28 April 2016
EMA/CHMP/404078/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

EndolucinBeta

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

Procedure No. EMEA/H/C/003999/0000

Note

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

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List of abbreviations

ccRCC	Clear cell renal cell carcinoma
CT	Computed tomography
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTANOC	[DOTA0-1-Nal3]octreotide
DOTATATE	[DOTA0,Tyr3]octreotate
DOTATOC	[DOTA0,Tyr3]octreotide
EDTA	Ethylene diamine tetraacetic acid
EDTMP	Ethylene diamine tetra methylene phosphonic acid
GMP	Good Manufacturing Practice
ICP-MS	Inductively coupled plasma mass spectrometry
i.v.	Intravenous
Lu	Lutetium
MTD	Maximum tolerated dose
n.c.a.	Non carrier added
NET	Neuroendocrine tumour
PET	Positron emission tomography
Ph. Eur.	European Pharmacopoeia
PRRT	Peptide receptor radionuclide therapy
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
RECIST	Response Evaluation Criteria In Solid Tumours
REE	Rare earth element
SWOG	Southwest Oncology Group
TNC	Tumour-to-normal-tissue activity concentration ratio
TND	Tumour-to-normal-tissue absorbed dose ratio
TLC	Thin Layer Chromatography
WHO	World Health Organisation
µm	Micrometer

Yb	Ytterbium
Yb2O3	Ytterbium Oxide

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ITG Isotope Technologies Garching GmbH submitted on 28 April 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for EndolucinBeta, 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 25 April 2014.

The applicant applied for the following indication: EndolucinBeta is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with Lutetium (^{177}Lu) chloride.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Lutetium (^{177} Lu) chloride was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0029/2015 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

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.

New active Substance status

The applicant requested the active substance Lutetium (^{177} Lu) chloride contained in the above medicinal product to be considered as a new active substance in comparison to the known products that contain the carrier-added Lutetium (^{177}Lu) chloride as the active substance previously authorised in the Union (Lumark and LutaPol), and claimed that Lutetium (^{177} Lu) chloride differs significantly in properties with regard to safety and efficacy from the already authorised substance.

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. Steps taken for the assessment of the product

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

Rapporteur: Patrick Salmon Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 28 April 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2015.
- The PRAC Rapporteur's RMP Assessment Report was circulated on 27 August 2015.
- During the meeting on 24 September 2015, 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 25 September 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 December 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on 29 January 2016.
- During the PRAC meeting on 11 February 2016, the PRAC endorsed the Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions.
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on 7 April 2016.
- During the meeting on 28 April 2016, 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 EndolucinBeta.

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. Likewise, 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 (^{177}Lu) has no intrinsic pharmacodynamics properties. It is a medium-energy β-emitter with a maximum energy of 0.5 MeV and a maximum tissue penetration of 2 mm. The average beta energy is approximately 0.13 MeV. ^{177}Lu also emits low-energy γ-rays at 208 keV (11%) and 113 keV (6.4%), allowing scintigraphy and subsequent dosimetry with the same therapeutic compound, if needed. The shorter β-range of ^{177}Lu compared to other radiotherapeutic agents such as yttrium provides better irradiation of small tumours, sparing surrounding tissue (the range of yttrium is 12 mm in tissue, due to the higher energy of 2.27 MeV). ^{177}Lu decays to stable hafnium (^{177}Hf) with a half-life of 6.647 days. The relatively long half-life of 177Lu provides logistic advantages that facilitate its supply to locations far from reactors.

EndolucinBeta contains ^{177}Lu, a radioisotope of Lutetium, as lutetium(^{177}Lu)chloride in solution. It contains 3-150 GBq Lutetium (^{177}Lu) chloride which corresponds to 0.73 – 37micrograms of Lutetium (^{177}Lu). The solution comes in a 2 ml and 10 ml vial where the volume 0.075 -3.75 ml. Lutetium (^{177}Lu) chloride is produced by the irradiation of highly enriched Ytterbium (^{176}Yb) in neutron sources with a thermal neutron flux between 10^{13} and 10^{16} $cm^{-2}s^{-1}$.

Non carrier added (n.c.a.) Lutetium (^{177}Lu) chloride is produced by the irradiation of highly enriched Ytterbium (^{176}Yb) in neutron sources with a thermal neutron flux between 10^{13} and 10^{16} $cm^{-2}s^{-1}$. The following nuclear reaction is ongoing in the irradiation:

$$^{176}\mathrm{Yb(n,\gamma)}^{177}\mathrm{Yb} \rightarrow {}^{177}\mathrm{Lu}$$

The produced Ytterbium (^{177}Yb) with a half-life of 1.9 h decays to Lutetium (^{177}Lu). In a chromatographic process, the accumulated Lutetium (^{177}Lu) is separated chemically from the original target material. Lutetium (^{177}Lu) emits both medium-energy beta particles and imageable gamma photons, and has a half-life of 6.647 days. The primary radiation emissions of Lutetium (^{177}Lu) are shown in Table 1.

Table 1: Lutetium (^{177}Lu) principle radiation emission data

Radiation	Energy (keV)*	Abundance (%)
Beta (β^-)	47.66	11.61
Beta (β^-)	111.69	9.0
Beta (β^-)	149.35	79.4
Gamma	112.9498	6.17

Gamma	208.3662	10.36

* mean energies are listed for beta particles

The produced Ytterbium (^{177}Yb) with a half-life of 1.9 h decays to Lutetium (^{177}Lu). Lutetium (^{177}Lu) decays by emission of beta radiation to stable Hafnium (^{177}Hf). In a chromatographic process, the accumulated Lutetium (^{177}Lu) is separated chemically from the original target material.

EndolucinBeta is indicated for the radiolabelling of carrier molecules which have been specifically developed for radiolabelling with this radionuclide. As EndolucinBeta is a radiopharmaceutical precursor, it is not designed to be given directly to patients. This solution is to be used for the labelling of peptides or proteins which subsequently are administered to patients to facilitate diagnosis and therapy by its radiation properties. The quantity of EndolucinBeta required for radiolabelling and the quantity of Lutetium (^{177}Lu) - labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use.

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

The final agreed indication was as follows:

- To be used only for the radiolabelling of carrier molecules, which have been specifically developed for radiolabelling with this radionuclide. Radiopharmaceutical precursor - Not intended for direct use in patients.

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

The quantity of EndolucinBeta required for radiolabelling and the quantity of Lutetium (^{177}Lu)- labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

2.2. Quality aspects

2.2.1. Introduction

EndolucinBeta is not intended to be administered directly to the patients. It is used as radiopharmaceutical precursor and may be coupled to a variety of molecules, facilitating diagnosis and therapy by its radiation properties.

The finished product is presented as radiopharmaceutical precursor, solution containing 40 GBq/ ml of Lutetium (^{177}Lu) chloride as active substance.

1 ml of solution contains 40 GBq Lutetium (^{177}Lu) chloride on activity reference time (ART), corresponding to 10 micrograms of Lutetium (^{177}Lu) as chloride.

Other ingredients are: hydrochloric acid solution.

The product is available in type I glass vial, with a bromobutyl stopper, closed with an aluminium seal as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of the active substance is Lutetium (^{177}Lu) chloride corresponding to the molecular formula $LuCl_3$ and has a relative molecular mass 282.3 g/mol.

Lutetium chloride ($LuCl_3$) is *a* colourless/white crystal.

The active substance ^{177}Lu is a synthetic radionuclide 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 (ii), the indirect method. This indirect method has certain advantages such as avoiding production of the long-lived radionuclide impurity ^{177m}Lu. The target ^{176}Yb is more than 99% pure and purification steps can also be employed as starting materials ^{176}Yb are chemically different from the desired product ^{177}Lu. Product produced by this method is of high purity with a high specific activity which has advantages in certain labelling and therapeutic applications.

From a quality point of view, notwithstanding the different isotopic distributions of Lutetium and different Specific Activity (expressed as GBq/mg), non-carrier-added Lutetium (^{177}Lu) Chloride and carrier-added Lutetium (^{177}Lu) Chloride are clearly the same active substance.

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 active substance lutetium (^{177}Lu) chloride in diluted hydrochloric acid solution.

Manufacture, characterisation and process controls

Lutetium (^{177}Lu) chloride is synthesized using commercially available well defined starting materials with acceptable specifications. The manufacturing process consists in the following steps: preparation of the manufacturing process, ampule manufacture and irradiation, target processing, radiochemical separation, formulation of the stock solution, sampling for quality testing.

Lutetium (^{177}Lu) is produced by the irradiation of highly enriched Ytterbium (^{176}Yb) in neutron sources with a thermal neutron flux. The following nuclear reaction is takes place during irradiation:

$$^{176}\text{Yb}\ (n,\ \gamma)^{177}\text{Yb} \rightarrow {}^{177}\text{Lu}$$

The produced Ytterbium (^{177}Yb) with a half-life of 1.9 h decays to Lutetium (^{177}Lu). In a chromatographic process, the accumulated Lutetium (^{177}Lu) is separated chemically from the original target material and is dissolved in 0.04 M HCl.

The active substance lutetium (^{177}Lu) chloride is not isolated during the manufacturing process; it is dissolved in diluted hydrochloric acid (0.04 M HCl).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

A type I glass vial internally coated with a chemically bonded layer of SiO2 is used as container closure for the stock solution. The vial remains all the time until dispensing of the stock solution in the hot cell. Certificates of analysis are provided confirming compliance with Type I Glass requirements as stated in the Ph Eur 3.2.1.

Specification

The active substance release specification includes tests for radioactivity concentration, appearance, identity (Gamma spectrometry), identity chloride (Ph Eur), pH, specific activity (ICP-MS),chemical purity (ICP-MS), radionuclidic purity (gamma spectroscopy), radiochemical purity (TLC), bacterial endotoxins (Ph Eur) and total organ carbon (TOC measurement).

The description of analytical procedures and validation of analytical procedures are described under the Finish product section. Moreover, the reference standards are those described for the finished product for the same reason.

Batch analysis data on three production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three production scale batches of active substance (i.e. stock solution) from the proposed manufacturer stored in the intended commercial package at room temperature for at least 11 days from the day of manufacturing.

The following parameters were tested*:* appearance, activity concentration (dose calibrator), identity ^{177}Lu (gamma spectrometry), identity chloride (Ph Eur), pH, chemical purity (ICP-MS), radiochemical purity (TLC), radiolabelling yield (TLC) and total organ carbon (TOC). Test methods correspond to those described for the finished product.

After storage of the stock solution at room temperature for at least 11 days from the day of manufacturing all parameters tested comply with the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period of up to 2 days with an expiry of 4 days from the date of manufacturing of the stock solution in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The composition of the finished product consists in Lutetium (^{177}Lu) as lutetium chloride as active substance in a solution of hydrochloric acid.

The stock solution is filled in 2 ml or 10 ml vials (and may be diluted by 0.04 M HCl) to obtain a defined activity concentration of 40 GBq/ml at ART.

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

A solution of ^{177}Lu in 0.04M HCl was chosen for the following reasons:

- 0.04 M HCl allows to maintain the pH of the finished product at maximum of 2 as requested by the draft monograph of the Ph. Eur. “Lutetium (^{177}Lu) solution for radiolabelling”.
- The concentration of 0.04 M HCl is suitable to keep the ^{177}Lu in solution, which is necessary for labelling of the carrier molecules.
- The pH of this solution is suitable to perform radiolabelling reactions by adding only minimal amounts of buffer solution.

The active substance Lutetium (^{177}Lu) is dissolved in dilute hydrochloric acid; thus it is in the chemical form of Lutetium (^{177}Lu) chloride. A classic compatibility study is not applicable in this case. The active substance is an inorganic substance that is not susceptible to degradation caused by interaction with excipients. As a radioactive element, the active substance is characterised by its physical half-life (6.647 days). Other instabilities are not expected.

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

Manufacture is a continuous process from starting material through to manufacture of the finished product. The product is sterilised by terminal sterilisation according to an accelerated cycle The finished product is sterilised by autoclaving and tested for sterility according to Ph. Eur. 2.6.1. Bacterial endotoxins are tested according to Ph. Eur. 2.6.14. Testing of sterility is performed retrospectively after the complete decay of radioactivity. The conditions of the solution, acidic pH (1 - 2) and gamma radiation are not favourable for the growth of microorganisms.

The product is available in type I glass vial, with a bromobutyl stopper, closed with an aluminium seal. Integrity of the stoppered and crimped vials was demonstrated by the dye ingress (methylene blue) method. All vials tested were shown to meet the acceptance criteria, whether automatically or manually crimped.

Fragmentation tests, in line with Ph. Eur. 3.2.9, were conducted to ensure that piercing of the rubber stopper with a subcutaneous needle does not damage the stopper; results complied with the Ph. Eur. Limit. A leaching study was conducted to observe levels of trace elemental impurities in the product.

Manufacture of the product and process controls

The active ingredient lutetium (^{177}Lu) chloride is not isolated during the manufacturing process; it is solved in diluted hydrochloric acid (0.04 M HCl). The manufacturing of finished product comprises the following main steps: filling, autoclaving, and secondary packaging. The process is considered to be a non-standard manufacturing process.

