ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 0.2 – 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.

Myelodysplastic syndrome and acute myeloid leukaemia
Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been observed after treatment with Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours (see section 4.8). This should be taken into account when considering the benefit/risk, especially in patients with possible risk factors like prior exposure to chemotherapeutic agents (such as alkylating agents).

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

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 including glomerular filtration rate (GFR) should be assessed at baseline and during treatment and renal protection should be considered, in accordance with clinical guidance of the radiolabelled medicinal product.

Hepatotoxicity

Cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours. Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients.

Hormone release syndromes

There have been reports of carcinoid crisis and other syndromes associated with release of hormones from functional neuroendocrine tumours following Lutetium (^{177}Lu) peptide receptor radionuclide therapy, which may be related to irradiation of tumour cells. Reported symptoms include flushing and diarrhoea associated with hypotension. Observation of patients by overnight hospitalisation should be considered in some cases (e.g. patients with poor pharmacologic control of symptoms). In case of hormonal crises, treatments may include: intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting.

Tumour lysis syndrome

Tumour lysis syndrome has been reported following Lutetium (^{177}Lu) radioligand therapy. Patients with a history of renal insufficiency and high tumour burden may be at greater risk and should be treated with increased caution. Renal function as well as electrolyte balance should be assessed at baseline and during treatment.

Extravasation

There have been reports of extravasation of Lutetium (^{177}Lu)-labelled ligands in the post-marketing setting. In case of extravasation, infusion of the medicinal product should be immediately ceased, and the nuclear medicine physician and the radiopharmacist should be promptly informed. Management should be in accordance with local protocols.

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/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 labelled 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 (^{177}Lu)-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

Female patients of reproductive potential should be advised to use contraception during the treatment with medicines labelled with EndolucinBeta and for 7 months after the last dose.
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.

Men of reproductive potential

Male patients with female partners of reproductive potential should be advised to use barrier method of contraception (e.g., condom) along with another highly effective contraceptive method during the treatment with medicines labelled with EndolucinBeta and for 4 months after the last dose.

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 labelling 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/Package Leaflet 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

Summary of the safety profile

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), not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

MedDRA system organ class	Very common	Common	Uncommon	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (see section 4.4)	Acute myeloid leukaemia (see section 4.4)	

MedDRA system organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders	Anaemia Thrombo-cytopenia Leukopenia Lymphopenia	Neutropenia		Pancytopenia
Endocrine disorders				Carcinoid crisis
Metabolism and nutrition disorders				Tumour lysis syndrome
Gastrointestinal disorders	Nausea Vomiting			Dry mouth
Skin and subcutaneous tissue disorders	Alopecia			

Description of selected adverse reactions

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

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

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.

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10X

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 medicinal 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 h post dose. Lutetium (^{177}Lu) chloride distributes mainly 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 h. For the next 28 days, further uptake of Lutetium (^{177}Lu) can be observed in the bone, which is compensated in part by radioactive decay. Taking into account the radioactive half-life of Lutetium (^{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 Lutetium (^{177}Lu)-chloride contains 2.4 µg Lutetium, corresponding to a human dose of 0.034 µg/kg. This dose is approximately 7 orders of magnitude lower than the intraperitoneal LD50 in mice and more than 5 orders of magnitude lower than the NOEL observed in cats. Therefore, Lutetium metal-ion toxicity of EndolucinBeta-labelled medicinal products can be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid, diluted

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.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

EndolucinBeta is not intended for direct use in patients.

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

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

If at any time in the preparation of this medicinal 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

ITM Medical Isotopes GmbH
Lichtenbergstrasse 1
85748 Garching/Munich
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: 06 July 2016
Date of latest renewal: 08 February 2021

10. DATE OF REVISION OF THE TEXT

MM/YYYY

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 $^{177}LuCl_3$ 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
Lower large intestine 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
Upper large intestine 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

Organ	Absorbed dose per unit radioactivity administered (mSv/MBq)				
	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)**
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 medicinal 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}Lu). Free non-bound Lutetium (^{177}Lu) should be consequently minimised.

