticals, not intended for direct administration to patients. In addition the quantity of the inorganic salt administered, lutetium trichloride, is too low to result in any pharmacological or toxicological effect in the human body.

Overall Extent of Exposure

The applicant has estimated total exposure to 177Lu based on their supply to different medical centers. The total extent of the exposure to Lumark is estimated at 2500 patients based on a shipped total of approx. 10,000 patient doses and a usual treatment scheme of 4 doses per patient. 504 of these patients have been included in the recent review of the side effects of ^{177}Lu-dotatate in patients with neuroendocrine tumors[23] . This number does not include patients exposed to ^{177}Lu-dotatate which includes ^{177}Lu manufactured by other manufacturers in the USA or Europe.

Dosimetry and biodistribution

To calculate the dosimetry, the applicant presented the following approach:

1. Assessment of existing published literature to available on biodistribution of free Lu3+ or LuCl3.

2. Estimation of biodistribution of free Lu3+ in mice/rats.

3. Calculation of absorbed dose per unit activity administered, based on biodistribution parameters.

4. Estimation of total effective dose.

The assessment of existing published literature on biodistribution of free Lu3+ or LuCl3, the estimation of biodistribution of free Lu3+ in mice/rats and the calculation of absorbed dose per unit activity administered, based on biodistribution parameters have been presented in the non-clinical section.

Calculation of absorbed dose per unit activity administered, based on biodistribution parameters

This parameter was then transposed to human organs, by assuming that the activity uptake in a human organ is the same as in a mouse or rat, corrected for the relative mass of that organ (related to total body weight):

$$\tilde{A}_{human\ organ} = \tilde{A}_{animal\ organ} \cdot \frac{Organ\ mass_{human} / Body\ mass_{human}}{Organ\ mass_{animal} / Body\ mass_{animal}}$$

Subsequently, the mean value of accumulated activity Ã in the human organs, was used as input for the software OlindaEXM (Vanderbilt University, Nashville, USA), which calculates dose per organ and total effective dose (according to the weighting factors of ICRP-60), based on biodistribution and physical parameters of a radionuclide. The OlindaEXM software also includes the S-factors mentioned in section 2, for the most common radionuclides.

The calculations were executed for both ^{177}Lu (half-life 6,647 d) and 177mLu (half-life 160.1 d), with ^{177m}Lu activity content set at 0.05% (specified limit for Lumark).

From the four literature sources cited, the article from Lungu et al. (2007)[16] has the most data points (13 organs, each with 7 time points). The curve-fitting for these data can be considered more accurate than for the other data. Therefore, these data were also used to execute the dosimetry calculations with OlindaEXM separately (only for ^{177}Lu).

For comparison, the dosimetry calculation was also executed (for ^{177}Lu and ^{177m}Lu) using the ICRP-30 lutetium biodistribution data originally submitted with the Lumark dossier:

• lutetium directly excreted: 37.5% in 1:1 faecal to urinary pathway ratio

• lutetium distributed: 60% to bone, 2% to the liver, 0.5% to the kidney

• biological half-live in the kidney: 10 days

• biological half-live in the bone and liver: 3500 days

Estimation of total effective dose

Based on this animal distribution data, the following dosimetry estimates was made, taking into account an energy per transformation of 0.147 MeV/transformation and when applying the following assumptions based on ICRP data (ICRP, 1981):

• 37.5% of the lutetium is directly excreted

• the remainder of the lutetium is distributed to the bone, liver and kidneys (60%, 2% and 0.5% respectively)

• lutetium is excreted from the kidneys with a biological half-life of 10 days and from the bone and liver with a biological half-life of 3500 days

it is then used to calculate the effective dose per tissue using the tissue weighting factors from ICRP-60 as presented in the table below.