Three batches have been manufactured in compliance with the process controls during validation and the finished product specifications, demonstrating the consistency and robustness of the manufacturing procedure. It can then be concluded that the manufacturing process of EndolucinBeta described is validated.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: activity per vial (dose calibrator), radioactivity concentration, appearance, identity ^{177}Lu (gamma spectrometry), identity chloride (Ph Eur), pH, specific activity (ICP-MS), chemical purity (ICP-MS), radionuclidic purity (gamma spectrometry), radiochemical purity (TLC), bacterial endotoxins (Ph Eur) and sterility (Ph Eur).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial scale batches of finished product stored under long term conditions at 25 ºC / 60% RH and under accelerated conditions at 40 ºC / 75% RH for up to 11 days according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Photostability is not tested because the product is packed in a lead container (secondary packing) and is not exposed to light.

Samples were tested for appearance, identity ^{177}Lu (gamma spectrometry), identity chloride (Ph Eur), pH, chemical purity (ICP-MS), radionuclidic purity (gamma spectrometry), radiochemical purity (TLC), bacterial endotoxins (Ph Eur), sterility (Ph Eur) and total organ carbon (TOC).

The analytical procedures used are stability indicating.

As would be expected with a product of this nature, very little change is observed on stability testing, aside from the obvious decay of radioactivity. The key parameters of radionuclidic and radiochemical purity remain essentially unchanged and all parameters are within the proposed specifications. The tests for sterility and

radionuclidic purity have been accomplished retrospectively after the complete decay (about 12 weeks) of radioactivity. The results for these parameters are also within the predefined limits.

Based on available stability data, the proposed shelf-life of up to 9 days from date of manufacturing as stated in the SmPC (section 6.3) are acceptable. The time of manufacture of the finished product shall mean the day of filling.

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.

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 for future quality development

Not applicable.

2.3. Non-clinical aspects

In support of their application, the applicant has performed a limited non-clinical program which consists of a non-GLP pharmacokinetic study to examine the distribution of ^{177}Lu in rats in case of accidental injection. The remaining sections of the non-clinical dossier have been provided by means of a literature review of the published data. The data submitted were assessed based on the legal basis of the application, and owing to the nature of the product being a radiopharmaceutical, requirements for the non-clinical aspects of the application were laid out in Annex 1 Part III Directive 2001/83/EC.

2.3.1. Introduction

No studies on the clinical pharmacology of $^{177}LuCl_3$ have been submitted, since this substance is not intended to be administered directly to the patient. The non-clinical sections of the dossier have been compiled from published literature except for the non-GLP rat dosimetry study, which was submitted by the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The element lutetium does not appear to have a natural physiological function and it is found only in traces in the body. The content in food is not monitored, but was found to be extremely low; some vegetables were found to have as little as 10 ppt in dry matter. From this it can be extrapolated that the natural uptake may be as low as a few micrograms per year[1] . Lutetium can be administered orally at high doses without inducing any signs of overt toxicity (single dose toxicity). Like other metal ions, lutetium ions do have a bacteriotoxic potential. With an effective concentration (EC50) of 1.57 µM, Lu3+ is more bacteriotoxic than La3+, Cd2+, or Zn2+ and approximately equally as bacteriotoxic as Cu2+[2].

^{177}Lu as a free (non-complexed) radioisotope

First reports on the medical use of ^{177}Lu were published in 1969, describing the use of this radioactive element for bone imaging in rabbits[3] . Whereas ^{177}Lu is currently used as an immunotherapeutic due to the emission of β-radiation with a range of only 2 mm compared to the range of 12 mm described for ^{90}Y, ^{177}Lu also emits γ-irradiation, enabling its use for radio-imaging purposes[4] . ^{177}Lu was discussed to be advantageous for bone imaging, due to the medium energy gamma radiation emitted and the half-life of more than six days, giving a balance between practical considerations for handling and duration of radiation exposure . Depending on the chelating agent used for administration, the radioactivity is distributed in different tissues. If highly stable complexes such as diethylene triaminepentaacetic acid (DTPA) are selected for administration, the radioactivity is excreted in urine prior to distribution in bone or other tissues. When complexes of low stability are formed, "radiocolloid" formation apparently takes place in vivo, and reticuloendothelial localisation is the result. However, if hydroxyethylenediamine tetracetic acid is used for complexing, forming a complex of intermediate stability, approximately 50% of the administered dose localises in the skeleton. The remainder is promptly cleared from the plasma by the kidneys, and the rate of clearance was found to be similar to that of ^{85}Sr, a radionuclide used previously. Despite these encouraging data, no further uses were described until 1985, when Bard et al.[5] described the use of ^{177}Lu in the treatment of rheumatoid arthritis in an experimental model in rabbits. The use of ^{177}Lu was tried to limit the proliferative response of the synovia to inflammation and to locally reduce/block the immune response in the joint, preventing the inflammation induced destruction of cartilage. Although some joints, which had received 0.35 mCi, showed signs of damage to the articular cartilage, this damage was not apparent with either of the two lower doses, indicating that a separation between pharmacological activity and toxicity is possible.

In a different study, it was evaluated whether ^{177}Lu could be utilised to image the parathyroid gland, aiming at localising potential parathyroid adenoma in a pre-surgical setting. Although certain enrichment in parathyroid tissue could be observed, the enrichment was not sufficient for imaging for lutetium.

^{177}Lu radioimmunotherapy

To evaluate the stability of chelated complexes, i.e. molecules which complex $^{177}Lu^{3+}$ presented in an aqueous solution, an in vitro method was developed and several complexing agents were compared. ^{177}Lu was found to form stable complexes with DOTA and with DOTA-based complexing agents such as 1, 4, 7, 10-tetraaza-N-(1-carboxy-3-(4-nitrophenyl)propyl)-N', N", N"'-tris(acetic acid) cyclododecane (PA-DOTA). These chelators molecules could be rapidly filled with ^{177}Lu in vitro, resulting in stable complexes with high (>98%) rates of labelling[6,7,8]. The complex with DOTA was found to be highly stable and mostly irreversible, with release of less than 5% of the label within 21 days of incubation in vitro[9].

Pharmacology of ^{177}Hf as a decay product from ^{177}Lu

^{177}Lu decays by β-emission of intermediate energy, accompanied by γ-emission of intermediate energy, to the stable isotope ^{177}Hf with a half-life of 6.647 days. Therefore, each individual exposed to ^{177}Lu is also exposed to ^{177}Hf. Whereas the highest cumulative dose of lutetium to be administered in patients depends on the intended application and on the carrier protein used, cumulative doses of up to 29.6 GBq ^{177}Lu (7.2 µg) are reported. Assuming a worst case scenario in which no ^{177}Lu is excreted before decay, the cumulative exposure would be up to 7.2 µg hafnium. Therefore the pharmacology of ^{177}Hf was also evaluated.

Hafnium, being a stable isotope, is present in nature and can be taken up by each individual in food, drinking water or as dust inhaled. The amount of Hf present in the human body is not known, but is negligible. It has no known biological role, and its salts generally have low toxicity. The element is poorly absorbed by the body, and poisoning by Hf compounds is not known. Plants take up small amounts of Hf from the soil in which they grow, and levels of 0.01-0.4 ppm (dry weight) have been recorded. No daily intake can be calculated from these data, but it is likely to be very low.

Secondary pharmacodynamic studies

Lutetium in its ionic form (Lu^{3+}) has been investigated as a membrane stabilising agent, inhibiting transmembrane calcium permeation. Using a rat aorta preparation in vitro, lutetium and other rare earth metals were investigated for their effects on calcium distribution and transmembrane calcium movements, using the radioactive isotope ^{45}Ca. In addition, the effects of lutetium on aortic smooth muscle contractions were examined, since calcium entry is essential for contractions. At a concentration of 1.5 mM in the bath solution, Lu^{3+} reduced the calcium uptake in the preparation and had a relaxant property, interpreted as membrane stabilisation[10]. Ionic lutetium was also shown to interfere with inhibitory γ-aminobutyric acid (GABA) neurotransmission, resulting in enhancement of GABA currents. The effect of Lu^{3+} was investigated in rat septal neurons in culture by using the whole-cell voltage-clamp technique. GABA (10 µM) currents were moderately enhanced by about 40% upon application of a concentration of 100 µM Lu^{3+} [11].

Safety pharmacology programme

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

In the isolated rabbit ileum preparation, lutetium chloride produced a concentration dependent relaxant effect, and at high concentrations (up to 40 mg) an irreversible paralysis was observed. The exact concentration in the bath solution is not given, since the reference volume is not given (most likely 40 mg/100 ml). If the rabbit ileum was pre-contracted with acetylcholine or nicotine, the contraction of these agents was antagonised with an antispasmodic EC50 of 0.6 and 0.5 mg/ml. In a different preparation, the cat superior ganglion preparation, lutetium had no ganglion blocking effect, indicating that the smooth muscle relaxant effect was due to a direct interaction with the muscle, in line with the reported calcium blocking activity of high concentrations of lutetium[,12].

Cardiovascular effects of intravenously administered lutetium chloride were investigated in the anaesthetised cat. No pharmacological effects on respiration or on the cardiovascular system were observed in the dose range 1 to 10 mg/kg lutetium chloride, upon cumulative dosing. The administration of 20 mg/kg was in the lethal dose range, resulting in lethality in 5 out of 10 cats. In animals which did not die upon administration of 20 mg/kg, a transient hypotension with concomitant reduction in blood flow was observed. Respiration was

not affected. In animals which died at this dose or at the highest tested dose of 40 mg/kg, a complete cardiovascular collapse, coupled with respiratory paralysis, was observed, leading to death. While no effect on ECG parameters were observed up to the dose of 10 mg/kg i.v., in animals dosed 20 mg/kg and above, pre-lethal changes included inversion of QRS complex, transient ventricular fibrillations, heart block, and changes in the T-wave morphology. However, even at this dose no QT-prolongation was reported. Within the dose range tested, lutetium chloride had no influence on the pharmacological response to acetylcholine, histamine, or electrical vagal stimulation. Neither atropine nor epinephrine had positive effects on the cardiovascular collapse induced in the lethal dose range of 20-40 mg/kg.

In a different experiment, lutetium chloride (10 mg/kg) was administered intravenously in non-anaesthetised rats, and the safety of this single dose administration was observed, with focus on hepatic metabolism. Lutetium administration had no effect on calcium accumulation at the dose level of 10 mg/kg i.v., but it resulted in increased concentration of calcium in various organs (liver, spleen, lungs and kidneys) at 20 mg/kg i.v., a dose which was found to be in the lethal dose range in cats. Lutetium (10 mg/kg) had no effect on hepatic metabolism, as indicated by a lack of change in hepatic cholesterol, triglycerides and phospholipids, serum lipids, and serum hepatic enzyme activity of aspartate transaminase (GOT or AST) and alanine transaminase (GPT or ALT)[13].

Hafnium

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

In the isolated guinea pig ileum preparation, hafnium chloride produced a concentration dependent relaxant effect, and at high concentrations (range tested: 10 to 200 mg, reference volume not given, most likely 10-200 mg/100 ml) an irreversible paralysis was obtained. If the rabbit ileum was pre-contracted with acetylcholine or nicotine, the contraction of these agents was antagonised with an antispasmodic EC50 of 128 and 99 mg (again, reference volume not given). In a different preparation, the cat superior ganglion preparation, hafnium had no ganglion blocking effect, indicating that the smooth muscle relaxant effect was due to a direct interaction with the muscle[14].

The cardiovascular effect of intravenously administered hafnium chloride was investigated in the anaesthetised cat. No pharmacological effects on respiration or the cardiovascular system were observed in the dose range 0.5 to 2 mg/kg, upon cumulative dosing. The administration of 5 mg/kg resulted in a transient hypotension with a concomitant reduction in blood flow. In these animals, respiration was not affected. At this dose, ECG changes were observed including changes in the height and direction of P- and T-wave, but no effect on the QT interval was reported. The administration of 10 mg/kg resulted in complete cardiovascular collapse, followed by respiratory paralysis. Prior to death, the respiratory rate was not affected. Within the dose range tested, hafnium chloride had no influence on the pharmacological response to acetylcholine, histamine, or electrical vagal stimulation. Neither atropine nor epinephrine had positive effects on the cardiovascular collapse induced at the lethal dose of 10 mg/kg.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies $LuCl_3$ has been submitted by the applicant (see non-clinical discussion).

2.3.3. Pharmacokinetics

The pharmacokinetic of ^{177}Lu is dependent on the carrier molecule radiolabelled with the isotope. In an effort to examine the dosimetry of $^{177}LuCl_3$ in case of accidental intravenous administration, a distribution study was carried out in rats.

The pharmacokinetic parameters and organ distribution of ^{177}Lu after intravenous injection of 15 MBq/kg $^{177}LuCl_3$ in PBS were investigated in male and female rats [Study report ITG-Lu-177-Dosimetry-001]. Each animal (n=24, two male and two female per sampling time) received 15 MBq/kg and the blood ^{177}Lu concentration was determined at 5 min, 1 h, 12 h, 2 days, 7 days and 28 days after tracer injection.

Maximum blood concentrations were observed after 5 min (the first sampling time) and were very low, reaching 0.08%ID/g in male and female rats, without gender difference. Based on the assumption that the blood amounts to 7% of body weight, only 1.52% injected dose was found in blood at this sampling time. Already after one hour, no radioactivity above background activity was found in blood, indicating that ^{177}Lu was rapidly cleared from the blood pool, immediately after administration. No terminal half-life could be calculated, but can be expected to be in the range of a few minutes only.

