SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

MON.LUTEC 37 GBq/mL Radiopharmaceutical Precursor, Solution
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
1 mL MON.LUTEC 37 GBq/mL Radiopharmaceutical Precursor, Solution contains 37 GBq Lutetium (^{177}Lu) Chloride at calibration time.

Each vial contains a volume varying from 0.1 mL – 5 mL corresponding to an activity ranging from 3.7 GBq to 185 GBq at calibration time.

Specific activity value at the end of production should be at least 500 GBq/ mg.

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

Excipients:

See section 6.1 for a full list of excipients.

3. PHARMACEUTICAL FORM

Radiopharmaceutical precursor, solution.
Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product, MON.LUTEC, is a radiopharmaceutical precursor. It is not intended for direct use in patients. It must be used only for radiolabeling of carrier molecules, which have been specifically developed and authorized for radiolabeling with this radionuclide.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
MON.LUTEC is only to be used by personnel qualified for *in vitro* radiolabeling.

The quantity of MON.LUTEC required for radiolabeling and the quantity of the medicinal

product to be radiolabeled with Lutetium(^{177}Lu) that is subsequently administered will depend on the medicinal product to be radiolabeled and its intended use. For additional information, please refer to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) of the medicinal product to be radiolabelled with MON.LUTEC.

Pediatric population
For more information concerning the pediatric use of Lutetium (^{177}Lu)-labelled medicinal products, refer to the Summary of Products Characteristics of the medicinal product to be radiolabeled.

Method of administration
MON.LUTEC is intended for *in vitro* radiolabeling of medicinal products, which are subsequently administered by the approved route.
MON.LUTEC should not be administered directly to the patient.
MON.LUTEC is for single use only.

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

Instructions on preparation of radiopharmaceuticals are given in section 12.

Additional information on special populations
Renal/Hepatic impairment
For more information concerning the use of medicinal products which are radiolabeled with Lutetium (^{177}Lu) in patients with renal/hepatic impairment, refer to the SmPC/PIL of the medicinal product to be radiolabeled with MON.LUTEC.

Pediatric Population
Medicinal products radiolabeled with MON.LUTEC must not be used in children and adolescents below 18 years of age.

Geriatric population
For more information concerning the use of medicinal products which are radiolabeled with Lutetium (^{177}Lu) in geriatric population, refer to the SmPC/PIL of the particular medicinal product to be radiolabeled with MON.LUTEC.

4.3 Contraindications

- Hypersensitivity to active ingredient or any one of the excipients given in section 6.1.
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).
- For information on contraindications to medicinal products which are radiolabelled with MON.LUTEC, refer to the SmPC/PIL of each particular medicinal product to be radiolabeled.

4.4 Special warnings and precautions for use

RADIOPHARMACEUTICALS SHOULD BE ADMINISTERED ONLY BY NUCLEAR MEDICINE PHYSICIANS IN NUCLEAR MEDICINE CENTERS.

Individual benefit/risk justification

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

General warnings

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

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

For information concerning special warnings and precautions for use of medicinal products which are radiolabeled with MON.LUTEC refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabeled.

Radiation protection

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

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

Pediatric Population

Medicinal products radiolabeled with MON.LUTEC should not be used in children and adolescents below 18 years of age.

Renal impairment and hematological disorders

Myelodysplastic syndrome and acute myeloid leukemia

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed after treatment with Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumors (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
Anemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with MON.LUTEC. 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 reported. A blood count should be taken at baseline and monitored regularly during treatment, in accordance with clinical guidance.

Renal irradiation
Radiolabeled somatostatin analogues are excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumors 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 radiolabeled 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 ^{177}Lu peptide receptor radionuclide therapy for neuroendocrine tumors. Liver function should be monitored regularly during treatment. Dose reduction may be necessary in patients with affected liver.

Hormone release syndromes:
There have been reports of carcinoid crisis and other syndromes associated with release of hormones from functional neuroendocrine tumors following ^{177}Lu peptide receptor radionuclide therapy, which may be related to irradiation of tumor cells. Reported symptoms include flushing and diarrhea associated with hypotension. Observation of patients by overnight hospitalization 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 abnormalities in patients with diarrhea and/or vomiting.