Table 9: Absorbed dose per unit activity administered for various tissues[16]

Tissue	Absorbed dose per unit activity (mGy. MBq^{-1})
Bone surface	0.15
Bone marrow	0.084
Liver	0.011
Kidneys	0.0094
Total effective dose per whole body in mGy per MBq ^{177}Lu administered.	0.25

The radiation dose received by the various organs following administration of a Lutetium (^{177}Lu)-labelled medicinal product will be dependent on the specific molecule being radiolabelled.

Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation will be available in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

The dosimetry table below is presented in order to evaluate the contribution of non-conjugated Lutetium(^{177}Lu) to the radiation dose following the administration of Lutetium (^{177}Lu)-labelled medicinal product or resulting from an accidental intravenous injection of Lumark.

The dosimetry estimates are based on biodistribution data provided by ICRP-30, showing bone, liver and kidneys as the significant target organs for the biodistribution of lutetium.

Table 10: Absorbed dose per unit activity administered for various tissues

	ICRP-30 data
Target Organ	**Dose / Injected Activity (mGy/MBq)**
Adrenals	0.018
Brain	0.017
Breasts	0.005
Gallbladder Wall	0.012
LLI Wall	0.868
Small Intestine	0.069
Stomach Wall	0.038
ULI Wall	0.327
Heart Wall	0.009
Kidneys	0.210
Liver	0.220
Lungs	0.010
Muscle	0.012
Ovaries	0.015
Pancreas	0.012
Red Marrow	1.090
Osteogenic Cells	7.530
Skin	0.007
Spleen	0.008
Testes	0.006
Thymus	0.007
Thyroid	0.011
Urinary Bladder Wall	0.240
Uterus	0.011
Total Body	**0.185**
Effective Dose (mSv/MBq)	***0.35***

Therefore, the total effective dose for 177Lu was:

- 0.35 mSv/MBq when considered biodistribution data from ICRP-30
- 0.21 mSv/MBq when using the biodistribution data

• 0.25 mSv/MBq when using only the data from Lungu et al (2007)[16].

The total effective dose for ^{177m}Lu, calculated using this method, amounts to 1.6% of the total effective dose from ^{177}Lu, based on a 0.05% radionuclidic impurity level.

Adverse events

The adverse events discussed are related to the use of peptides or antibodies in general radiolabelled with ^{177}Lu as Lumark is not intended to be administered on its own to patients.

Following therapy with radiolabelled peptides or antibodies, kidney retention and renal function loss may become apparent many years after the radiation therapy. The uptake mechanism of radioactivity from radiolabelled peptides in the kidney is mainly tubular reabsorption of the peptide, not receptor binding, causing predominant changes in the arteriolar-glomerular area, rather than the tubular epithelium, and leading to glomerular sclerosis. This may result in renal function loss and even end-stage renal disease.

Prevention of radiation nephropathy from radiolabelled peptides or antibodies is usually accomplished by co-infusion of positively charged amino acids, in particular lysine and arginine. Typically, a renal dose reduction of 25% can be reached with these mixed amino acids.

The prevention of bladder radiotoxicity can be managed through patient hydration or patient catheterisation. The urinary bladder is a target organ mainly for excretion mechanism and can be considered a late radiation toxicity due to the slow cell division rate.

In the review article presented by Teunissen *et al.* (2011)[23], adverse events after PRRT with ^{177}Lu-dotatate were analysed in a total of 504 patients. With respect to the most prevalent clinical use of Lumark, the most frequently occurring side effects noted after administration of ^{177}Lu-dotatate included nausea (25% of patients), vomiting (10%) and abdominal pain (10%) but these effects may also (partly) be caused by the co-infusion of the renal protective amino acids. This therapy also resulted in acute haematological toxicity in 10% of the patients. Temporary mild hair loss was noticed in 62% of the patients. Serious late toxicity includes myelodysplastic syndrome in four out of the 504 patients and renal insufficiency in 2 patients and 3 patients with serious liver toxicity from the same cohort.

The safety of Lumark can be considered as those relating to the radioactivity of the product and those related to free lutetium.