The distribution of ^{177}Lu in the evaluated organs, corrected for the decay of radioactivity, is displayed in **Table 5** below.

Table 2: Biodistribution of ^{177}Lu radioactivity, corrected for the decay of ^{177}Lu, in male and female rats (pooled data, no gender difference) as %ID/g after administration of 15 MBq/kg, n=4 per sampling time [Study report ITG-Lu-177-Dosimetry-001]

Average ID%/g Time post injection	5 min	± SD	1 hour	± SD	12 hours	± SD
Adrenal glands	0.00	0.00	0.08	0.10	0.00	0.00
Bladder	0.00	0.00	0.00	0.00	0.00	0.00
Blood	0.08	0.04	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Caecum	0.00	0.00	0.00	0.00	0.00	0.00
Colon	0.00	0.00	0.00	0.00	0.00	0.00
Duodenum	0.00	0.00	0.00	0.00	0.00	0.00
Fat	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.01	0.02	0.04	0.03	0.23	0.06
Heart	0.04	0.04	0.01	0.02	0.00	0.00
Ileum	0.00	0.00	0.00	0.00	0.04	0.05
Jejunum	0.00	0.00	0.00	0.00	0.00	0.00
Kidneys	0.04	0.03	0.04	0.01	0.07	0.01
Liver	8.08	4.56	9.56	2.96	7.28	2.41
Lung	0.19	0.14	0.22	0.08	0.04	0.01
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Rectum	0.00	0.00	0.05	0.09	0.00	0.00
Spleen	4.04	2.54	5.26	1.43	5.84	1.91
Stomach	0.04	0.05	0.09	0.12	0.16	0.26
Testicles	0.00	0.00	0.00	0.00	0.01	0.01
Ovaries	0.09	0.12	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid glands	0.16	0.32	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.00	0.00	0.00	0.00

Average ID%/g Time post injection	48 hours	± SD	7 days	± SD	28 days	± SD
Adrenal glands	0.05	0.11	0.00	0.00	0.00	0.00
Bladder	0.03	0.04	0.00	0.00	0.00	0.00
Blood	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Caecum	0.01	0.01	0.00	0.00	0.00	0.00
Colon	0.01	0.02	0.00	0.00	0.00	0.00
Duodenum	0.02	0.02	0.00	0.00	0.00	0.00
Fat	0.09	0.13	0.00	0.00	0.00	0.00
Bone	0.58	0.21	0.84	0.20	1.02	0.16
Heart	0.01	0.01	0.01	0.02	0.00	0.00
Ileum	0.03	0.02	0.00	0.00	0.00	0.00
Jejunum	0.00	0.00	0.59	1.19	0.00	0.00
Kidneys	0.13	0.03	0.35	0.09	0.10	0.21
Liver	6.27	1.60	4.59	1.84	0.88	0.27
Lung	0.03	0.00	0.03	0.02	0.00	0.00
Pancreas	0.01	0.02	0.00	0.00	0.00	0.00
Rectum	0.04	0.05	0.00	0.00	0.00	0.00
Spleen	5.50	1.20	6.50	3.20	2.77	0.70
Stomach	0.09	0.05	0.09	0.06	0.00	0.00
Testicles	0.00	0.00	0.00	0.00	0.00	0.00
Ovaries	0.01	0.02	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid glands	0.35	0.70	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.00	0.00	0.00	0.00

The highest amount of ^{177}Lu radioactivity was detected in the liver and spleen, followed by the lung shortly after administration, and by bone later on, but with a much lower content. The content in the kidneys remained low throughout the study.

After one hour the activity was: 9.56%ID/g in the liver and 5.26%ID/g in the spleen, whereas the activity in the lungs as the third most exposed organ reached only 0.22%ID/g and bone and kidney were only exposed to 0.04%ID/g.

After seven days the remaining activity, corrected for the decay of ^{177}Lu, was: 4.59%ID/g in the liver, and 6.50%ID/g in the spleen, the maximum concentration reached in the spleen. The content in bone had increased to 0.84%ID/g, whereas no activity remained in any of the other organs, except for the jejunum (0.59%ID/g), kidneys (0.35%ID/g), stomach (0.09%ID/g), lung (0.03%ID/g) and heart (0.01%ID/g). This indicates that the bone accumulates lutetium released from other organs.

After 28 days (the last sampling time) the remaining activity, corrected for the decay of 177Lu, was: 0.88%ID/g in the liver, and 2.77%ID/g in the spleen. The content in bone had increased to 1.02%ID/g, with practically no activity remaining in any of the other organs, indicating that the bone still accumulated

lutetium released from other organs. Considering that after 28 days, 177Lu has already decayed by 4.2 half-lives, the actual remaining activity in the bone at this time is only 0.06%ID/g.

No apparent gender difference could be observed for the distribution of 177Lu in this study.

The absorption from the injection site was found to be fairly complete within 24 hours. After 24 hours, less than 20% of radioactivity had been excreted in urine and faeces, and only 2-3% were found in the liver, whereas about 80% were found in the skeleton, with little radioactivity in the remaining body. Exact figures were not given for different organs, but the authors describe that there was no enrichment in blood, and only limited retention in muscle and skin. Initially the content in the gastrointestinal tract was about 10 times as high as in blood or muscle, but decreased thereafter. The kidney was found to be an organ of accumulation for the heavier lanthanoids including lutetium, and the urinary route was found to be the primary route of excretion for these lanthanoids. The liver was found to be only a secondary organ of storage for the heavier lanthanoids, whereas the skeleton was found to be the primary organ or storage, with slow clearance from bone (again, no detailed data were given for lutetium).

A published intravenous (i.v.) biodistribution study in rats with “cold” Lutetium chloride and other chlorides of rare earth elements (REEs - yttrium, cerium, praseodymium, europium, dysprosium, ytterbium) indicated that REEs in general are rapidly cleared from blood but are retained in the organs for a prolonged period of time. The rats received a low dose (9-10 mg/kg) or a high dose (18-20 mg/kg) of REE. At 1 day after i.v. administration, more than 78% of the REEs injected were distributed into liver, bone and spleen. Specifically, the major organs in which Lutetium accumulated (at 10 and 20 mg/kg) were the liver (64-67%), bone (11-15%) and spleen (5%). Only minor Lutetium amounts (< 2%) were detected in lungs and kidneys[15].

Following intravenous dosing, the distribution of $^{177}LuCl_3$ in rabbits, complexed in hydroxyethylenediamine tetracetic acid (HEDTA), was described by O’Mara et al. In this study, the utility of the lutetium isotope for bone imaging was evaluated. According to the publication, HEDTA was selected as the complexing agent, which forms complexes of intermediate stability, preventing the formation of "radiocolloids".

Using this complex, approximately 50% of the administered dose localised in the skeleton. The remainder was promptly cleared from the plasma by the kidneys, and the rate of clearance was similar to that of the well-known bone imaging radionuclide strontium-85. In fact, about 50% of administered dose was found to be localised in the skeleton within one hour of administration, with little change after three and 24 hours, indicating stable distribution to bone (see Table 2). In contrast, little content was found in the marrow and liver or in the skeleton, and this amount decreased over time, indicating clearance from the tissue and no further accumulation. For the determination of tissue distribution in rabbits, the amount of radioactivity in whole organ was related to the fractional weight of the respective organ relative to the body weight. For this calculation, it was assumed that 10% of the whole body weight accounts for skeleton, 42% for muscle, and 4% for bone marrow.

Table 3: Tissue distribution of ^{177}Lu-HEDTA complex in rabbits following intravenous dosing, % dose in whole organ (data are not corrected for decay of ^{177}Lu)[3]

	Bone [%]	Muscle [%]	Marrow [%]	Liver [%]
1 h post dose	51.20	9.13	2.98	7.34
3 h post dose	50.40	1.89	1.15	1.31

24 h post dose	53.81	1.40	0.73	1.23

Similar distribution data were also reported for lutetium oxide, administered intraperitoneally to mice after solubilisation in KHSO4[16] . About 50% of radioactivity was found in the skeleton, with little clearance over time. From other organs evaluated, the liver revealed to be the organ with highest exposure, followed by the kidney, spleen, and, with low exposure, the lung.

After intravenous injection of Lu-chloride, lutetium is predominantly but slowly excreted in the urine[3]. According to Durbin et al. [17], faecal excretion is also observed. The authors found that about 20% of the administered radioactivity following intramuscular administration was excreted within 24 hours. Following intravenous administration of $^{177}LuCl^3$ at a dose of 15 MBq/kg in PBS in male and female rats [ITG-Lu-177-Dosimetry-001], slow clearance of radioactivity from the whole body could be observed. Disregarding the radioactive decay of ^{177}Lu to calculate the clearance of the administered dose by excretion only (i.e. assuming that no radioactive decay took place), it was shown that after 28 days an average of 30.3% of the injected dose remained in the body, with 17.8%ID in bone, 10.5%ID in liver and 1.8%ID in spleen, indicating that about 70% was cleared. Considering that after 28 days more than four half-lives of ^{177}Lu have passed, resulting in a decay of more than 94% of the administered radioactivity, the remaining radioactivity in the body is about 1.8% of the administered dose. Part of the ^{177}Lu administered i.v. is taken up in bone, and no clearance other than radioactive decay from bone was observed. After 28 days, 17.8%ID (as ^{177}Lu or ^{177}Hf) is found in bone.

2.3.4. Toxicology

Single dose toxicity

Lutetium: single dose toxicity

The single dose toxicity of lutetium chloride in mice, administered intraperitoneally or orally, was reported by Haley et al. 1964. The symptoms of acute (intraperitoneal) toxicity were writhing, ataxia, laboured respiration, walking on toes with back arched, and sedation. The first deaths occurred within 24 hours, and the peak was at 48 hours. The intraperitoneal LD50 of lutetium chloride was 315 (267-372) mg/kg, corresponding to 197 mg lutetium/kg. The oral LD50 in mice was 7100 (6633-7590) mg/kg, corresponding to 4435 mg lutetium/kg. The subcutaneous administration of 10 mg/mouse of LuCl3 did not result in lethality, but at the injection site local calcification could be observed. From these data a subcutaneous LD50 of > 312 mg/kg lutetium can be derived[18]. In a different study, the intraperitoneal LD50 of lutetium nitrate was evaluated in female mice and rats. The animals were dosed intraperitoneally and were observed for 30 days following the administration. In mice, an LD50 of the nitrate salt of 290 (259-325) mg/kg, corresponding to a dose of the metal of 108 (97-121) mg/kg, was determined. It is to be noted that in this study some animals died late, i.e. more than seven days following dosing. In rats, an intraperitoneal LD50 of 335 mg/kg, corresponding to a dose of the metal of 125 (110-142) mg/kg, was determined[19].

Single dose toxicity information following intravenous administration can be derived from safety pharmacology studies conducted in anaesthetised cats (see non-clinical safety pharmacology). From these data, the intravenous LD50 can be deferred as 20 mg/kg in anaesthetised cats, corresponding to a dose of 12.5 mg/kg lutetium.

The incidence of osteosarcoma after the injection a dose of unconjugated EndolucinBeta in mice was evaluated in a study by Müller et al.[20,21], mice were administered carrier added solutions of ^{177}Lu. Although the solution and the route of administration differ from EndolucinBeta, Müller et al. found for a 185 MBq/kg dose a total skeletal dose of 28 Gy, was associated with a 12.5% incidence of osteosarcomas. Although the data are not quite clear on the relationship between total dose and incidence of sarcoma, it can be stated that the probability of osteosarcoma development after an extremely unlikely administration of 7.5 GBq of non-conjugated ^{177}Lu would be well below 12.5%.

Repeat dose toxicity

Lutetium: repeat dose toxicity (90 days)

The repeat dose oral toxicity of $LuCl^3$ was evaluated in CRW rats. Animals were fed a diet containing 0.01, 0.1 or 1% $LuCl_3$ for a period of 90 days. Based on a daily food consumption of 100 g/kg body weight, this resulted in a maximum daily exposure of 625 mg lutetium/kg body weight. Animals were monitored throughout the study for signs of toxicity including haematology and at the end of the study the animals were dissected. Apart from macroscopic pathology, a limited number of core organs, i.e. heart, lung, liver, kidney, spleen, pancreas, adrenals and small intestine, were evaluated histologically. The feeding of $LuCl_3$ had no influence on behaviour, growth rate, haematology, and gross pathology. No signs of toxicity were seen evaluating the histology of the selected organs. Therefore, the NOEL of orally administered lutetium chloride was set at 1% in the diet, corresponding to about 1000 mg lutetium chloride/kg body weight or 625 mg lutetium/kg body weight.

Genotoxicity

The applicant did not submit genotoxicity studies. According to Annex 1 Part III of Dir 2001/83/EC, as amended, in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes, mutagenicity studies on the radionuclide are not considered to be necessary.

Carcinogenicity

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

Subcutaneously administered lutetium resulted in formation of local calcification at the injection site within one week after the administration, but it was not evaluated whether this local irritant effect induced cell transformation[19]. The local effect of hafnium oxychloride, administered at a concentration of 3 mM (about 20 µg/mouse administered locally), was evaluated in mice. Local intradermal injection resulted in the formation of dysplastic cartilage at the site of injection, as could be observed five months after administration. The effect was comparable to the local activity of zirconium chloride, whereas other metal salts with known carcinogen potential including beryllium, cadmium, chromium, cobalt, and nickel, did not induce this local reaction[22].