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 should be immediately informed. Management should be in accordance with local protocols.

Tumor lysis syndrome
Tumor lysis syndrome has been reported following Lutetium (^{177}Lu) radioligand therapy. Patients with a history of renal impairment and high tumor 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.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies of MON.LUTEC with other medicinal products have been performed. The possible use of chelating therapies could interfere with the use of medicinal products which are labeled with MON.LUTEC.

For information concerning interactions associated with the use of medicinal products which are labeled with MON.LUTEC, please refer to the SmPC/PIL of the radiolabeled medicinal product.

Additional information on special populations

Pediatric Population:

No interaction studies of MON.LUTEC with other medicinal products have been conducted regarding pediatric population.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: X

Women of childbearing potential / Contraception

When an administration of radiopharmaceutical 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 ionizing 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/available (approved) test.

Pregnancy

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

Lactation

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

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.

Please refer to Summary of Product Characteristics/Patient Information Leaflet of the medicinal product to be labeled for further information concerning the use of medicinal products which are labeled with MON.LUTEC.

4.7 Effects on ability to drive and use machines

Effects on ability to drive or use machines following treatment by medicinal products which are labeled with MON.LUTEC is specified in the Summary of Product Characteristics/Patient Information Leaflet of the medicinal product to be radiolabeled.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions following the intravenous administration of medicinal products which are labeled with Lutetium (^{177}Lu) prepared by radiolabeling with MON.LUTEC, will be dependent on the specific medicinal product which is labeled. Such information is available in the Summary of Product Characteristics/Patient Information Leaflet of the medicinal product to be labeled.

For each patient, exposure to ionizing radiation must be justifiable on the basis of likely clinical benefit. The dose resulting from the activity administered should be as low as reasonably achievable considering the need to obtain the intended therapeutic result.

Exposure to ionizing 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.

Tabulated list of adverse reactions

Adverse reactions are listed below regarding the 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) and not known (cannot be estimated from the available data)

Adverse drug reaction	**Frequency category**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (see section 4.4)	Common
Acute myeloid leukemia (see section 4.4)	Uncommon
Blood and lymphatic system disorders	
Anaemia	Very common
Thrombocytopenia	
Leukopenia	
Lymphopenia	
Neutropenia	Common
Pancytopenia	Not Known
Endocrine disorders	
Carcinoid crisis	Not Known
Metabolism and nutritional disorders	
Tumor lysis syndrome	Not Known

Gastrointestinal disorders	
Nausea	Very common
Vomiting	
Cottonmouth	Not Known
Skin and subcutaneous tissue disorders	
Alopecia	Very common

Description of selected adverse reactions:
Cottonmouth has been reported among patients with metastatic castration-resistant prostate cancer receiving PSMA-targeted Lutetium (^{177}Lu)-labelled radioligands and has been transient.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

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

The following preparations must be available in medical institutions which MON.LUTEC is used for labeling 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 exchanging calcium ions with Lutetium (^{177}Lu) ions in the complex. 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 via 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 the first hour after overdose, when the radionuclide is circulating in or available to tissue fluids and plasma. However, more than 1 hour after overdose does not preclude the administration and effective action of chelator, although

reduced efficiency. Intravenous administration should not be continued for more than 2 hours.

In all cases, the blood parameters of the patient should be monitored and appropriate actions immediately taken if there is evidence of damage to the blood marrow.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Other Therapeutic Radiopharmaceuticals
ATC code: V10XX04

Lutetium (^{177}Lu) chloride is obtained by irradiation of ^{176}Lu with neutrons. Lutetium (^{177}Lu) decays by emission of beta radiation of maximal 498 keV to ^{177}Hf-Hafnium. ^{177}Lu-Lutetium has a half- life of 6.647 days.