Adverse events after PRRT with ^{177}Lu-dotatate were analysed in a total of 504 patients. With respect to the most prevalent clinical use of Lumark, the most frequently occurring side effects noted after administration of ^{177}Lu-dotatate included nausea (25% of patients), vomiting (10%) and abdominal pain (10%) but these effects may also (partly) be caused by the co-infusion of the renal protective amino acids. This therapy also resulted in acute haematological toxicity in 10% of the patients. Temporary mild hair loss was noticed in 62% of the patients. Serious late toxicity includes myelodysplastic syndrome in four out of the 504 patients and renal insufficiency in 2 patients and 3 patients with serious liver toxicity from the same cohort.

Serious adverse event / deaths / other significant events

No death has resulted from the administration of any ligand radiolabeled with ^{177}Lu trichloride up to now.

Overdose

The applicant has stated that as Lumark will be used within hospitals only and administered by healthcare professionals only, this excludes any intentional overdose. Any unintentional overdose would be related to radiological safety aspects rather than medicinal safety aspects. However, no incidents describing such unintentional overdose have been described in the literature up to now.

Laboratory findings

The applicant did not submit laboratory data (see safety discussion).

Safety in special populations

As this is a radioactive medicinal product, it is contraindicated for use during pregnancy.

Safety related to drug-drug interactions and other interactions

No data on safety related to drug-drug interaction was submitted (see clinical safety discussion).

Discontinuation due to adverse events

No data on discontinuation due to adverse events was submitted (see clinical safety discussion).

Post marketing experience

No data on post-marketing experience was submitted (see clinical safety discussion).

2.6.1. Discussion on clinical safety

Taking into consideration the doses of lutetium administered, it is unlikely than any toxicity would result from lutetium excess with the use of Lumark. The quantity of ^{177}Lu chloride to be administered to humans, 10 - 20 µg equivalent to 0.15 – 0.25 µg/kg, is extremely low and lacks any pharmacological or toxicological significance. According to the CPMP/ICH/286/95 Guideline on safety studies for clinical trials and marketing authorizations, under these circumstances no additional pharmacological, general toxicity or genotoxicity studies are necessary.

It is accepted that as a radiolabelling agent that Lumark will not be given on its own to subjects and that precise safety data on a Lumark/complex medicine will have to be supplied with such an application. To this end the use of the animal data from the studies presented is considered useful and then the modelling to extrapolate from the rodent models to humans allows for a comparison of the estimated dosimetry to the previous ICRP-30 data presented. Across the studies the values and trends are similar, with kidneys and liver showing rapid clearance and accumulation in the bone over time. Values in other organs and tissues are relatively low. Without exposing human subjects to free Lutetium, this approach is acceptable. The applicant proposes to still use the dose estimates based on the ICRP-30 data. This is acceptable and is considered the most conservative approach.

The main safety issues to be considered in relation to ^{177}Lu radioactivity are due to the 6-day half-life of ^{177}Lu and the emission of low energy gamma rays. The emission of gamma rays (113 keV, and 208 keV) is of concern with regards to exposure to personnel preparing and administering the radiopharmaceutical as well as to individuals who come into contact with the patient who has received the ^{177}Lu-labelled radiopharmaceutical. There is the potential risk identified of the development of osteosarcoma as ^{177}Lu is taken up and accumulated in the bones. It is recommended to add a binding agent such as DTPA prior to intravenous administration of ^{177}Lu-labeled conjugates in order to form a complex with free ^{177}Lu, leading to rapid renal clearance. This has been adequately addressed in the SmPC section 4.9. It is expected that in centres where this radiolabel will be used, the necessary special precautions for disposal and other handling and preparation of radiopharmaceuticals would be taken into consideration to minimise radiation exposure and further guidance is provided in the SmPC in sections 6.6 and 12, respectively. It is not possible to describe likelihood and effect of ^{177}Lu accumulation in bone or liver specifically, as this depends on the labelled compound. The amount of free Lu-ions should be maintained as low as possible to avoid unnecessary accumulation of ^{177}Lu in the bone. This statement is included in the SmPC.