Reproduction Toxicity

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

The applicant did not submit further data on the chemical toxicity of lutetium or hafnium on the reproductive function, and on the teratogenic potential of either compound (see non-clinical discussion).

Local Tolerance

Local tolerance of lutetium chloride

Data on the local tolerance of free lutetium from administration of LuCl3 are described by Haley et al. (1964). The administration of concentrated lutetium chloride (1:1 solution) to eyes resulted in local irritation and delayed ulceration of the cornea, which healed completely within two weeks. If crystalline lutetium chloride (0.5 g) was applied to intact skin, no irritation was caused. In contrast, if the crystalline compound was brought in contact with abraded skin, the reaction was severe, showing strong irritation peaking at 24 hours. The irritated skin healed only after 35 days with formation of scar tissue. The intradermal administration resulted in a concentration dependent local irritation or necrosis, and at the lowest concentration tested (1:104 and 1:105 dilution in water), a moderate local irritation was induced. Healing occurred with formation of nodules within six weeks after administration. Histopathological evaluation of these nodules revealed the presence of crystalline deposits of unknown composition. Foreign body giant cells surrounded the crystals, and fibroblasts were found in the outer area.

Other toxicity studies

The solution of $^{177}LuCl_3$ in 0.04 M hydrochloric acid solution is acidic at a pH of 1-2. With paravenous injection or infusion into small or collapsed large veins, tissue damage and necrosis can occur, which may be irreversible[23] . In case of accidental administration of Lutetium (^{177}Lu) chloride n.c.a. ITG to the patient, the catheter or affected area should be irrigated with isotonic saline solution.

Studies on impurities

Carrier free ^{177}Lu chloride is produced by the irradiation of highly enriched (> 99%) ytterbium (^{176}Yb) in neutron sources with a thermal neutron flux between 10^{13} and 10^{16} $cm^{-2}s^{1}$, resulting in the generation of ^{177}Ytterbium, which declines rapidly with a half-life of 1.9 h to ^{177}Lu. The chromatographic process to separate ytterbium from ^{177}Lu utilises alpha-hydroxy-isobutyric acid (HIBA, CAS no. 594-61-6) in small amounts, and hence HIBA is a known impurity of $^{177}LuCl_3$. HIBA can be classified as a residual solvent in the drug substance and drug product.

Based on a thorough evaluation of HIBA exposure and in line with current guidelines, the HIBA exposure of patients undergoing treatment with lutetium containing radiopharmaceuticals is well below the qualification thresholds of current guidelines. From a toxicological point of view, the product specification of 100 µg/ml total carbon, corresponding to a maximum content of 216.9 µg HIBA per ml stock solution, is acceptable for $^{177}LuCl_3$ drug substance. HIBA does not require further toxicological qualification.

The only other ingredient is diluted hydrochloric acid. This excipient conforms to the requirements for pharmaceutical excipients.

2.3.5. Ecotoxicity/environmental risk assessment

EndolucinBeta contains no-carrier-added preparation of (^{177}Lu) chloride which exhibits very high radionuclidic purity. No detectable tracers of long-lived ^{177m}Lu ($t_{1/2}$ = 160.44 days) are present in the preparation. As specified in the SmPC, 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. Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials and any unused medicinal product or waste material should be disposed of in accordance with local requirements. An environmental risk from any unused EndolucinBeta can be excluded.

With regard to products excreted by the patient, the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) states that environmental risk assessment studies are not required for vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids, because they are unlikely to result in a significant risk to the environment. Lutetium (^{177}Lu) chloride dissociates to elemental ^{177}Lu and chloride when in Solution, and is therefore an electrolyte. In addition, ^{177}Lu has no pharmacological action and decays to stable ^{177}Hf, which is also without any pharmacological effect. This decay takes place with a half-life of 6.647 days, meaning that after 33 days (five half-lives) only 3% of radioactive ^{177}Lu remain. It is assumed that ^{177}Lu will be in the body for most of its radioactive 'life-time', and not in the environment.

Screening for PBT (persistence, bioaccumulation and toxicity) is required for substances with a logKow > 4.5. However, since lutetium trichloride, is an inorganic salt its logKow will by all means be negative. Therefore no screening for PBT will be necessary.

Therefore, no environmental risk is to be expected from the use of EndolucinBeta.

2.3.6. New active substance

The applicant was asked to provide further justification for the claim of the new active substance. The applicant justified based on the qualitative and quantitative composition of EndolucinBeta where the non-carrier added EndolucinBeta has at production a specific activity of > 3500 GBq/mg, and at the end of shelf-life, 9 days after production, the specific activity is still > 3000 GBq/mg, whereas for the carrier added Lumark a specific activity of 500 GBq/mg at production is reported. Hence, in EndolucinBeta virtually all lutetium is ^{177}Lu, whereas in Lumark only approximately 12.5 % of all lutetium is ^{177}Lu, the remaining 87.5 % representing other isotopes. In addition, 0.05 % of the radioactivity in Lumark may originate from the long-lived isotope ^{177m}Lu (half-life 160.1 days). Given these differences, the ultimate specific activity of a ligand labelled with EndolucinBeta can be expected to be up to 8 times higher than when labelling with carrier added Lutetium (^{177}Lu) chloride solutions. The applicant has submitted literature which supported the claim that this difference in specific activity might lead to improved clinical peptide receptor radiotherapy response and an improved efficacy in certain tumour models and consequently, for the treatment of several human tumours.

2.3.7. Discussion on non-clinical aspects

A limited non-clinical program which consists of a non-GLP pharmacokinetic study to examine the distribution of ^{177}Lu in rats has been submitted. The remaining sections of the non-clinical dossier have been compiled from published literature consisting of information on lutetium trichloride and other lanthanides. Overall, it can be agreed that the primary pharmacodynamic function of ^{177}Lu is to provide stable labelling for localised radioimmunotherapy and diagnosis which will be dependent on the specificity of the carrier molecule. The isotope itself, at the concentration present in EndolucinBeta, is not expected to have any intrinsic pharmacological properties/response. Hence, the pharmacodynamic properties of ^{177}Lu-labelled medicinal products prepared by radiolabelling with ^{177}Lu chloride n.c.a. prior to administration will be dependent on the type of the medicinal product to be radiolabelled. As a result, the need for dedicated pharmacodynamic studies is not considered necessary.

The secondary pharmacodynamics of ionic lutetium are limited to effects on transmembrane calcium permeation and hence smooth muscle contractions. These effects were demonstrated *in vitro* in rat aorta preparations at concentrations (1.5 mM) far above those used in EndolucinBeta. Ionic lutetium was also shown to interfere with inhibitory γ-aminobutyric acid (GABA) neurotransmission, resulting in enhancement of GABA currents. Again, the concentration found to be active was 100 µM, i.e. well in excess of that achieve with EndolucinBeta. Based on current knowledge, one would rather conclude that Lu^{3+} had a moderate blocking effect on calcium channels. However, the concentrations required to inhibit calcium permeation and hence inhibit smooth muscle contraction, as demonstrated in vitro (1.5 mM), are far above the concentrations which may be reached with $^{177}LuCl_3$ in vivo, using ^{177}Lu for radioimmunotherapy.

The effect of Lu^{3+} was investigated in rat septal neurons in culture by using the whole-cell voltage-clamp technique. GABA (10 µM) currents were moderately enhanced by about 40% upon application of a concentration of 100 µM Lu^{3+} . Again, concentrations found to be active were well above the concentration reached if ^{177}Lu is used for radioimmunotherapy. Doses in the range of several mg/kg, and not ng/kg, would be required to achieve these concentrations.

No pharmacodynamic drug interactions have been published with $LuCl_3$ nor are any expected given the lack of pharmacodynamic effects seen with $LuCl_3$.

The pharmacokinetic of ^{177}Lu is dependent on the carrier molecule radiolabelled with the isotope. In an effort to examine the dosimetry of $^{177}LuCl_3$ in case of accidental intravenous administration, a distribution study was carried out in rats. The absorption of the ^{177}Lu was examined following IV injection with 15 MBq/kg $^{177}LuCl_3$. In the male and female rat, following intravenous administration, Lutetium (^{177}Lu) chloride is rapidly cleared from the blood: at 5 min post injection, only 1.52% of the injected activity (%ID) is found in blood (corresponding to 0.08%ID/g) and no activity above background levels remains 1 hour post dose. The main organs where Lutetium (^{177}Lu) chloride distributes mainly are to the liver, spleen and bone. After one hour, the amount in the liver is 9.56% of the injected activity per gram (%ID/g) and in the spleen 5.26%ID/g. In bone, the content increases from 0.01%ID/g at 5 min to 0.23%ID/g after 12 hours. For the next 28 days, further uptake of ^{177}Lu can be observed in the bone, which is compensated in part by radioactive decay. Taking into account the radioactive half-life of ^{177}Lu of 6.647 days, the radioactivity remaining in the bone after 28 days is only about 0.06%ID/g.

The accumulation as the rate of clearance was dependent on radioactive decay. After 28 days, an average of 30.3% of the injected dose is still found in the body, with 17.8 % in bone, 10.5 % in liver and 1.8 % in

spleen. Faecal and urinary elimination is slow. As a result of both excretion and radioactive decay, the total radioactivity remaining in the body after 28 days is about 1.8% of the injected dose. Thus radioactive decay is thought to contribute significantly to overall clearance and this finding is supported in bone - ^{177}Lu is taken up and no clearance other than radioactive decay could be demonstrated.

Toxicology was described from the literature which is acceptable given that the toxicological properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with EndolucinBeta prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled (SmPC section 5.3). The toxicological properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with EndolucinBeta prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled. The toxicity of non-radioactive Lutetium chloride has been studied in different mammalian species and using different administration routes. The intraperitoneal LD_{50} in mice was found to be approximately 315 mg/kg. In cats, no pharmacological effects on respiration and cardiovascular function were observed up to a cumulative intravenous dose of 10 mg/kg. A high dose of 10 GBq of ^{177}Lu-chloride contains 2.4 µg Lutetium, corresponding to a human dose of 0.034 µg/kg. This dose is approximately 7 orders of magnitude lower than the intraperitoneal LD_{50} in mice and more than 5 orders of magnitude lower than the NOEL observed in cats. Therefore, Lutetium metal-ion toxicity of EndolucinBeta (^{177}Lu)-labelled medicinal products can be excluded.

The most significant toxicological feature of radioactive lutetium chloride, concerns its uptake in bone. This uptake in bone is significant as this has been shown to result in osteosarcomas in mice, the risk is related to excessive distribution and accumulation to bone tissue. Accumulation to bone/liver/spleen, the main targets for accumulation in animals, is absent in humans and it is considered unlikely that high levels of free ^{177}Lu would be present in clinically relevant levels following administration of EndolucinBeta. This is a valid argument however it does not exclude the possibility of formation of osteosarcoma, this has been added as a potential important risk to the applicant's RMP. As a result, the SmPC advises the inclusion of a chelator in the final formulation to bind and facilitate rapid renal clearance of any free ^{177}Lu (see section 12 of the SmPC).

No mutagenicity data was presented in line with Annex 1 Part III of Directive 2001/83/EC, as amended.

No data on reproductive and developmental toxicity has been published as the product is not to be administered directly to humans. However, the use of EndolucinBeta is contraindicated in established or suspected pregnancy or when pregnancy has not been excluded and is highlighted accordingly in the SmPC section 4.3.

An ERA has not been conducted for EndolucinBeta. This is considered acceptable given that EndolucinBeta is a radiopharmaceutical precursor. An ERA will be performed with the final radiolabelled product. With respect to the radioactive environmental impact $^{177}LuCl_3$, 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 significant risk to the environment. The special precautions for storage and special precautions for disposal and other handling of unused medicinal product has been adequately justified in the SmPC section 6.4 and 6.6, respectively.

The justification of EndolucinBeta as a New Active Substance is based on the premise that the matrix of the active moiety can contribute to the pharmaco-kinetics and biodistribution of the active moiety and in this

manner can result in differences in efficacy and safety. The Applicant has pointed to the potential differences in the elemental impurities levels between Lumark and EndolucinBeta with the sum of impurities in Lumark potentially up to 200 μg/ml compared with EndolucinBeta of up to 22 μg/ml. These differences along with the fact that all EndolucinBeta is ^{177}Lu compared to 12.5% in Lumark form the basis of the argument that the matrix of the active moiety is different.

The Applicant has described a number of preclinical studies where they attempt to demonstrate that these differences in the matrix of the active moiety can result in differences in efficacy and safety. The Melis *et al* [24] reference provides some direct comparison of carrier versus non-carrier added ^{177}Lu and shows that less DOTATATE is required to attach the same amount of ^{177}Lu when using non-carrier added ^{177}Lu. The authors conclude that this increased specific activity might lead to improved clinical peptide receptor radiotherapy response. However, in the results section of the abstract the authors reveal that in a rat tumour model, both forms of ^{177}Lu lead to tumour size reduction at 8 days and complete remission at 30 days. This data suggests that despite the potential differences in biodistribution, efficacy is unaffected. In the absence of shown differences in efficacy and safety and taking also into account the absence of comparison in any of the other studies which provides no further substantiation of this claim, the claim of New Active Substance status is not supported.

