ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EndolucinBeta 40 GBq/mL radiopharmaceutical precursor, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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).
The ART is 12:00 pm (noon) on the scheduled day of radiolabelling as indicated by the customer and can be within 0 to 7 days starting from the day of manufacture.

Each 2 mL vial contains an activity ranging from 3 – 80 GBq, corresponding to 0.73 – 19 micrograms of Lutetium (^{177}Lu), at ART. The volume is 0.075 – 2 mL.

Each 10 mL vial contains an activity ranging from 8 – 150 GBq, corresponding to 1.9 – 36 micrograms of Lutetium (^{177}Lu), at ART. The volume is 0.075 – 3.75 mL.

The theoretical specific activity is 4,110 GBq/mg of Lutetium (^{177}Lu). The specific activity of the medicinal product at ART is indicated on the label and always greater than 3,000 GBq/mg.

Non carrier added (n.c.a.) Lutetium (^{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} $cm^{-2}s^{-1}$. The following nuclear reaction is ongoing in the irradiation:

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

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

Lutetium (^{177}Lu) decays by emission of beta radiation to stable Hafnium (^{177}Hf).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Radiopharmaceutical precursor, solution. Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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

Posology

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.

Paediatric population

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.

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.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

4.4 Special warnings and precautions for use

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required

therapeutic effect.
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.

Renal impairment and haematological disorders

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.

Cases of myelodysplastic syndrome and acute myeloid leukaemia have been reported following Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.

Myelosuppression

Anaemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with Lutetium (^{177}Lu). Most events are mild and transient. In some patients more than one cell line may be affected. A blood count should be taken at baseline and monitored regularly during treatment, in accordance with clinical guidance.

Renal irradiation

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

Radiation protection

Point-source approximation shows that the average dose rate experienced 20 hours after administration of a dose of 7.3 GBq EndolucinBeta labeled 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/h. In most countries, the exposure limit for hospital staff is set the same as for the general public at 1 mSv/year. When taking the 3.5 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 labeled radiopharmaceuticals without wearing radiation protection. Of course, the nuclear medicine staff is expected to wear standard radiation protection.
Any other person in close vicinity of the treated patient should be informed about possibilities to reduce his/her exposure due to radiation emitted from the patient.

Specific warnings

For information concerning special warnings and special precautions for use of Lutetium (177Lu)-labelled medicinal products refer also to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

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

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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.

Pregnancy

The use of lutetium (^{177}Lu)-labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk of ionizing radiation to the foetus (see section 4.3).

Breast-feeding

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.

Fertility

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

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

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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.

Adverse reactions are divided into groups according to the MedDRA convention frequencies: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Blood and lymphatic system disorders

very common: Anaemia, thrombocytopenia, leukopenia and lymphopenia

Description of selected adverse reactions:

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

Reporting of suspected adverse reactions

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

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: not yet assigned.

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.

Lutetium (^{177}Lu) emits β-particles of moderate maximum energy (0.498 MeV) with a maximum tissue penetration of approximately 2 mm. Lutetium (^{177}Lu) also emits low-energy γ-rays which allow scintigraphic, biodistribution and dosimetry studies with the same Lutetium (^{177}Lu)-labelled medicinal products.

Paediatric population

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 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic 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.

Distribution after inadvertent intravenous administration of Lutetium (^{177}Lu) chloride

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. Lutetium (^{177}Lu) chloride distributes mainly tothe 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.
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.

5.3 Preclinical safety data

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 LD50 in mice was found to be approximately 315 mg/kg. In cats, no pharmacological effects on respiration and cardiovascular function were observed up to a cumulative intravenous dose of 10 mg/kg. A high dose of 10 GBq of ^{177}Lu-chloride contains 2.4 µg Lutetium, corresponding to a human dose of 0.034 µg/kg. This dose is approximately 7 orders of magnitude lower than the intraperitoneal LD50 in mice and more than 5 orders of magnitude lower than the NOEL observed in cats. Therefore, Lutetium metal-ion toxicity of EndolucinBeta (^{177}Lu)-labelled medicinal products can be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid solution

6.2 Incompatibilities

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.