There is a contraindication in hypersensitivity to the active substance or to any of the excipients listed in section 6.1 and Pregnancy (see section 4.6). For information on contraindications to particular Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Lumark, refer to the Summary of Product Characteristics/package leaflet of each particular medicinal product to be radiolabelled.

Effects on ability to drive or use machines following treatment by Lutetium (^{177}Lu)-labelled medicinal products is specified in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

Adverse reactions following the intravenous administration of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Lumark, will be dependent on the specific medicinal product being used. Such information is supplied in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely clinical benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself.

When the precursor is bound to a carrier molecule the content of radioactive free Lutetium (^{177}Lu) is supposed to be less than the stated amounts depending on the carrier used. Relevant data is included in the Summary of Product Characteristics of the labeled medicinal products.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect. Lumark is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates.

Radiation protection

Administration of a high activity (7.400 MBq) of the Lutetium(^{177}Lu)-labelled medicinal product results in an average radiation dose rate at 1 m distance from the patient of 4-11 µSv/h after 24 hours. This is below the threshold considered acceptable for discharge from the clinic (20 µSv/h). For a person in the vicinity of the patient, assuming continuous exposure at 2 m and infinite biological half-life (no disposal by the patient after discharge from the hospital), this dose rate will result in an overall dose of approximately 0.6 mSv, which is approximately one half of the dose limit set for general public (1 mSv/year).

Precautions with respect to relatives, carers and hospital staff are provided in section 6.6.

Women of childbearing potential

When an administration of radioactive medicinal products to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient. Before the use of ^{177}Lu -labelled medicinal products, pregnancy should be excluded using an adequate/validated test.

Pregnancy

The use of Lutetium (^{177}Lu)-labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3).

Breast-feeding

Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted and the expressed feeds discarded. .

Fertility

According to literature reports and taking a conservative approach (maximum patient dose of 10 GBq, average labeling yield and no additional measures), it may be considered that ^{177}Lu-labelled medicinal products do not lead to reproductive toxicity including spermatogenetic damage in male testes or genetic damage in male testes or female ovaries.

Further information concerning the use of ^{177}Lu-labelled medicinal products is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

Incompatibilities

Radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates, with Lutetium (^{177}Lu) chloride is very sensitive to the presence of trace metal impurities.

It is important that all glassware, syringe needles etc., used for the preparation of the radiolabelled medicinal product are thoroughly cleaned to ensure freedom from such trace metal impurities. Only syringe needles (for example non-metallic) with proven resistance to dilute acid should be used to minimize trace metal impurity levels.

In the absence of compatibility studies, this medicinal product must not be mixed with medicinal products other than the medicinal products to be radiolabelled.

2.6.2. Conclusions on the clinical safety

The safety of Lumark can be considered as those relating to the radioactivity of the product and those related to free lutetium. As Lumark is intended to be administered labelled to a carrier molecule, the safety and extent of exposure will be dependent on the carrier molecule. For the purpose of an application for a radiopharmaceutical for radiolabelling, the safety of Lumark has been adequately addressed.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The PRAC considered that the risk management plan version 3.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRACand CHMP.

The CHMP endorsed the Risk Management Plan version 4 with the following content:

Safety concerns

The Applicant identified the following safety concerns:

Table 11: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Radiotoxicity including occupational exposure and inadvertent exposure • Developmental Toxicity including reproductive toxicity
Important potential risks	• Medication Errors associated with preparation and

Summary of safety concerns	
	procedures • Osteosarcoma
Missing information	None

The PRAC agreed.