2.3.8. Conclusion on the non-clinical aspects

^{177}Lu has no pharmacological action and decays to stable ^{177}Hf, which is also without any pharmacological effect. There is no general concern over the toxicity of the lutetium in the preparation as it is not to be administered directly in humans. The safety of ^{177}Lu will be evaluated further considering that single and repeated dose toxicity studies will be provided for the carrier medicinal products using the ^{177}Lutetium radiolabel. 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.

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

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

2.4.2. Pharmacokinetics

No clinical pharmacology studies were submitted with this application (see clinical pharmacology discussion). The applicant submitted a review and discussion of the published literature on the pharmacokinetic properties of ^{177}Lu. Lutetium (^{177}Lu) chloride n.c.a. is a precursor to be used for radiolabelling purposes in combination with other medicinal products consisting of a suitable linker (chelator) and a disease-specific carrier.

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. Lutetium (^{177}Lu) chloride n.c.a. is not intended to be directly administered to the patient. The pharmacokinetics of a radiopharmaceutical would be dependent on the carrier molecule labelled with EndolucinBeta. 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. $^{177}LuCl_3$ has no primary pharmacodynamic function and only very few data are available on the general pharmacodynamics of lutetium as a metal ion and $^{177}LuCl_3$, administered as a free soluble radioactive metal salt. Ionic lutetium in general appears to have no pharmacological function, but radioactive lutetium salts have been investigated for a few clinical applications.

No interaction studies of Lutetium (^{177}Lu) chloride with other medicinal products have been performed.

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 medicinal product to be radiolabelled.

The pharmacodynamic properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with EndolucinBeta, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

2.4.5. Conclusions on clinical pharmacology

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

2.5. Clinical efficacy

2.5.1. Dose response studies

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

2.5.2. Clinical utility

The applicant submitted clinical data from the literature to support the clinical utility of EndolucinBeta when attached to a relevant carrier or ^{177}Lu radionuclide in treatment of neuroendocrine tumours (NET).

^{177}Lu as a radiopharmaceutical for neuroendocrine tumors

Peptide Receptor Radionuclide Therapy

Peptide Receptor Radionuclide Therapy (PRRT) is a form of molecular targeted therapy which is performed by using a small peptide that is coupled with a radionuclide emitting beta radiation. Somatostatin analogues labelled with radionuclides are a good example of PRRT. Because the majority of neuroendocrine tumours (NET) express somatostatin receptors which bind to somatostatin, they can be successfully targeted, and PRRT was found to be more effective in lesions with higher receptor expression. In advanced and metastasised NET, the use of surgery, external beam radiotherapy and chemotherapy as cytoreductive options is limited[4]. As an additional option, treatment with radiolabelled somatostatin analogues is considered to be important in the management of patients with inoperable or metastasised NET, [25], [26] , [27], [28]. Recently, it has been suggested that repeated cycles of PRRT may also have potential in the neoadjuvant setting[29].

PRRT in this indication includes the use of ^{177}Lu-labelled somatostatin analogues, and evidence of its clinical efficacy has been confirmed by various reviews of exploratory clinical trials[30, 31, 32, 33, 34, 35, 36] thereby supporting the therapeutic utility of ^{177}Lu in targeted *in vivo* radiotherapy.

For incorporation of a radiometal into a peptide structure, a chelator is required. For the coupling of the radionuclide and the somatostatin analogue in PRRT, the chelator DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) has been frequently used. As outlined below, several studies on ^{177}Lu-based PRRT have investigated the use of different thermodynamically stable chelator somatostatin analogues, such as [DOTA^{0},Tyr^{3}]octreotide (DOTATOC), [DOTA^{0},Tyr^{3}]octreotate (DOTATATE) and [DOTA^{0}-1-Nal^{3}]octreotide (DOTANOC). DOTATATE differs from DOTATOC only in that the C-terminal threoninol is replaced with threonine[, 37].

In patients with somatostatin receptor-positive tumours, it was found that the uptake of radioactivity, expressed as a percentage of the injected dose of ^{177}Lu-DOTATATE, was comparable with the use of ^{111}In-DOTATOC in the kidneys, spleen and liver, but was three to four times higher in four out of five tumours[38]. Another investigation compared ^{177}Lu-DOTATOC and ^{177}Lu-DOTATATE in patients[39]. For both peptides there was a fast clearance from the blood expressed as percentage of injected activity (%IA). During the first day, the blood clearance of ^{177}Lu-DOTATOC was slightly faster than that of ^{177}Lu-DOTATATE but the difference did not reach significance. Thereafter, blood clearance for both peptides was nearly the same. The cumulative excreted activity in the urine was higher for ^{177}Lu-DOTATOC than for ^{177}Lu-DOTATATE, at 81% versus 71%. The mean residence time ratio (^{177}Lu-DOTATATE vs. ^{177}Lu-DOTATOC) was 2.1 for

tumour, 1.5 for spleen and 1.4 for kidneys. This indicates that the radiation doses for the spleen and kidneys are lower with ^{177}Lu-DOTATOC while the tumour-absorbed dose (or uptake) appears higher following administration of ^{177}Lu-DOTATATE. The tumour-absorbed dose is important for the therapeutic success of PRRT but dose-limiting factors are the radiation exposure of the kidney and/or bone marrow[40, 41, 42]. Thus, both compounds (^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC) are potentially useful.

Schuchardt et al.[43] analysed the *in vivo* behaviour of the ^{177}Lu-labelled peptides DOTATATE, DOTATOC and DOTANOC by measuring organ and tumour kinetics, and by performing dosimetric calculations. In total, 253 patients with metastasised NET who underwent PRRT were examined. Out of these, 185 patients received ^{177}Lu-DOTATATE, 59 were treated with ^{177}Lu-DOTATOC and 9 received ^{177}Lu-DOTANOC. ^{177}Lu-DOTATOC had the lowest uptake/dose delivered to normal organs and the highest tumour-to-kidney ratio. ^{177}Lu-DOTATATE was shown to deliver the highest tumour dose (due to the longer residence time in the malignant lesions). The dose to whole body, spleen and kidneys was highest for ^{177}Lu-DOTANOC. Both ^{177}Lu-DOTATOC and ^{177}Lu-DOTATATE were considered by the authors suitable for PRRT.

The same group[44] correlated the uptake, residence time and resulting mean absorbed dose in the kidneys with the post-therapy effect on renal function using ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC during consecutive cycles of PRRT in 22 patients with metastatic NET. The patients were followed up for 6-12 months. Uptake, residence time and mean absorbed dose to the kidneys were slightly, but significantly, higher for ^{177}Lu-DOTATATE. The tumour-to-kidney ratio was numerically higher for ^{177}Lu-DOTATOC. There were no statistically significant changes in renal function parameters with either ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC. The authors concluded that ^{177}Lu-DOTATOC delivers a slightly, but significantly, lower renal dose but both compounds are considered safe radiopharmaceuticals concerning renal toxicity.

Based on Phase 2 trials, more than 1,000 patients suffering from advanced NET have been treated with ^{90}Y- or ^{177}Lu-labelled DOTATOC or DOTATATE in Europe by 2012; objective response rates of 20-40% were observed. It has been reported that some European centres perform 400 treatments with ^{177}Lu-DOTATATE (7.4 GBq each) per year[45]. Also centres outside Europe already used ^{177}Lu-DOTATATE in hundreds of patients suffering from various types of neuroendocrine-originated tumours[46, 47].

Therapeutic studies with ^{177}Lu-DOTATOC in somatostatin receptor-positive cancers

Relapsed NET

Forrer et al.[48] performed a prospective study with ^{177}Lu-DOTATOC in 27 patients with relapsed NET. All patients received 7.4 GBq of i.v. ^{177}Lu-DOTATOC. Restaging was performed after 8-12 weeks. ^{177}Lu-DOTATOC showed a high specific uptake by somatostatin receptor-positive tumours. The γ-component of ^{177}Lu allowed acquisition of scintigraphic images of high quality. After restaging, a partial remission was observed in 2 patients, a minor response in 5 patients, stable disease in 12 patients and progressive disease in 8 patients. ^{177}Lu-DOTATOC therapy was well tolerated. No serious adverse events occurred. The authors concluded that ^{177}Lu-DOTATOC therapy in patients with relapse after ^{90}Y-DOTATOC treatment is feasible, safe and efficacious. Similar results were obtained in another study in patients switched to ^{177}Lu-DOTATOC therapy following disease relapse after initial therapy with ^{90}Y-DOTATOC[49].

Kratochwil et al.[50] investigated the efficacy of ^{90}Y- and/or ^{177}Lu-DOTATOC when infused into the hepatic artery of 15 patients with liver metastases arising from NET. Complete remission was achieved in 1 (7%) patient and partial remission was observed in 8 (53%) patients, 6 patients were classified as stable (40%).

The concomitant decrease of elevated serum tumour marker confirmed the radiologic response. Median time to progression was not reached within a mean follow-up period of 20 months.

Villard et al.[51] compared the efficacy and safety of combined treatment with ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC versus treatment with ^{90}Y-DOTATOC alone in patients with metastasised neuroendocrine cancers. Patients were treated with repeated cycles of ^{90}Y-DOTATOC or with cycles alternating between ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC. A total of 486 patients completed three or more treatment cycles; 237 patients received ^{90}Y-DOTATOC and 249 patients received ^{90}Y-DOTATOC + ^{177}Lu-DOTATOC. Patients receiving the combination had a significantly longer survival than patients receiving ^{90}Y-DOTATOC alone (5.51 vs. 3.96 years, p = 0.006). The rates of severe haematologic toxicities and severe renal toxicity were comparable between groups. The authors advocated the combined use because of the complementary characteristics of the radioisotopes. ^{90}Y has a long-range, high-energy emission that allows for the deposition of high radiation doses in large metastases and ^{177}Lu has a short-range, lower-energy emission that allows concentration of most of its dose in small metastases.

In a comparative study conducted by Romer et al.[52], patients with advanced NET underwent repeated cycles of ^{90}Y-DOTATOC or ^{177}Lu-DOTATOC until progression of disease or permanent adverse events. Overall, 910 patients underwent 1,804 cycles of ^{90}Y-DOTATOC and 141 patients underwent 259 cycles of ^{177}Lu-DOTATOC. The median survival after ^{177}Lu-DOTATOC and after ^{90}Y-DOTATOC was comparable (45.5 vs. 35.9 months, p = 0.49). Subgroup analyses revealed a significantly longer survival for ^{177}Lu-DOTATOC in patients with low tumour uptake, solitary lesions and extra-hepatic lesions. The rate of severe transient hematotoxicities was lower after ^{177}Lu-DOTATOC 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).

Somatostatin receptor-positive metastatic paraganglioma and phaeochromocytoma

Forrer et al.[53] evaluated the efficacy and safety of radiolabelled DOTATOC in 28 patients with surgically incurable somatostatin receptor-positive metastatic paraganglioma and phaeochromocytoma. Most patients received initial treatment with ^{90}Y-DOTATOC followed by 2 cycles of 7.4 GBq ^{177}Lu-DOTATOC. Restaging was performed at 8-12 weeks after the last treatment cycle. At restaging, 2 partial remissions and 5 minor responses were found. In addition, there were 2 mixed responses; 13 patients showed a stable disease and 6 patients remained progressive. Time to progression ranged from 3 to > 42 months. The treatment was well tolerated. The authors concluded that radiolabelled DOTATOC appears to be a treatment option for surgically incurable paragangliomas because of low toxicity and long-lasting remissions.

Metastatic gastrinomas

Grozinsky-Glasberg et al.[54] retrospectively studied 11 patients with metastatic gastrinomas. Nine patients received alternately ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC for progressive disease; 2 patients received ^{177}Lu-DOTATATE. PRRT induced symptomatic improvement in all patients. Periodic radiological surveillance showed complete response in 1 patient, partial tumour response in 5 patients and tumour stabilisation in 5 patients. In 7 patients, the anti-tumour effect of PRRT persisted after a median period of 14 months. Four patients died due to tumour progression. The authors concluded that PRRT seems to be a promising tool for the management of patients with inoperable or progressive metastatic gastrinomas.

Other uses of ^{177}Lu-DOTATOC

Recently, it has been suggested that gamma probe-guided surgery after tandem PRRT with ^{177}Lu-DOTATOC and ^{90}Y-DOTATOC is feasible and appears to be more sensitive than ^{68}Ga-DOTATOC PET/CT. This technique might achieve a more complete tumour resection through intra-operative detection of very small lesions directly after PRRT[55].

Therapeutic studies with ^{177}Lu-DOTATATE in neuroendocrine gastro-entero-pancreatic tumours

Kwekkeboom et al. performed a study in 35 patients with neuroendocrine gastro-entero-pancreatic tumours. Patients were treated at doses of 3.7, 5.5 or 7.4 GBq ^{177}Lu-DOTATATE up to a final cumulative dose of 22.2-29.6 GBq, with treatment intervals of 6-9 weeks. Three months after the final administration, complete remission was found in 1 patient (3%), partial remission in 12 (35%), stable disease in 14 (41%) and progressive disease in 7 patients (21%). Grade 3 anaemia, leucocytopenia and thrombocytopenia occurred after 0%, 1% and 1% of administrations, respectively. Serum creatinine and creatinine clearance did not change significantly. The authors concluded that in view of the high success rate of ^{177}Lu-DOTATATE therapy and the absence of serious side effects, it should be used in patients with gastro-entero-pancreatic tumours without waiting for tumour progression.