6.3 Shelf life

Up to 9 days from the date of manufacture.

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

6.4 Special precautions for storage

Store in the original package in order to avoid unnecessary radiation exposure.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Colourless type I glass 2 mL or 10 mL vial with a V-shaped and flat bottom, respectively, with a bromobutyl stopper, closed with an aluminium seal.

The vials are placed into a lead container for protective shielding and packed in a metallic can and an outer carton.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

EndolucinBeta is not intended for direct use in patients.

<u>General warning</u>

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.

7. MARKETING AUTHORISATION HOLDER

ITG Isotope Technologies Garching GmbH
Lichtenbergstrasse 1
D-85748 Garching
Germany

8. MARKETING AUTHORISATION NUMBER(S)

2 mL vial: EU/1/16/1105/001
10 mL vial: EU/1/16/1105/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 July 2016

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

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.

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.

Table 2: Estimated organ absorbed radiation doses and effective doses (mSv/MBq) after inadvertent intravenous administration of ^{177}LuCl3 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.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Before use, packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber.

Lutetium (^{177}Lu) is a 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.

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

ITG Isotope Technologies Garching GmbH
Lichtenbergstrasse 1
Garching b. Muenchen
Bayern, 85748
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

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

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

D. 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

METALLIC CAN and OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

EndolucinBeta 40 GBq/mL radiopharmaceutical precursor, solution
Lutetium (^{177}Lu) chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL of solution contains 40 GBq of Lutetium (^{177}Lu) chloride at activity reference time (ART).

3. LIST OF EXCIPIENTS

Excipient: Hydrochloric acid solution

4. PHARMACEUTICAL FORM AND CONTENTS

Radiopharmaceutical precursor, solution.

VOLUME: …mL
ACTIVITY: …GBq/vial at ART ART: {DD/MM/YYYY 12:00 CET }
Specific activity: …GBq/mg at ART

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For administration after *in vitro* radiolabelling.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {DD/MM/YYYY, hh:00 CET}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to avoid unnecessary radiation exposure.

Storage should be in accordance with local regulations for radioactive substances.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ITG Isotope Technologies Garching
GmbH D-85748 Garching/Germany

12. MARKETING AUTHORISATION NUMBER(S)

2 mL vial: EU/1/16/1105/001
10 mL vial: EU/1/16/1105/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LEAD POT

1. NAME OF THE MEDICINAL PRODUCT

EndolucinBeta 40 GBq/mL radiopharmaceutical precursor, solution
Lutetium (^{177}Lu) chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL of solution contains 40 GBq of Lutetium (^{177}Lu) chloride at activity reference time (ART).

3. LIST OF EXCIPIENTS

Excipient: Hydrochloric acid solution

4. PHARMACEUTICAL FORM AND CONTENTS

Radiopharmaceutical precursor, solution.

VOLUME: …mL
ACTIVITY: …GBq/vial at ART ART: {DD/MM/YYYY 12:00 CET }
Specific activity: …GBq/mg at ART

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For administration after *in vitro* radiolabelling.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {DD/MM/YYYY, hh:00 CET}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to avoid unnecessary radiation exposure.

Storage should be in accordance with local regulations for radioactive substances.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ITG Isotope Technologies Garching GmbH
D-85748 Garching/Germany

12. MARKETING AUTHORISATION NUMBER(S)

2 mL vial: EU/1/16/1105/001
10 mL vial: EU/1/16/1105/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL (2 mL, 10 mL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

EndolucinBeta 40 GBq/mL

Lutetium (^{177}Lu) chloride

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:{DD/MM/YYYY, hh:00 CET}

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

VOLUME: …mL
ACTIVITY: …GBq/vial ART: {DD/MM/YYYY 12:00 CET }

6. OTHER

ITG Isotope Technologies Garching GmbH
D-85748 Garching
Germany

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

EndolucinBeta 40 GBq/mL radiopharmaceutical precursor, solution
Lutetium (^{177}Lu) chloride

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given the medicine combined with EndolucinBeta because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise the procedure.
- If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EndolucinBeta is and what it is used for

EndolucinBeta is not a medicine and it is not intended to be used on its own. It has to be used in combination with other medicines (carrier medicines).