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 12: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Radiotoxicity including occupational exposure and inadvertent exposure	(Proposed) text in SmPC: **4.4 Special warnings and precautions for use** General warnings Radioactive medicinal products should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official authorities. Radioactive medicinal products should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. **6.6 Special precautions for disposal and other handling** General warning Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. For instruction on extemporary preparation of the medicinal product, see section 12. If at any time in the preparation of this product the integrity of this container is compromised it should not be used. Administration procedures should be carried out in a way to minimise risk of contamination of the	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	medicinal product and irradiation of the operators. Adequate shielding is mandatory. The surface dose rates and the accumulated dose depend on many factors. Measurements on the location and during work are critical and should be practiced for more precise and instructive determination of overall radiation dose to the staff. Healthcare personnel are advised to limit the time of close contact with patients injected with ^{177}Lu-radiopharmaceuticals. The use of television monitor systems to monitor the patients is recommended. Given the long half-life of ^{177}Lu it is specially recommended to avoid internal contamination. For this reason it is mandatory to use protective high quality (latex/nitrile) gloves in any direct contact with the radiopharmaceutical (vial/syringe) and with the patient. For minimising radiation exposure with repeated exposure there is no recommendation except the strict observance of the above ones. The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Any unused product or waste material should be disposed of in accordance with local requirements. **12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** Before use, packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber. Lutetium (^{177}Lu) is a bèta/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. The vial should never be opened and must be kept inside its lead shielding. The product should be aseptically withdrawn through the stopper using sterilized single use needle and syringe after disinfection of the stopper. Appropriate aseptic precautions should be taken, in order to maintain the sterility of LUMARK and to maintain sterility throughout the labelling procedures.	
Developmental Toxicity including reproductive toxicity	(Proposed) text in SmPC: **4.3 Contraindications**	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	- Pregnancy (see section 4.6). **4.6 Fertility, pregnancy and lactation** <u>Women of childbearing potential</u> When an administration of radioactive medicinal products to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient. Before the use of ^{177}Lu –labelled medicinal products, pregnancy should be excluded using an adequate /validated test. <u>Pregnancy</u> The use of ^{177}Lu -labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3). <u>Breast-feeding</u> Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted and the expressed feeds discarded. <u>Fertility</u> According to literature reports and taking a conservative approach (maximum patient dose of 10 GBq, average labeling yield and no additional measures), it may be considered that ^{177}Lu-labelled medicinal products do not lead to reproductive toxicity including spermatogenetic damage in male testes or genetic damage in male testes or female ovaries. Further information concerning the use of ^{177}Lu-labelled medicinal products is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.	
Medication Errors associated with preparation and procedures	(Proposed) text in SmPC: **4.1 Therapeutic inciations** Lumark is a radiopharmaceutical precursor. It is not intended for direct use in patients. This medicinal product must be used only for the radiolabelling of	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	carrier molecules, which have been specifically developed for radiolabelling with this radionuclide. **4.2 Posology and method of administration** Lumark is only to be used by specialists experienced with *in vitro* radiolabelling. … Method of administration Lumark is intended for *in vitro* radiolabelling of medicinal products, which are subsequently administered by the approved route. Lumark should not be administered directly to the patient. For instructions on extemporary preparation of the medicinal product before administration, see section 12. **4.4 Special warnings and precautions for use** … Individual benefit/risk justification Lumark is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates. … Specific warnings … Radioactive medicinal products should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. **6.2 Incompatibilities** Radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates, with Lutetium (^{177}Lu) chloride is very sensitive to the presence of trace metal impurities. It is important that all glassware, syringe needles etc, used for the preparation of the radiolabelled medicinal product are thoroughly cleaned to ensure freedom from such trace metal impurities. Only syringe needles (for example non-metallic) with proven resistance to dilute acid should be used to minimize trace metal impurity levels. In the absence of compatibility studies, this medicinal product must not be mixed with medicinal products other than the medicinal products to be radiolabelled. **6.6 Special precautions for disposal and other handling** Lumark is not intended for direct use in patients. … Radiopharmaceuticals should be prepared in a	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. For instruction on extemporary preparation of the medicinal product before administration, see section 12. **12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** Appropriate aseptic precautions should be taken, in order to maintain the sterility of Lumark and to maintain sterility throughout the labelling procedures. The complexing agent and other reagents should be added to the vial with $^{177}LuCl_3$. Free $^{177}LuCl_3$ 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 ^{177}Lu-labeled conjugates in order to form a complex with free ^{177}Lu, if present, leading to a rapid renal clearance of ^{177}Lu.	
Osteosarcoma	(Proposed) text in SmPC: **12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** Free $^{177}LuCl_3$ 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 ^{177}Lu-labeled conjugates in order to form a complex with free ^{177}Lu, if present, leading to a rapid renal clearance of ^{177}Lu.	