The pharmacodynamic properties of medicinal products which are labeled with Lutetium (^{177}Lu) prepared by radiolabeling with MON.LUTEC, will depend on the medicinal product to be labeled. Before administration please refer to the Summary of Product Characteristics/Patient Information Leaflet of the medicinal product to be labeled.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of the studies with Lutetium (^{177}Lu) chloride product 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 the paediatric patients. This waiver does not extend to any diagnostic or therapeutic uses of the medicinal product when linked to a carrier molecule (see Section 4.2 for information on paediatric use).

5.2 Pharmacokinetic characteristics

General properties:

The pharmacokinetic properties of the medicinal products which are labeled with Lutetium (^{177}Lu), prepared by radiolabeling with MON.LUTEC, will be dependent on the properties of the medicinal product to be labeled. For information on this before administration please refer to Summary of Product Characteristics/Patient Information Leaflet of the medicinal product to be labeled.

Absorption
There is no available data.

Distribution

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

When the distribution pattern in blood is examined, 2 hours after administration, 15% of Lutetium is found in the blood cells and remaining 85% is found in the serum.

A more detailed study of the biodistribution of Lutetium (^{177}Lu) chloride in mice confirms the relatively high uptake in the liver, kidneys and bone marrow The results indicated that lutetium (^{177}Lu) chloride is accumulated in the bone marrow and emphasizes the importance of all Lutetium (^{177}Lu) to be peptide-bound at injection, as well as the *in-vivo* stability of the radionuclide-chelate-complex during therapy.

Biotransformation
There is no available data.

Elimination
There is no available data.

Linearity/non-linearity
There is no available data.

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

5.3 Preclinical safety data

The toxicological properties of medicinal products which are labeled with Lutetium (^{177}Lu) prepared by radiolabeling with MON.LUTEC, will be dependent on the medicinal product to be labeled.

Animal toxicity studies have not been conducted with MON.LUTEC.

The toxicity of Lutetium (^{177}Lu) chloride has been studied in different mammals and with different administration routes. Intraperitoneal administration resulted in generalized peritonitis with adhesion and accumulation of some ascetic fluid. By intraperitoneal route, the LD50 is approximately 300 mg/kg in mice and rats. By intravenous route, the LD50 in rats and mice ranges from 30 to 60 mg/kg. Intravenously administrated doses resulted in varying effects on

blood pressure and a decreased heart rate. Electrocardiograms showed no irregularities in cardiac rhythm and conduction. Respiratory effects were mild and variable. No gross differentiating changes were found of the tissues demonstrating no evidence of acute damage resulting from the experiment. The studies suggest that the intravenous toxicity of the ionic compounds of the rare earth elements would decrease with atomic weight resulting in Lutetium (^{177}Lu) being the least toxic of the series.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Water for injection

6.2 Incompatibilities

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

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

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

6.3 Shelf life

12 days from the production date.

6.4 Special precautions for storage

Store below 25°C in its lead shield container.
Store in the original package in order to protect from radiation.
Storage of radiopharmaceuticals should be in accordance with national regulations for radioactive materials.

6.5 Nature and content of container

MON.LUTEC is packaged in a colourless, Type I glass vial, with 10 mL or 3 mL filling volume, closed with bromobutyl stopper and aluminum overseal.

Each vial contains a volume varying from 0.1 mL – 5 mL corresponding to an activity ranging

from 3.7 GBq to 185 GBq at calibration time.

Each pack contains one vial in a lead shield.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

MON.LUTEC is not intended for direct use in patients.

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

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

For special warnings and precautions regarding the use of medicinal products which are labelled with lutetium (^{177}Lu), please refer to the Summary of Product Characteristics/Patient Information Leaflets of the medicinal product which is labelled.

For instructions on preparation of the medicinal product in the hospital, before administration, see section 12.
If integrity of this container is compromised at any time during the preparation of this product, the product should not be used.

Administration procedures should be carried out in a way to minimize risk of contamination of the medicinal product and irradiation of the personnels. Adequate shielding is mandatory.