EndolucinBeta is a type of product called a radiopharmaceutical precursor. It contains the active substance Lutetium (^{177}Lu) chloride which gives off beta-radiation, allowing a localised radiation effect. This radiation is used to treat certain diseases.

EndolucinBeta has to be combined with a carrier medicine in a process called radiolabelling before administration. The carrier medicine then takes the EndolucinBeta to the disease site in the body.

These carrier medicines have been specially developed for use with Lutetium (^{177}Lu) chloride and may be substances that have been designed to recognise a particular type of cell in the body.

The use of a medicine radiolabelled with EndolucinBeta does involve exposure to radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

Please refer to the package leaflet of the medicine that is to be radiolabelled with EndolucinBeta.

2. What you need to know before the medicine radiolabelled with EndolucinBeta is used

The medicine radiolabelled with EndolucinBeta must not be used
- if you are allergic to Lutetium (^{177}Lu) chloride or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or believe you may be pregnant.

Please refer to the package leaflet of the medicine that is to be radiolabelled with EndolucinBeta for additional information.

Warnings and precautions
EndolucinBeta is not to be administered directly to patients.
Take special care with the medicine that is radiolabelled with EndolucinBeta:
- if you have renal impairment or bone marrow disease.

Treatment with Lutetium (^{177}Lu) radioligand therapy may lead to the following side effects
- a reduced number of red blood cells (anaemia)
- a reduced number of platelets in the blood (thrombocytopenia) which are important to stop bleeding
- a reduced number of white blood cells (leukopenia, lymphopenia or neutropenia) which are important for protecting the body against infection

Most of these events are mild and only temporary. Because Lutetium (^{177}Lu) can sometimes affect your blood cells, your doctor will do blood tests before you start and at regular intervals during treatment.

A small number of patients have developed cancers of the bone marrow (myelodysplastic syndrome) and of the blood (leukaemia) following treatment with Lutetium (^{177}Lu) for neuroendocrine tumours. It is unknown whether these cancers were caused by Lutetium (^{177}Lu).

During peptide-receptor radionuclide therapy for neuroendocrine tumours, radiolabelled somatostatin analogues are excreted by the kidneys. Your doctor will therefore take a blood test to measure your kidney function before you start and during treatment.

Please refer to the package leaflet of the medicine that is to be radiolabelled with EndolucinBeta for additional warnings and precautions.

Children and adolescents
EndolucinBeta is not to be used directly in childrens and adolescent patients under 18 years old.

Other medicines and medicines radiolabelled with EndolucinBeta
Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines since they may interfere with the procedure.
It is not known whether Lutetium (^{177}Lu) chloride may interact with other medicines as specific studies have not been carried out.

Pregnancy and breast-feeding
You must inform the nuclear medicine doctor before the administration of medicines radiolabelled with EndolucinBeta if there is a possibility you might be pregnant, if you have missed your period or if you are breast-feeding.

When in doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure.

If you are pregnant
Medicines radiolabelled with EndolucinBeta must not be administered if you are pregnant.

If you are breast-feeding
You will be asked to stop breast-feeding.
Please ask your nuclear medicine doctor when you can resume breast-feeding.

Driving and using machines
There could be effects on your ability to drive and to use machines due to the medicine used in combination with EndolucinBeta. Please read the package leaflet of that medicine carefully.

3. How the medicine radiolabelled with EndolucinBeta is used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Medicines radiolabelled with EndolucinBeta will only be used in special controlled areas. This product will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this product and will keep you informed of their actions.

The nuclear medicine doctor supervising the procedure will decide on the quantity of a medicine radiolabelled with EndolucinBeta to be used in your case. It will be the smallest quantity necessary to achieve the appropriate outcome, depending on the medicine you take with EndolucinBeta and what it is used for.