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Lumark is a radio-pharmaceutical precursor intended solely for radio-labelling purposes with other medicinal products such as monoclonal antibodies, peptides or other substrates for radio-nuclide therapy. As a precursor, Lumark is not intended to be given directly to patients.

Published data has demonstrated the clinical utility of ^{177}Lu in neuroendocrine tumour therapy with evidence of its role in the management of patients with gastroenteropancreatic neuroendocrine tumours (GEP-NET). There is some evidence of its role in the diagnosis and treatment of patients with advanced prostate cancer where ^{177}Lu-labelled antibodies have been used in the diagnosis and treatment of patients with metastasised prostate cancer.

Thus, appropriate information to support an indication as a radio-pharmaceutical precursor for radiolabelling has been provided. Relevant non-clinical and clinical information related to the clinical use of the carrier molecules, which have been specifically developed and authorised for radio-labelling with this radionuclide, are to be included in the SmPC of the carrier molecules.

Uncertainty in the knowledge about the beneficial effects

The clinical utility in breast cancer, brain tumours and bone metastases is still in the non-clinical phase and there is not enough clinical evidence to support the clinical utility in these therapies. The clinical utility in prostate cancer is based on studies with small patient numbers and larger studies may be required to support the currently available data in the diagnosis and treatment of patients with prostate cancer.

Risks

Unfavourable effects

There are no major safety concerns with regards to free ^{177}Lu as the doses of Lumark administered are expected to be very low and are unlikely to be associated with toxicity. ^{177}Lu has a relatively short half-life of 6.647 days. Moreover, and as for all radioactive products, unfavourable effects relating to the radioactivity would be expected. These include carcinogenicity, mutagenicity, and effects on different tissues. For ^{177}Lu, the accumulation of the radiopharmaceutical in bone has been evidenced in non-clinical studies. However, the risk has been addressed in the SmPC with the recommended use of the chelator DTPA to minimise the risk of free ^{177}Lu. Radiotoxicity would also be dependent on the radiation characteristics of ^{177}Lu in Lumark as well as on the carrier molecule to which Lumark is labelled. Following therapy with radiolabelled peptides or antibodies, kidney retention and renal function loss, bladder radiotoxicity, haematological toxicity, myelodysplastic syndrome and liver toxicity have been reported. In addition to radiation exposure to the patient, the risk of radiation exposure to other individuals is also a risk, considering the emission of gamma and β particles from ^{177}Lu. Exposure to ionising radiation must be justified on the basis of likely clinical benefit. However, the radiation safety of Lumark in its use as radiopharmaceutical precursor has been adequately addressed in the product information.

Uncertainty in the knowledge about the unfavourable effects

^{177}Lu has a long half-life in particular in tissues like bone and liver and accumulation in these organs is likely. As ^{177}Lu is intended to be a radiolabel, the pharmacokinetics is dependent on the pharmacokinetics of the carrier

molecule. The radiation effect of accumulation in these organs is not known although this effect would also be dependent on the carrier molecule.

Benefit-risk balance

Importance of favourable and unfavourable effects

Radionuclides like ^{177}Lu have longer half-life equivalent to the biological half-life of the peptide or antibody they are intended to be coupled with. ^{177}Lu emits both gamma and β particles providing relatively high radiation dose on the target tissue, reducing radiation exposure of other parts of the body.