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

ITM Medical Isotopes 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 (PSURs)**

The requirements for submission of PSURs 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.

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

Hydrochloric acid, diluted

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.

Store 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

ITM Medical Isotopes GmbH
85748 Garching/Munich, 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

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

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

Hydrochloric acid, diluted

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.

Store 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

ITM Medical Isotopes GmbH
85748 Garching/Munich, 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

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

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



ITM Medical Isotopes GmbH
85748 Garching/Munich
Germany

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

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
2. What you need to know before the medicine radiolabelled with EndolucinBeta is used
3. How the medicine radiolabelled with EndolucinBeta is used
4. Possible side effects
5. How EndolucinBeta is stored
6. Contents of the pack and other information

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) 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. A reduced number of all 3 types of blood cells (red blood cells, platelets, and white blood cells - pancytopenia), requiring treatment discontinuation has been described in some patients.

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. Talk to your doctor if you experience shortness of breath, bruising, nose bleeds, bleeding from your gums, or if you develop a fever.

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.

Treatment with Lutetium (^{177}Lu) may cause disturbances of liver function. Your doctor will take a blood test to monitor your liver function during treatment.

Lutetium (^{177}Lu)-labelled medicines may be administered directly into your vein through a tube known as a cannula. There have been reports of leakage of the fluid into the surrounding tissue (extravasation). Tell your doctor if you experience any swelling or pain in your arm.

After neuroendocrine tumours are treated with Lutetium (^{177}Lu), patients may experience symptoms associated with release of hormones from the tumour cells, known as a carcinoid crisis. Tell your doctor if you feel faint or dizzy or experience flushing or diarrhoea following your treatment.

Treatment with Lutetium (^{177}Lu) may cause tumour lysis syndrome, due to the rapid breakdown of tumour cells. This may result in abnormal blood test results, irregular heartbeat, kidney failure or seizures within a week of treatment. Your doctor will perform blood tests to monitor you for this syndrome. Tell your doctor if you have muscle cramping, muscle weakness, confusion, or shortness of breath.

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 children 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 a female patient who can get pregnant
You should use effective birth control during treatment with medicines labelled with EndolucinBeta and for 7 months after completing the treatment.

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.

If you are a male patient
You should use effective birth control during treatment with medicines labelled with EndolucinBeta and for 4 months after completing the treatment.

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 radiopharmaceuticals. Medicines radiolabelled with EndolucinBeta will only be used in special controlled areas. This medicine 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 medicine 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
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)
- Nausea
- Vomiting

Side effects reported among patients treated for neuroendocrine tumours:

Very common (may affect more than 1 in 10 people):
- Mild temporary hair loss

Common (may affect up to 1 in 10 people):
- Bone marrow cancer (myelodysplastic syndrome)
- A reduced number of white blood cells (neutropenia)

Uncommon (may affect up to 1 in 100 people):
- Bone marrow cancer (acute myeloid leukaemia)

Not known (frequency cannot be estimated from the available data):
- Carcinoid crisis
- Tumour lysis syndrome (rapid breakdown of tumour cells)
- A reduced number of red blood cells, platelets, and white blood cells (pancytopenia)
- Dry mouth

Bone marrow cancer (myelodysplastic syndrome and acute myeloid leukaemia) has been reported in patients several years after treatment with Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.

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.

This medicine does not require any special temperature storage conditions.

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 (ART), corresponding to 10 micrograms of Lutetium (^{177}Lu) (as chloride).
  (GBq: GigaBecquerel is the unit in which radioactivity is measured).
- The other ingredient is hydrochloric acid, diluted.

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.

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

ITM Medical Isotopes GmbH
Lichtenbergstrasse 1
85748 Garching/Munich
Germany
info@itm-radiopharma.com

This leaflet was last revised in MM/YYYY

Other sources of information

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