Administration of the medicine radiolabelled with EndolucinBeta and conduct of the procedure
EndolucinBeta must be used only in combination with another medicine (carrier medicine) which has been specifically developed and authorised for being combined with Lutetium (^{177}Lu) chloride. The administration will depend on the type of the carrier medicine. Please read the package leaflet of that medicine.

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of the medicine radiolabelled with EndolucinBeta, you should
The nuclear medicine doctor will inform you if you need to take any special precautions after receiving the medicine radiolabelled with EndolucinBeta. Contact your nuclear medicine doctor if you have any questions.

If you have been given more medicine radiolabelled with EndolucinBeta than you should
Since the medicine radiolabelled with EndolucinBeta is handled by a nuclear medicine doctor under strictly controlled conditions, there is only a very small chance of possible overdose. However, in the case of an overdose or an inadvertent intravenous injection of the unlabelled product, you will receive appropriate treatment that will remove the radionuclide from the body.

Should you have any further questions on the use of the medicine radiolabelled with EndolucinBeta, ask your nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, the medicine radiolabelled with EndolucinBeta can cause side effects, although not everybody gets them.

Dry mouth has been reported among patients with prostate cancer receiving treatment with Lutetium (^{177}Lu) and has been temporary.

Very common side effects (may affect more than 1 in 10 people):

- Reduction in blood cell counts (platelets, red or white blood cells)

After the medicine radiolablelled with EndolucinBeta is administered, it will deliver certain amounts of ionising radiation (radioactivity) which can induce a certain risk of cancer and development of hereditary defects. In all cases, the risk of the radiation is outweighed by the potential benefit of receiving the radiolabelled medicine.

For more information, refer to the package leaflet of the particular medicinal product to

be radiolabelled.

Reporting of side effects
If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How EndolucinBeta is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

The following information is intended for the specialist only:

Keep this medicine out of the sight and reach of children.

EndolucinBeta must not be used after the expiry date and time which is stated on the label after EXP.
EndolucinBeta will be stored in the original package that provides protection from radiation.

6. Contents of the pack and other information

What EndolucinBeta contains
- The active substance is Lutetium (^{177}Lu) chloride.
  1 mL sterile solution contains 40 GBq Lutetium (^{177}Lu) chloride on the activity reference time (corresponding to 10 micrograms of Lutetium (^{177}Lu) as Lutetium (^{177}Lu) chloride).
  (GBq: GigaBecquerel is the unit in which radioactivity is measured).
- The other ingredient is hydrochloric acid solution.

What EndolucinBeta looks like and contents of the pack
EndolucinBeta is a radiopharmaceutical precursor, solution. It is presented as a clear and colourless solution in a colourless type I glass 2 mL or 10 mL vial with a V-shaped and flat bottom, respectively, with a bromobutyl stopper, closed with an aluminium seal.
Each pack contains 1 vial placed into a lead container for protective shielding and packed in a metallic can and an outer carton.

The volume of one vial ranges from 0.075 – 3.75 mL solution (corresponding to 3 – 150 GBq at activity reference time). The volume depends on the quantity of medicine combined with EndolucinBeta required for administration by the nuclear medicine doctor.

Marketing Authorisation Holder and Manufacturer

ITG Isotope Technologies Garching
GmbH Lichtenbergstrasse 1
D-85748 Garching
Germany
Tel: + 49-89-289 139-08
info@itg-garching.de

This leaflet was last revised in {month YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

The complete SmPC of EndolucinBeta is provided as a separate document in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC.

Annex IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATIONS

Scientific conclusions
Taking into account the PRAC Assessment Report on the PSUR(s) for lutetium isotope of mass 177, the scientific conclusions of CHMP are as follows:

Haematological disorders

Haematological disorders including anaemia, thrombocytopenia and leukopenia have been reported with considerable consistency from a number of studies describing the use of Lutetium 177 - Peptide receptor radionuclide therapy (Lu177-PRRT) for neuroendocrine tumours (NETs) in the pre-authorisation phase. Similarly, in the recent randomised clinical trial NETTER -1 the incidences of any grade of thrombocytopenia, lymphopenia and leucopenia were significantly higher in the Lu177-DOTATE treatment arm than in the control arm. There was also weak evidence of a higher incidence of anaemia in the treatment arm and a non-significant numerical imbalance in the percentage of patients with neutropenia. Haematological disorders are listed as an adverse effect of Lu177 PRRT in several European guidelines on its use. Three cases describing haematotoxicity with Lu177-PRRT for NETs have been received in Eudravigilance. All describe a temporal relationship and a positive rechallenge is suggested in one.