Teunissen et al.[56] evaluated the quality of life in patients with metastatic somatostatin receptor-positive gastro-entero-pancreatic tumours treated with ^{177}Lu-DOTATATE. Fifty patients who had been treated with 22.2 to 29.6 GBq of ^{177}Lu-DOTATATE and had a follow-up of at least 3 months were studied. Twenty-four patients had regression, 19 had stable disease, 6 had progressive disease, and one had a non-assessable disease status. ^{177}Lu-DOTATATE therapy significantly improved the quality of life status as well as several function and symptom scales, especially in those patients with proven tumour regression. The results were confirmed in a subsequent study (performed by the same group) in 265 patients with gastro-entero-pancreatic or bronchial neuroendocrine tumours treated with ^{177}Lu-DOTATATE[57].

Kwekkeboom et al. conducted a study in 131 patients with metastasized or inoperable endocrine gastro-entero-pancreatic tumours positive for somatostatin receptors. The patients were treated up to a cumulative dose of 22.2 to 29.6 GBq of ^{177}Lu-DOTATATE. A favourable effect on tumour size was observed in 47% of patients, with a median time to progression of > 36 months. The latter compared favourably with chemotherapy. Serious side effects were rare. A sub-analysis of patients with somatostatin receptor-positive foregut carcinoid tumours of bronchial, gastric or thymic origin showed an overall remission rate of 50%[58] .

The treatment effects of ^{177}Lu-DOTATATE therapy were described in another large group of patients with gastro-entero-pancreatic neuroendocrine tumours[59] . Patients were treated up to a cumulative dose of 27.8 to 29.6 GBq, usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Toxicity analysis was done in 504 patients and efficacy analysis in 310 patients. Complete and partial tumour remissions occurred in 2% and 28% of patients, respectively. Minor tumour response occurred in 16%. Median time to progression was 40 months. Median overall survival from start of treatment was 46 months and median overall survival from diagnosis was 128 months. Compared with historical controls, there was a survival benefit of 40 to 72 months from diagnosis. Treatment with ^{177}Lu-DOTATATE had few adverse effects. Any hematologic toxicity grade 3 or 4 occurred after 3.6% of administrations. Serious adverse events that were likely attributable to the treatment were myelodysplastic syndrome in 3 patients, and temporary, nonfatal liver toxicity in 2 patients.

Kunikowska et al.[60] performed a non-randomised study with a combination of simultaneously administered radionuclides. A cocktail of 50% ^{90}Y-DOTATATE + 50% ^{177}Lu-DOTATATE was used in 25 patients with

disseminated NET and compared to another group of 25 patients treated with ^{90}Y-DOTATATE alone. Overall survival was significantly longer in patients treated with the combination (p = 0.027). Tumour response and progression-free survival were not significantly different between treatments. Side effects were rare and mild. The authors suggest that the therapy with tandem radioisotopes (^{90}Y-/^{177}Lu-DOTATATE) provides longer overall survival than with a single radioisotope (^{90}Y-DOTATATE), with a comparable safety profile. The study confirmed preliminary results gathered in 16 patients with NET refractory to conventional therapy[61] .

Bodei et al.[62] performed a Phase 1-2 study to evaluate the efficacy and safety of ^{177}Lu-DOTATATE administered in multiple cycles to patients with unresectable/metastatic somatostatin receptor-positive tumours (mainly NET). Fifty-one patients received escalating doses of ^{177}Lu-DOTATATE (Group 1: 3.7-5.18 GBq/cycle, Group 2: 5.18-7.4 GBq/cycle). Cumulative activities ranged from 3.7 to 29.2 GBq. Partial and complete responses occurred in 15 of 46 (32.6%) assessable patients. The median time to progression was 36 months. Overall survival was 68% at 36 months. ^{177}Lu-DOTATATE was well tolerated up to 29 GBq cumulative activity. The maximum tolerated dose/cycle was not reached.

In another Phase 2 study, Claringbold et al.[63] investigated the efficacy and safety of capecitabine combined with ^{177}Lu-DOTATATE for the treatment of disseminated, progressive, unresectable NET. Enrolled Patients (N = 33) received four cycles of 7.8 GBq ^{177}Lu-DOTATATE at 8-weekly intervals. Chemotherapy with oral 1,650 mg/m^2 capecitabine for 14 consecutive days was commenced in the morning of radionuclide therapy. Cycles of capecitabine were repeated every 8 weeks at the time of each subsequent radiopeptide infusion. Tumour control and stabilisation of disease was obtained in 94% of patients. The addition of capecitabine chemotherapy did not increase the minimal toxicity of ^{177}Lu-DOTATATE radiopeptide therapy. The same group conducted a similar study in which a comparable treatment schedule was applied in patients with advanced NET (N = 35). However, temozolomide was added during the last five days of each capecitabine cycle. The authors conclude that ^{177}Lu-DOTATATE, in combination with capecitabine and temozolomide, was well tolerated and showed substantial tumor control rates[64] .

Sansovini et al.[65] evaluated the efficacy and safety profile of ^{177}Lu-DOTATATE in patients with advanced G1-G2 pancreatic neuroendocrine tumours. Fifty-two consecutive patients were treated at two different therapeutic doses of 18.5 or 27.8 GBq in five cycles, according to the patient's kidney function and bone marrow reserve. Both therapeutic doses resulted in antitumor activity, with 12% complete response, 27% partial response and 46% stable disease in the high-dose group, whereas 4% showed complete response, 15% partial response and 58% stable disease in the low-dose group. No major acute or delayed haematological toxicity were reported. The authors concluded that progression-free survival was significantly longer (p = 0.05) after a total activity of 27.8 GBq.

Van Vliet et al.[66] investigated RECIST, SWOG criteria, modified RECIST (mRECIST) and modified SWOG (mSWOG) criteria in patients with NET treated with ^{177}Lu-DOTATATE. Two-hundred sixty-eight patients were studied. The rates of objective response, stable disease and progressive disease were 28%, 49% and 24%, respectively, according to RECIST; 25%, 49% and 26%, respectively, according to SWOG; 44%, 33% and 24%, respectively, according to mRECIST; and 45%, 29% and 26%, respectively, according to mSWOG. The authors concluded that with all 4 scoring systems, patients with progressive disease had a significantly shorter overall survival than patients with an objective response or stable disease.

In the context of a non-randomised Phase 2 trial in the USA, Delpassand et al. enrolled 37 patients with grade 1 and grade 2 disseminated and progressive gastro-entero-pancreatic NET. Repeated cycles of radiotherapy were administered. In each cycle, patients received 7.4 GBq of ^{177}Lu-DOTATATE via i.v. infusion

up to a cumulative dose of 29.6 GBq. Among 32 evaluable patients, partial response and minimal response to treatment were seen in 28% and 3%, respectively, and stable disease was observed in 41% of patients. In total, 28% had progressive disease. The authors concluded that a response to treatment was significantly associated with lower burden of disease in the liver. Moreover, no significant acute or delayed hematologic or kidney toxicity was observed.

Other uses of ^{177}Lu-DOTATATE

^{177}Lu also emits low-energy γ-rays which allow direct imaging and dosimetry after therapy[67, 68]. Based on a study in 39 patients with metastatic NET, it has also been suggested that pre-treatment dosimetry is possible with ^{177}Lu-DOTATATE, giving the opportunity to tailor therapies more accurately[69].

^{177}Lu as a radiopharmaceutical to treat painful bone metastases

Ethylene diamine tetra methylene phosphonic acid (EDTMP) forms stable complexes with various radiometals and these EDTMP-radiometal complexes concentrate in the skeleton in proportion to osteoblastic activity[70].

Yuan et al.[72] conducted a Phase 2 study with ^{177}Lu-labelled EDTMP to assess its efficacy and safety in the palliative treatment of bone pain in patients with breast cancer and hormone refractory prostate cancer with bone metastases. Sixteen patients were enrolled in the trial and were subsequently divided into two groups, the low-dose group (1.295 GBq) and the high dose group (2.59 GBq). An obvious reduction in the mean pain score was observed at 2 to 6 weeks after the administration of ^{177}Lu-EDTMP. The rate of complete responses in bone pain palliation was 55% in Group 1 and 80% in Group 2 at 6 weeks after treatment. The authors conclude that doses as high as 2.59 GBq were well tolerated and that the study indicate that ^{177}Lu-EDTMP is an effective and safe treatment for palliation of metastatic bone pain in patients with prostate or breast cancer.

Shinto et al.[71] also evaluated the potential of ^{177}Lu-EDTMP for palliation of metastatic bone pain. Ten patients with disseminated skeletal metastases received a single bolus infusion of ^{177}Lu-EDTMP (3.7 GBq). A significant reduction in the mean pain score was noted in all patients. The initial mean pain score of 8.44 dropped to 5.73 within 1 month of treatment. The toxicity of the agent was assessed by analysing complete blood counts. None of the patients experienced blood-related toxicity.

In an effort to exploit the potential of other bone-seeking agents for imaging and therapy, ^{177}Lu-labelled complexes of DOTA derivatives (i.e. bisphosphonate monoamide analogues) have been in development[72].

^{177}Lu as a radiopharmaceutical to radiolabel monoclonal antibodies for radioimmunotherapy

For radioimmunotherapy, radionuclides are attached to monoclonal antibodies (or to fragments thereof). In the past, mainly ^{131}I or ^{90}Y were used for that purpose. Recently, it has been suggested that other radionuclides, such as ^{177}Lu, with better physical properties will further improve the safety of this therapy[73].

Radioimmunotherapy combines biologic and radiolytic mechanisms to destroy targeted tumour cells. In addition, the crossfire effect of the β-radiation as well as the bystander effect may kill malignant cells that do not express the target protein or may be poorly vascularised[74]. For the coupling of ^{177}Lu with the antibody, the chelator DOTA is usually used. Some review articles provide evidence for the clinical utility of ^{177}Lu-labelled monoclonal antibodies in targeted *in vivo* radioimmunotherapy[75, 76].

Antibody CC49

CC49 is a murine monoclonal antibody that recognises the tumour-associated glycoprotein 72. An initial Phase 1 study of i.v. ^{177}Lu-labelled CC49 (using the chelator PA-DOTA) in 9 patients with previously treated advanced adenocarcinoma revealed no antitumour response[77] .

In another early Phase 1 study, 12 ovarian cancer patients who failed chemotherapy received intraperitoneal ^{177}Lu-CC49 antibody. One of 8 patients with gross disease had > 50% tumour reduction after therapy, while six progressed and one went off study with stable disease. Of patients with microscopic or occult disease, one relapsed at 10 months and three remained without evidence of disease after 18 months. The maximum tolerated dose (MTD) could not be reached with levels of 0.37, 0.67, 0.93 and 1.11 GBq/m^2. The author concluded that intraperitoneal radioimmunotherapy with ^{177}Lu-CC49 was well tolerated and appears to have anti-tumour activity against chemotherapy-resistant ovarian cancer in the peritoneal cavity[78].

Alvarez et al.[79] conducted a Phase 1-2 study of intraperitoneal ^{177}Lu-CC49 antibody in 27 ovarian cancer patients who failed chemotherapy. One of 13 patients with gross disease had > 50% tumour reduction after therapy. Seven of 9 patients with < 1 cm nodules progressed in ≤ 21 months. Of patients with microscopic or occult disease, one relapsed at 10 months and four of five remained without evidence of disease at > 6 to 35 months. Bone marrow suppression was the dose-limiting toxic effect. The MTD was assessed at 1.67 GBq/m^2.

In a Phase 1 study, Meredith et al.[80] examined the feasibility of combining subcutaneous interferon and intraperitoneal Taxol (paclitaxel) with intraperitoneal ^{177}Lu-CC49. In total, 46 patients with recurrent or persistent ovarian cancer were enrolled. The MTD for ^{177}Lu-CC49 was 1.48 GBq/m^2 when given with interferon + 100 mg/m^2 Taxol. Four of 17 patients with measurable disease had a partial response and 4 of 27 patients with non-measurable disease had progression-free intervals of 18+, 21+, 21+ and 37+ months. The authors concluded that the combination of intraperitoneal Taxol with ^{177}Lu-CC49 and interferon was well tolerated, with bone marrow suppression being the dose-limiting toxicity. The same group analysed data from 92 patients > 5 years after intraperitoneal radionuclide therapy with ^{90}Y- or ^{177}Lu-CC49 to determine prognostic factors. A statistically significant improvement in progression-free survival was noted for less bulky disease and younger age. Dose escalation of radionuclide did not change risk of progression. Therefore, the authors concluded that this therapy may have therapeutic efficacy at modest dose levels[81].

Antibody J591

Prostate-specific membrane antigen (PSMA) is a well-established, prostate cancer-restricted, cell-surface antigen. J591 is a monoclonal de-immunised murine anti-PSMA antibody which has been developed to target the extracellular domain of PSMA. J591 can be used to deliver radioisotopes to prostate cancer cells[82] .

A Phase 1 trial of ^{177}Lu-labelled J591 (up to three doses using the chelator DOTA) was performed in 35 patients with progressing androgen-independent prostate cancer[83, 84]. Biologic activity was seen in 4 patients experiencing ≥ 50% declines in prostate-specific antigen (PSA) levels lasting from 3+ to 8 months. An additional 16 patients (46%) experienced PSA stabilisation for a median of 60 days. The authors concluded that excellent targeting of known sites of prostate cancer metastases was seen. The MTD of ^{177}Lu-J591 was assessed at 2.59 GBq/m^2. Myelosuppression was the dose limiting toxicity. The authors concluded that multiple doses of 1.11 GBq/m^2 were well tolerated.