Clinical utility of ^{177}Lu in particular in neuroendocrine tumours has been demonstrated as being well-established. As a radiopharmaceutical precursor, claims of clinical benefit should be the subject of assessment of an application for a radiopharmaceutical labelled with ^{177}Lu.

The risk of radiation to patients and to others is not unlike with other radionuclides and is dependent on the pharmacokinetics of the carrier molecule and necessary precautions with using radiopharmaceuticals would be expected when using any carrier molecule labelled with ^{177}Lu. For individual radiopharmaceuticals labelled with ^{177}Lu, the exposure to radiation, including any radiation effect of accumulation, should be justified by the expected clinical benefit. This should be the subject of assessment in any applications for these medicinal products.

Benefit-risk balance

There are no unresolved issues, which would have a negative impact on the benefit/risk balance of the product. The clinical utility of Lumark in the diagnosis and treatment of certain tumours has been demonstrated. The risk associated with radiation is as expected with other radionuclides and information on minimising this risk has been provided in the RMP and the product information.

Discussion on the benefit-risk balance

Lumark is a radiopharmaceutical precursor and is not intended to be administered on its own to patients. As a result, the benefits and risks of the intended administration of a 177Lu radiolabeled carrier will be assessed independently. For the purpose of an application for a radiopharmaceutical for radiolabelling, the clinical utility and the safety of Lumark has been adequately addressed.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lumark in the as a radiopharmaceutical precursor, not intended for direct use in patients, and to be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide is favourable and 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).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that 177lutetium is qualified as a new active substance.

References

1 Haley TJ et al (1964) Pharmacology and toxicology of lutetium trichloride. J Pharm Sci. 53, 1186-8.

2 Weiss GB (1975) Interactions between several rare earth ions and calcium ions in vascular smooth muscle. J Pharm Exp Ther 195(3): 557-64.

3 Pearce FL and White JR (1981) Effect of lanthanide ions on histamine secretion from rat peritoneal mast cells. Br J Pharmac 72(2): 341-7.

4 Yang Z et al (2000) Potent and competitive inhibition of malic enzymes. Biochem Biophys Res Comm 274(2): 440-4.

5 Jong M, et al. (2005) Combination radionuclide therapy using 177Lu- and 90Y-labeled somatostatin analogs. J Nucl Med. 46(Suppl 1):13S–17S

6 Miao Y1, et al. (2007) Therapeutic efficacy of a 177Lu-labeled DOTA conjugated alpha-melanocyte-stimulating hormone peptide in a murine melanoma-bearing mouse model. Cancer Biother Radiopharm. Jun;22(3):333-41.

7 Kam BL, et al (2012) Lutetium-labelled peptides for therapy of neuroendocrine tumours. Eur J Nucl Med Mol Imaging, Feb;39 (Suppl 1)103-12.

8 Dalmo J , et al. (2012) Biodistribution of 177Lu-octreotate and111In-minigastrin in female nude mice transplanted with human medullary thyroid carcinoma GOT2. Oncol. Reports, 27(1): 174-181.

9 Luckey TD et al (1975) Feasibility studies in rats fed heavy metals as multiple nutrient markers. J Nutr 105(6), 660-9.

10 W. Durbin, M. H. et al. (1956) Metabolism of the lanthanons in the rat. Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N. Y.), 91:78 – 85.

11 Higasi T et al (1973) On the accumulation of rare earth elements in animal tumour. Int J Nucl Med 1(2): 98-101.

12 Hisada K and Ando A (1973) Radiolanthanides as promising tumor scanning agents. J Nucl Med 14(8): 615-7.

13 Müller WA et al (1977) Organ distribution studies of lutetium-177 in mouse. Int J Nucl Med Biol 5(1): 29-31.

14 Nakamura Y et al (1997) Differences in behavior among the chlorides of seven rare earth elements administered intravenously to rats. Fund Appl Toxicol 37(2): 106-16 .