Haematological disorders have also been observed following Lu177 PSMA-targeted therapy for metastatic castrate-resistant prostate cancer (mCPRC). Additionally, the association is biologically plausible based on the known mechanism of action.

Based on the available evidence, the PRAC recommends that the product information for Lu177 should be updated in order to advise prescribers and patients of this issue.

Therapy-related myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)

Therapy-related myeloid neoplasms (t-MNs) were reported in 1-2 % of patients treated with Lu177 PRRT for neuroendocrine tumours in a number of studies conducted prior to authorisation of Lu177. Moreover, recently published analysis of Lu177-DOTATATE in patients with neuroendocrine tumours (Brabander et al 2017) reported cases of myelodysplastic syndrome and acute leukaemia. According to the interim analysis of the NETTER-1 study published earlier this year, there was one case of MDS in the Lu-177 DOTATATE arm.

The MAH has received 3 post-marketing reports of MDS and 1 post-marketing report of AML. An additional bone-marrow examination confirmed case was identified in Eudravigilance in a patient without a history of previous chemo- or radiotherapy, after 4 cycles of Lu177 PRRT for metastatic carcinoid tumour of the ileum.

The potential association with therapy-related myeloid neoplasms is considered to be biologically plausible. Moreover, the effect appears to be rather specific, in that no other type of malignancy has been described. There is also some coherence with what is known about the long-term safety profile of other radiopharmaceuticals such as radioactive iodine. MDS / AML do not yet appear to have been observed during Prostate-specific membrane antigen targeted (PSMA-targeted) radioligand therapy for mCRPC (including that using Lu177). However, the toxicity may not have been observed due to different prognosis of the disease.

Consequently, the PRAC is of the view that healthcare professionals and patients should be advised that cases of MDS / AML have been reported following treatment with Lu177-PRRT for NETs and that a product information update is warranted.

Renal dysfunction

Radiolabelled somatostatin analogues are eliminated by the kidney. Biopsy-confirmed radiation nephropathy with thrombotic microangiopathy has been observed in association with another radioligand, 90Y-DOTATATE, and can lead to chronic kidney disease. Lu177 has a shorter penetration than 90Y, however. Data from the NETTER-1 study did not show evidence of renal

toxicity in association with Lu177 thus far. Moreover, while a small number of relevant post-marketing reports have been received, they are confounded by previous medical history. However, patients in the studies to date including NETTER-1 and in the post-marketing cases have received amino acid infusions. This is in accordance with European clinical guidelines which list radiation nephropathy as a possible adverse effect of radioligand therapy of neuroendocrine tumours and recommend the use of amino acid infusions as renal protection.

Radiation nephropathy does not yet appear to have been observed in the context of PSMA-targeted radioligand therapy for mCRPC.

Taking all the information into consideration, the PRAC considers that the product information should be updated in order to reflect the available evidence and current guidance.

Xerostomia

An association between xerostomia and Lu177 is biologically plausible in the context of Lu177-PSMA radioligand therapy for mCRPC because the salivary glands express PSMA and are radiosensitive organs. A number of dosimetry analyses have observed the salivary glands to be among the organs to receive the highest dose during radioligand therapy for mCRPC. Moreover, an effect on the salivary glands has been observed during radioligand therapy for mCRPC with radioisotopes other than Lu177. According to the summary tabulation, the MAH has not yet received any reports of xerostomia. However, it is considered that as it tends to be mild and transient, under-reporting is likely.

Based on the biologic plausibility and available evidence the PRAC recommends that the Product Information be updated with a reflection of the current evidence.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisations

On the basis of the scientific conclusions for lutetium isotope of mass 177 the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing lutetium isotope of mass 177 is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisations should be varied.