Antibody cG250 (girentuximab)

The chimeric antibody cG250 (girentuximab) is reactive with carbonic anhydrase IX, a heat-sensitive transmembranous glycoprotein which is ubiquitously expressed in clear cell renal cell carcinoma (ccRCC). Expression in normal tissues is restricted to the gastrointestinal mucosa and gastrointestinal-related structures with much lower expression levels than in ccRCC. Patients with metastatic ccRCC have a dismal prognosis[85].

Stillebroer et al.[88] conducted a Phase 1 radioimmunotherapy study with ^{177}Lu-labelled cG250 (conjugated with DOTA) in 23 patients with progressive metastasized ccRCC. Groups of 3 patients received ^{177}Lu-cG250, starting at a dose level of 1.11 GBq/m^2 with dose increments of 0.37 GBq/m^2 per group. Patients could receive a total of three treatment cycles. The MTD was assessed at 2.405 GBq/m^2 because higher doses resulted in dose-limiting myelotoxicity. Most patients (74%) demonstrated stable disease at 3 months after the first treatment, and 1 patient showed a partial response that lasted for 9 months. Mean growth of target tumour lesions was reduced from 40.4% during the last 3 months before study entry to 5.5% at 3 months after the first treatment cycle. The authors concluded that radioimmunotherapy with ^{177}Lu-cG250 may stabilise previously progressive metastatic ccRCC.

Rituximab

Rituximab, is approved for the treatment of non-Hodgkin lymphoma and it has been shown that DOTA-rituximab (4:1) can be labelled with ^{177}Lu with sufficient stability while the immunoconjugate retains its immunoreactivity[86].

Forrer et al.[87, 88] conducted a Phase 1-2 study with ^{177}Lu-DOTA-rituximab in 31 patients suffering from relapsing follicular, mantle cell or other indolent B-cell lymphomas. To evaluate the MTD, the dosage of the radiopharmaceutical was adjusted according to body surface area. The MTD was assessed at 1.67 GBq/m^2. Thrombocytopenia and leucopenia were the dose-limiting toxicities. Clinical responses were observed at all dose levels and for all lymphoma entities. Some of the responses were durable; the longest follow-up was > 8 years. At time of reporting, 11 patients were alive and 8 patients were disease-free. The authors concluded that ^{177}Lu-DOTA-rituximab treatment was a safe and feasible option for the lymphoma entities investigated.

2.5.3. Discussion on clinical efficacy

No original clinical efficacy studies were conducted by the applicant as information related to clinical efficacy obtained from the precursor alone is not considered relevant in the present case. Information on the clinical utility of the radiopharmaceutical precursor (^{177}Lu) when attached to appropriate carrier molecules was provided.

The Applicant presented relevant and recent published articles to demonstrate the clinical utility of ^{177}Lu in patients with neuroendocrine tumours using ^{177}Lu-labelled somatostatin analogues. The applicant presents recent publications documenting therapeutic effects in neuroendocrine gastro-entero-pancreatic tumours, as well as some very recent studies looking at palliative treatment of bone pain in patients with breast cancer.

For the purpose of this application, it is sufficient that clinical utility in neuroendocrine tumours has been demonstrated. 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.

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.

EndolucinBeta is not to be administered directly to the patient, but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides, vitamins or other substrates.

For more information concerning paediatric use of Lutetium (^{177}Lu)-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled. The European Medicines Agency has waived the obligation to submit the results of the studies with EndolucinBeta in all subsets of the paediatric population on grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. This waiver does however not extend to any therapeutic uses of the product when linked to a carrier molecule (see section 4.2 of the SmPC for information on paediatric use).

2.5.4. Conclusions on the clinical efficacy

It is the view of the CHMP that clinical utility of EndolucinBeta 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 EndolucinBeta as a radiolabel.

2.6. Clinical safety

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

The safety of EndolucinBeta has been considered from two perspectives: safety relating to lutetium itself attached to an appropriate carrier and safety relating to radioactivity.

Patient exposure

The applicant did not provide information on patient exposure.

Radiation protection

Point-source approximation shows that the average dose rate experienced 20 hours after administration of a dose of 7.3 GBq EndolucinBeta labelled radiopharmaceutical (residual radioactivity 1.5 GBq) by a person at 1 meter distance from the patient's body centre with an abdominal radius of 15 cm is 3.5 µSv/h. Doubling the distance to the patient to 2 meters reduces the dose rate by a factor of 4, to 0.9 µSv/h. The same dose in a patient with an abdominal radius of 25 cm yields a dose rate at 1 meter of 2.6 µSv/h. The generally accepted threshold for discharge of the treated patient from the hospital is 20 µSv/hr. In most countries, the exposure limit for hospital staff is set the same as for the general public at 1 mSv/year. When taking the 3.5 µSv/h dose rate as an average, this would allow hospital staff to work approx. 300 hours/year in close vicinity of patients treated with EndolucinBeta labelled radiopharmaceuticals without wearing radiation protection. Of

course, the nuclear medicine staff is expected to wear standard radiation protection. Further precautions with respect to relatives, carers and hospital staff are provided in section 6.6 of the SmPC.

Dosimetry and biodistribution

Dosimetry data on Lutetium (177Lu) chloride n.c.a.

The dosimetry of 177Lu chloride n.c.a. has been assessed in a study in rats (see non-clinical section). Using the animal data collected in the rat biodistribution and dosimetry study, the dosimetry estimates were based on a rat biodistribution study performed according to MIRD pamphlet no.16, and the calculations were performed using the OLINDA 1.1 software package. Time points for measurements were 5 minutes, 1 hour, 12 hours, 2 days, 7 days and 28 days. Propagation for the various age classes was carried out according to Stabin and Siegel[89], using different body phantoms for the various age classes. The resulting estimated organ absorbed radiation doses and effective doses are given in Table 7 below.

The extrapolated data show that after (accidental) injection of $^{177}LuCl_3$ in man, the spleen (5.7 mSv/MBq) and the liver (5.6 mSv/MBq) absorb most of the administered radioactive dose, followed by the osteogenic cells (2.2 mSv/MBq). All other organs absorb less than 1 mSv/MBq each, with the red marrow absorbing 0.59 mSv/MBq, the kidneys 0.37 mSv/MBq, the adrenals 0.21 mSv/MBq, and the remainder ≤ 0.1 mSv/MBq each. Overall, the absorbed radiation doses increase with decreasing age, as with any radionuclide. The total effective dose is 0.534 mSv/MBq in a 73.7 kg adult, increasing to 3.88 mSv/MBq in a 9.7 kg one-year-old. Thus, with accidental injection of for example one GBq $^{177}LuCl_3$ (each vial delivered contains an activity ranging from 3 to 150 GBq), the total effective dose would be 0.53 Sv for an adult, which could be associated with first clinical signs of radiation toxicity, such as nausea and fatigue[90]. From the dosimetry **Table 5**, the lowest dose of 0.3 GBq administered accidentally would result in radiation toxicity to individual organs.

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

Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation is 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 a Lutetium (^{177}Lu)-labelled medicinal product or resulting from an accidental intravenous injection of EndolucinBeta.

Table 4: Estimated organ absorbed radiation doses and effective doses (mSv/MBq) after intravenous administration of 177LuCl3 for various human age classes, based on data collected in rats (n=24)

Absorbed dose per unit radioactivity administered (mSv/MBq)					
Organ	**Adult 73.7 kg**	**15 years old 56.8 kg**	**10 years old 33.2 kg**	**5 years old 19.8 kg**	**1 year old 9.7 kg**
Adrenals	0.2130	0.3070	0.4450	6.0400	0.9120
Brain	0.0056	0.0068	0.0089	1.3500	0.0197
Breasts	0.0107	0.0134	0.0239	0.0377	0.0697
Gallbladder Wall	0.1090	0.1240	0.1610	0.2530	0.4500
LLI Wall	0.0104	0.0097	0.0167	0.0292	0.0522
Small Intestine	0.1090	0.0244	0.0434	0.0731	0.1260
Stomach Wall	0.0556	0.0381	0.0648	0.1040	0.1860
ULI Wall	0.0297	0.0334	0.0609	0.1050	0.1830
Heart Wall	0.0415	0.0535	0.0805	0.1190	0.2090
Kidneys	0.3720	0.4490	0.6460	0.956	1.7200
Liver	5.5600	7.5600	11.900	17.900	35.700
Lungs	0.0574	0.0808	0.1140	0.1720	0.3230
Muscle	0.0143	0.0180	0.0260	0.0386	0.0697
Ovaries	0.0106	0.0129	0.0224	0.0379	0.0709
Pancreas	0.0663	0.0818	0.1250	0.1900	0.3050
Red Marrow	0.5910	0.6670	1.2300	2.6200	6.6000
Osteogenic Cells	2.1500	2.8100	4.5900	7.8000	18.800
Skin	0.0073	0.0091	0.0140	0.0217	0.0412
Spleen	5.7300	8.5000	13.500	21.600	40.700
Testes	0.0022	0.0029	0.0049	0.0088	0.0188
Thymus	0.0102	0.0128	0.0179	0.0276	0.0469
Thyroid	0.0058	0.0075	0.0113	0.0206	0.0377
Urinary Bladder Wall	0.0043	0.0056	0.0116	0.0247	0.0435
Uterus	0.0085	0.0102	0.0184	0.0331	0.0635
Rest of Body	0.2330	0.2990	0.5060	0.8380	1.6900
Effective Dose (mSv/MBq)	**0.534**	**0.721**	**1.160**	**1.88**	**3.88**

The effective dose to a 73.7 kg adult resulting from an inadvertently injected intravenous activity of 1 GBq would be 534 mSv.

Radioimmunotherapy of Neuroendocrine tumours

Currently the primary clinical use of ^{177}Lu is the treatment of neuroendocrine tumours, targeting the somatostatin receptor (SSTR) subtype 2 with somatostatin analogues, which are ^{177}Lu labelled, using DOTA and derivatives of DOTA as chelating agents . Different peptide ligands have been tried, starting with octreotide, which was later replaced with [Tyr^3]octreotide, a ligand with higher selectivity to the SSTR subtype 2. This ligand binds to the SSTR subtype 2, but also to subtype 3 and 5. The selective binding is

associated with a high affinity for SSTR-expressing tissues, including SSTR-positive tumours, with very little uptake in other tissues (except kidneys). The coupling with ^{177}Lu results in a high exposure of the tumour tissue to energy primarily from the β-decay, sparing the surrounding tissue due to the low penetration depth of about 2 mm.

Adverse events

Safety of ^{177}Lu-based PRRT

Adequate dosimetry is mandatory for effective and safe PRRT and dose-limiting organs are usually either the kidneys or the bone marrow[91].

After PRRT with ^{177}Lu-DOTATATE, the radioactivity concentration in the bone marrow is identical to that in the blood with no significant binding of the radiopharmaceutical to bone marrow precursor stem cells. An individual calculation of the bone marrow absorbed dose is necessary due to high between-patient variability.

The kidneys are critical organs in PRRT because somatostatin analogues are mainly excreted renally. After being filtered by glomeruli, radiopeptides are reabsorbed and retained from the proximal tubule; renal toxicity occurs because of irradiation of the radiosensitive glomeruli by activity retained in the relatively radioresistant tubular cells. The radiation dose to the kidneys may pose an important limit to the amount of radioactivity that can be administered safely[92] . Hence, there is the need for kidney protection when PRRT (e.g. with ^{177}Lu-DOTATOC, ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC) is applied in patients with somatostatin receptor-positive tumours. Most centres therefore combine the treatment with some form of amino acid infusion to inhibit tubular reabsorption of the radiopeptide.

Renal function loss and even end-stage renal disease have been reported after PRRT with ^{90}Y-DOTATOC[93] . The range of beta particles (β-) from ^{90}Y is maximally 12 mm which is long enough to reach the glomeruli; however, the range of the ^{177}Lu-electrons is shorter (approximately 2 mm) which causes a lower average decline in creatinine clearance compared to patients treated with ^{90}Y-labelled carriers. In a study performed by Valkema et al., the median decline in creatinine clearance was 7.3% per year in patients treated with ^{90}Y-DOTATOC and 3.8% per year in patients treated with ^{177}Lu-DOTATATE ($p = 0.06$). Other studies did also suggest that ^{177}Lu-DOTATATE is less toxic to the kidneys than ^{90}Y-DOTATOC[94].

Studies showed that ^{177}Lu-DOTATOC could be less toxic to the kidneys than ^{177}Lu-DOTATATE[,] , both compounds have been assessed as safe radiopharmaceuticals with regard to renal toxicity.

The complete side effect profile of a maximum injected activity of 7.4 GBq per cycle of ^{177}Lu-DOTATATE was analysed in a large cohort of 504 patients with gastro-entero-pancreatic NET (1,772 treatments between January 2000 to August 2006). Acute side effects occurring within 24 hours after the administration of the radiopeptide were nausea after 25% of administrations, vomiting after 10%, and abdominal discomfort or pain after 10%. Acute haematological toxicity was often mild and transient with grade 3 or 4 toxicity (WHO criteria) in 3.6% of administrations calculated on a per-cycle basis or 9.5% of patients on a per-patient basis (at least one of several cycles). Temporary mild hair loss occurred in 62% of patients but alopecia was rare. Serious delayed adverse events that were likely attributable to treatment were myelodysplastic syndrome in 3 patients, and temporary, non-fatal liver toxicity in 2 patients. In 6 patients (approximately 1%) with highly hormonally active NET, a hormone-related crisis occurred after administration due to massive release of bioactive substances. With adequate treatment, all patients eventually recovered[95]. In the other studies with ^{177}Lu-DOTATATE, no major acute or delayed renal or haematological toxicity was observed[,] . In one of these

studies, the occurrence of nausea and vomiting was attributed to the co-administration of hyperosmolar solution of amino acids because the symptoms subsided shortly after completion of therapy.