15 Schmitt A et al (2003) Biodistribution and dosimetry of 177Lu-labeled [DOTA,TYR]Octreotate in male nude mice with human small cell lung cancer. Cancer Biother Radiopharm 18(4): 593-9.

16 V. Lungu et al (2007) Labelling of Dotatate with 177Lu and 131I for diagnosis and Targeted Therapy: In Vitro and In Vivo Comparative Evaluation; IAEA Technical Report 458 14:233-256.

17 A. Repetto-Llamazares et al (2013) Biodistribution and Dosimetry of 177Lu-tetulomab, a New Radioimmunoconjugate for Treatment of Non-Hodgkin Lymphoma; Current Radiopharmaceuticals 6(1):20-27.

18 H. Yousefnia et a. (2014) Production, quality control, biodistribution assessment and preliminary dose evaluation of 177Lu-PDTMP as a possible bone palliative agent; Nuclear Medicines Communication 35:99-107.

19 Bruce DW et al (1963) The acute mammalian toxicity of rare earth nitrates and oxides. Toxicol Appl Pharmacol 5, 750-9

20 Graca JG et al (1964) Comparative toxicity of stable rare earth compounds. Arch Environm Health 8, 555-64.

21 Müller WA et al (1980) Studies on incorporated short-lived ß-emitters with regard to the induction of late effects. Rad Environm Biophys 18 (1):1-11.

22 Müller WA et al (1977) Organ distribution studies of lutetium-177 in mouse. Int J Nucl Med Biol 5, 29

23 Teunissen JJM et al (2011) Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr Relat Cancer 18: S27-S51.

24 deJong M et al (2001) 177Lu-Dotatate for somatostatin receptor-targeted radionuclide therapy. Int J Canc 92(5): 628-33

25 Kwekkeboom, DJ et al. (2003) Treatment of patients with gastro-entero-pancreatic (GeP) tumours with the novel radiolabeled somatostatin analogue [177Lu-DOTA0, Tyr3]octreotate. Eur. J. Nucl. Med. Mol. Imaging 30: 417–422.

26 Kwekkeboom, D. J. et al. (2008) Treatment with the radiolabeled somatostatin analog [177Lu-DOTA0, Tyr3]octreotate: toxicity,efficacy, and survival. J. Clin. Oncol.; 26: 2124–2130.

27 Amir Sabet et al. Outcome and toxicity of salvage therapy with 177Lu-octreotate in patients with metastatic gastroenteropancreatic neuroendocrine tumours). Eur J Nucl Med Mol Imaging 2014, 41:205–210.

28 Romer A et al. Somatostatin-based radiopeptide therapy with [177Lu-DOTA]-TOC versus [90Y-DOTA]-TOC in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):214-22.

29 Seregni, E et al. Treatment with tandem [90Y]DOTA-TATE and [177Lu]DOTA-TATE of neuroendocrine tumours refractory to conventional therapy. Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):223-30.

30 Yao D et al (2002) The utility of monoclonal antibodies in the imaging of prostate cancer. Sem Urol Cancer 20 (3): 211-18.

31 David KA et al (2006) Clinical utility of radiolabeled monoclonal antibodies in prostate cancer. Clinic Genour Cancer 4 (4): 249-56.

32 Salouti M et al (2011) Preparation and biological evaluation of 177Lu conjugated PR81 for radioimmunotherapy of breast cancer. Nucl Med Biol 38 (6): 489-55.

33 d'Huyvetter M et al (2012) Development of 177Lu-nanobodies for radioimmunotherapy of HER2-positive breast cancer: evaluation of different bifunctional chelators. Contrast Media Mol Imaging 7(2): 254-64.

34 Liu C et al (2012) Timing and optimized acquisition parameters for the whole-body imaging of 177Lu-EDTMP towards performing bone pain palliation treatment. Nucl Med Commun 33(1): 90-6.

35 Bulte JWN (2011) Science to practice: can theranostic fullerenes be used to treat brain tumours? Radiology 261 (1): 1-2.