Safety of ^{177}Lu-based Radioimmunotherapy

Preliminary data from various clinical studies (mainly Phase 1) with ^{177}Lu-labelled monoclonal antibodies suggest that the grade of toxicity was dose-dependent as demonstrated in dose escalating studies[79, 79, 83, 84, 85, 87].

For certain ^{177}Lu-labelled antibodies (e.g. 177Lu-J591), the liver, spleen or kidney might be critical organs based on radiation dosimetry estimates[96]. In the same population, myelotoxicity after treatment with ^{177}Lu-J591 could be predicted on the basis of the amount of radioactive dose administered. The cross-fire effect of high-energy β^--particles within the bone and the marrow may deliver radiation doses non-uniformly[97].

No local reactions were observed in humans, healthy volunteers and patients suffering from advanced anthraco-silicosis or sarcoidosis, given intradermal injection of hafnium oxychloride. The study was specifically designed to evaluate whether hafnium (and other metal salts) could induce local persistent tissue reactions, and therefore patients were evaluated for up to nine months. In none of the patients administered intradermal hafnium oxychloride, a tissue reaction was observed[98].

Serious adverse event / deaths / other significant events

No death has resulted from the administration of any ligand radiolabeled with ^{177}Lu up to now. A study has shown that myelodysplastic syndrome is a rare but serious complication of treatment with ^{177}Lu-DOTATATE.

In most articles describing the use of i.v. ^{177}Lu-DOTATOC, no serious adverse effects, including kidney toxicity, were reported[,]. In one large study (910 patients received 1,804 cycles of ^{90}Y-DOTATOC and 141 patients received 259 cycles of ^{177}Lu-DOTATOC), the rate of severe transient haematotoxicities was lower after ^{177}Lu-DOTATOC treatment compared with ^{90}Y-DOTATOC (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).

Laboratory findings

A study in 47 patients with NET showed a significant decrease in mean serum calcium levels after treatment with ^{177}Lu-DOTATATE, resulting in mild hypocalcaemia in about 20% of patients. It was concluded that serum calcium levels should be monitored after PRRT. Sierra et al.[99] reported that lymphocyte toxicity in PRRT is mainly due to the selective targeting of B-cells. The drop in B-cells was more pronounced with ^{90}Y-DOTATOC than after ^{177}Lu-DOTATATE administration.

Safety in special populations

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

The handling of ^{177}Lu-labelled pharmaceuticals implies an increase of the personnel exposure. One study evaluated the skin equivalent doses during ^{177}Lu-DOTATOC labelling and administration. The authors concluded that the use of appropriate protection devices and procedures allows the observance of generally accepted dose limits for exposed workers[100].

Safety related to drug-drug interactions and other interactions

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

Capecitabine chemotherapy did not increase the minimal toxicity of ^{177}Lu-DOTATATE radiopeptide therapy; neither did the addition of capecitabine and temozolomide[101].

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

The results from published experience with ^{177}Lu-labelled carrier molecules clearly support the overall clinical safety of ^{177}Lu in targeted *in vivo* radiotherapy.

The safety profiles of ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC in PRRT are well documented.

The results from published clinical experience with ^{177}Lu-labelled carrier molecules such as ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC suggest that ^{177}Lu can be well tolerated and adverse drug reactions are manageable in patients receiving the targeted radiotherapy. The dose-limiting organs upon ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC therapy are usually either the kidneys or the bone marrow. If kidney protective agents are used, renal adverse effects are usually mild. Most frequent acute adverse effects include nausea, vomiting and abdominal discomfort/pain which can be controlled by supportive measures. Other, usually reversible, side effects are bone marrow depression and impaired renal function. Hormonal crises occur infrequently.

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

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. The risk has been included as an important potential risk in the RMP. There is the potential risk identified of the development of osteosarcoma as ^{177}Lu is taken up and accumulated in the bones.

Extrapolation of animal data to man suggest that after accidental injection of Lutetium (^{177}Lu) chloride n.c.a. ITG, the highest absorption is to be expected is in the spleen (5.7 mSv/MBq) and the liver (5.6 mSv/MBq), followed by the osteogenic cells (2.2 mSv/MBq). The total effective dose would be 0.534 mSv/MBq in a 73.3 kg adult. All other organs absorb less than 1 mSv/MBq. Accidental injection of one GBq $^{177}LuCl_3$ in an adult, given the total effective dose would be 0.53 mSv/MBq for an adult, could result in the first clinical sign of radiation toxicity (nausea and fatigue). In a 5 year old, this would result in severe radiation toxicity and in a one year might be fatal were the total effect dose increases to 3.88 mSv/MBq – the absorbed radiation doses increase with decreasing age. However, $^{177}LuCl_3$ is for in vitro labelling only and is not to be administered directly, so this data reflects at best a very worst case scenario. 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.

Renal impairment and bone marrow compromise: Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. It is recommended to perform individual radiation dosimetry assessments of specific organs, which may not be the target organ of therapy.

When an administration of radiopharmaceuticals 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. As a result, developmental toxicity including reproductive toxicity is included as an important identified risk in the RMP.

Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, 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.

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.

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

The presence of free Lutetium (^{177}Lu) chloride in the body after an inadvertent administration of EndolucinBeta will lead to increased bone marrow toxicity and haematopoietic stem cell damage. Therefore, in case of an inadvertent administration of EndolucinBeta, the radiotoxicity for the patient must be reduced by immediate (i. e. within 1 hour) administration of preparations containing chelators like Ca-DTPA or Ca-EDTA in order to increase the elimination of the radionuclide from the body.

The following preparations must be available in medical institutions, which use EndolucinBeta for labelling of carrier molecules for therapeutic purposes:

- Ca-DTPA (Trisodium calcium diethylenetriaminepentaacetate) or

- Ca-EDTA (Calcium disodium ethylenediaminetetraacetate)

These chelating agents help with the elimination of Lutetium (^{177}Lu) radiotoxicity by an exchange between the calcium ion in the complex and the Lutetium (^{177}Lu) ion. Due to the capacity of the chelating ligands (DTPA, EDTA) of forming water soluble complexes, the complexes and bound Lutetium (^{177}Lu) are rapidly eliminated by the kidneys.

1 g of the chelating agents should be administered by slow intravenous injection over 3 – 4 minutes or by infusion (1 g in 100 – 250 mL of glucose, or sodium chloride 9 mg/mL (0.9%) solution for injection).

The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of chelator with reduced efficiency. Intravenous administration should not be protracted over more than 2 hours.

In any case, the blood parameters of the patient have to be monitored and the appropriate actions immediately taken if there is evidence of radiotoxicity.

The toxicity of free Lutetium (^{177}Lu) due to in-vivo release from the labelled biomolecule in the body during therapy could be reduced by post-administration of chelating agents.

Radiolabelling of medicinal products, such as monoclonal antibodies, peptides, vitamins 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 minimise 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.

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 instructions on extemporary preparation of the medicinal product before administration, 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 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 Lutetium (^{177}Lu)-labelled radiopharmaceuticals. The use of television monitor systems to monitor the patients is recommended. Given the long half-life of Lutetium (^{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 resulting from repeated exposition 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 medicinal product or waste material must be disposed of in accordance with local requirements.

Before use, packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber. Medication errors associated with preparation and procedures has been included as an important potential risk in the RMP.

Lutetium (^{177}Lu) is a beta(-)/gamma emitter. Activity measurements using an ionization chamber are very sensitive to geometric factors and therefore should be performed only under geometric conditions which have been appropriately validated.

Usual precautions regarding sterility and radioactivity should be respected.

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product should not be used.

The complexing agent and other reagents should be added to the vial with Lutetium (^{177}Lu)chloride. Free Lutetium (^{177}Lu) is taken up and accumulates in the bones. This could potentially result in osteosarcomas. It is recommended to add a binding agent such as DTPA prior to intravenous administration of Lutetium (^{177}Lu)-labelled conjugates in order to form a complex with free Lutetium (^{177}Lu), if present, leading to a rapid renal clearance of Lutetium (^{177}Lu).

Adequate quality control of the radiochemical purity of ready to use radiopharmaceuticals gained after radiolabelling with EndolucinBeta should be assured. Limits for radiochemical impurities should be set recognising the radiotoxicological potential of Lutetium-177. Free non-bound Lutetium-177 should be consequently minimised.

There is a contraindication for hypersensitivity to the active substance or to any of the excipients listed in section 6.1. and established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6). For information on contraindications to particular Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with EndolucinBeta, refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

2.6.2. Conclusions on the clinical safety

The safety of EndolucinBeta can be considered as those relating to the radioactivity of the product and those related to free lutetium. As EndolucinBeta 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 EndolucinBeta has been adequately addressed.

2.7. Risk Management Plan

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 procedures Osteosarcoma
Missing information	None

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

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Radiotoxicity including occupational exposure and inadvertent exposure	Warnings in section 6.6 of the SmPC as per Core SmPC for radiopharmaceuticals. Instructions on handling are given in section 12 of the SmPC. Instructions on the storage in original lead shielding are given in section 6.4 SmPC. Warning in section 4.1 of the SmPC: “EndolucinBeta is a radiopharmaceutical precursor, and it is not intended for direct use in patients.” Corresponding wording in section 4.2 of the SmPC: “Method of administration EndolucinBeta is intended for in vitro radiolabelling of medicinal products which are subsequently administered by the approved route. EndolucinBeta should not be administered directly to the patient.”Special warnings regarding radiolabelling, radiological safety including gamma dose constant have been	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	made in section 4.4 and 6.6 of the SmPC.	
Developmental toxicity including reproductive toxicity	Contraindication in section 4.3 of the SmPC: "- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6)" Corresponding wording in section 4.6 of the SmPC. "Pregnancy Lutetium (177Lu)-labelled medicinal products are contraindicated in established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3)."Special warning on undesirable effects in section 4.8 of the SmPC: "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."	Not applicable.
Medication errors associated with preparation and procedures	Warning in section 4.1 of the SmPC: "EndolucinBeta is a radiopharmaceutical precursor, and it is not intended for direct use in patients." "Method of administration EndolucinBetais intended for in vitro radiolabelling of medicinal products which are subsequently administered by the approved route. EndolucinBeta should not be administered directly to the patient." Special warnings regarding radiolabelling, radiological safety including gamma dose constant have been made in section 4.4 and 6.6 of the SmPC.	Not applicable.
Osteosarcoma	Special warning on undesirable effects in section 4.8 of the SmPC: "Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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."	

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.

Conclusion

The CHMP and PRAC considered that the risk management plan version 02 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. 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.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group accepted to omit the pharmaceutical form as well as the statement "For administration after *in vitro* radiolabelling" from the vial label based on space constraints. This decision was based on the fact that the vial is only to be removed from the lead pot (these particulars appear on the lead pot label) right before administration.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, EndolucinBeta (lutetium (^{177}Lu) chloride) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

EndolucinBeta 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, EndolucinBeta is not intended to be given directly to patients.

A review of the literature was performed in order to document the clinical utility of ^{177}Lu. The clinical utility of ^{177}Lu has been demonstrated in the management of patients with gastroenteropancreatic neuroendocrine tumours (GEP-NET).

Uncertainty in the knowledge about the beneficial effects

None.

Risks

Unfavourable effects

There are no major safety concerns with regards to free ^{177}Lu as the doses of EndolucinBeta 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 EndolucinBeta as well as on the carrier molecule to which EndolucinBeta is labelled. ^{177}Lu-DOTATOC and ^{177}Lu-DOTATATE are well tolerated in PRRT with low risk of toxicity, if adequate kidney protective measures are applied and dose limits are respected. The dose-limiting organs are usually the kidneys or the bone marrow.

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 EndolucinBeta in its use as radiopharmaceutical precursor has been adequately addressed in the product information.

Uncertainty in the knowledge about the unfavourable effects

Toxicity of free ^{177}Lu due to in-vivo release from the labelled biomolecule in the body during therapy could occur. ^{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

No clinical studies have been performed as benefit and efficacy will be determined by the safety and efficacy of the compounds with the carrier molecules (peptides, antibodies) which have been specifically developed and authorised for radiolabelling with this radionuclide. Clinical utility of ^{177}Lu in particular in neuroendocrine tumours has been demonstrated. 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

The clinical utility of EndolucinBeta 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. There are no unresolved issues, which would have a negative impact on the benefit/risk balance of the product.

Discussion on the benefit-risk balance

EndolucinBeta 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 ^{177}Lu will be assessed independently when it is added to a carrier molecule. For the purpose of an application for a radiopharmaceutical for radiolabelling, the clinical utility and the safety of EndolucinBeta 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 EndolucinBeta 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

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, non-clinical and clinical properties of the active substance, the CHMP considers that ^{177}Lu (EndolucinBeta) is not qualified as a new active substance as it does not differ significantly in properties with regard to safety and efficacy from the previously authorised substance.

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