The surface dose rates and the accumulated dose depend on many factors. Measurements on the location and during operation are critical and should be carried out rigorously, the determination of overall radiation dose of personnel is the guidance. Healthcare personnel are advised to limit the time of close contact with patients injected with the final product which is prepared with Lutetium (^{177}Lu). The use of screen monitor systems to monitor the patients is recommended. Considering the long half-life of Lutetium (^{177}Lu), it is specially recommended to avoid internal contamination. Therefore, it is mandatory to use protective high quality (latex/nitrile) gloves in any direct contact with the radiopharmaceutical (vial/syringe) and the patient. For minimizing radiation exposure resulting from repeated exposure, there is no additional specific 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.

MON.LUTEC is for single use only.

Since the unused product or waste materials have radioactive characteristics, they should be disposed of in accordance with local requirements for radioactive material.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2019/703

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorization: 19.12.2019
Date of last renewal:-

10. DATE OF REVISION OF THE TEXT

07.2025

11. DOSIMETRY

The radiation dose received by the various organs following the administration of a medicinal products which are labeled with Lutetium (^{177}Lu) will depend on the specific molecule that is radiolabelled.
Information on radiation dosimetry of each different medicinal product following the administration of the radiolabelled preparation will be available in the Summary of Product Characteristics/Patient Information Leaflet of the medicinal product to be labeled.

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

The dosimetry data which are given in the table, estimates are based on biodistribution data provided by ICRP-30, showing bone, liver and kidneys as the significant target organs for the

biodistribution of lutetium.

Table 1. Absorbed dose per unit activity administered for various tissues

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

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Before use, packaging and radioactivity should be checked. Activity should be measured using an ionization chamber. Lutetium (^{177}Lu) is a beta(-)/gamma emitter. Activity measurements using an ionization chamber are very sensitive to geometrical factors. Therefore, they should only be performed under geometrical conditions which have been appropriately validated.

Usual precautions regarding sterility and radioactivity should be respected.

The vial should never be opened and must be kept inside its lead shielding. The product should be aseptically withdrawn through the stopper using sterilized single use needle and syringe after disinfection of the stopper.

Appropriate aseptic precautions should be taken, in order to maintain the sterility of MON.LUTEC and to maintain sterility throughout the labelling procedures.

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)-labeled conjugates in order to form a complex with free Lutetium (^{177}Lu), if present, leading to a rapid renal clearance of Lutetium (^{177}Lu).

MON.LUTEC 37 GBq/mL Radiopharmaceutical Precursor, Solution

Recommended Labeling Procedure for c.a. ^{177}Lu (200-600 µl 0.05 M HCl)

Preparation of ^{177}Lu -bound compounds

Required Materials:

1. Sodium L-Ascorbate (Ultra-pure)
2. L-Ascorbic Acid (Ultra-pure)
3. Water (Ultra-pure)
4. PSMA 617 / I&T
5. DOTA-TATE / TOC
6. 0.9% Saline (Sodium Chloride)
7. 0.22 µm Sterile Filter
8. Sterile Vial
9. Micro-pipettes with tips
10. pH Strips or Electronic pH meter
11. Needles
12. Digital HotPot (Dry Heater) or Fully Automated Synthesizer
13. Quality Control Equipments (HPLC and TLC)

Calculation of Peptide Amounts to be Used

- PSMA; **0,9 µg** per **1 mCi** ^{177}Lu
- DOTA; **1 µg** per **1 mCi** ^{177}Lu

Preparation of Buffer for ^{177}Lu-PSMA and ^{177}Lu-DOTA Compounds

- 80 mg Sodium L-ascorbate is dissolved in 1 ml ultra-pure water.
- 20 mg L-ascorbic acid is dissolved in 1 ml ultra-pure water.

- Mix Sodium L-ascorbate and L-ascorbic acid solutions in a vial and dissolve them completely with shaking.

Radiolabelling Procedure for ^{177}Lu-PSMA and ^{177}Lu-DOTA Compounds

- Add calculated amount of peptide to vial which contains buffer.
- Mix buffer vial well, check pH value (pH 4-6).
- Add the above buffer-peptide mixture to the Lutetium (bulk) vial with needle.
- For the reaction occur, the Lutetium vial is kept in the HotPot at 100°C for 25 minutes.
- After the heating process is completed, the Lutetium vial is removed from the heater and allow it to cool for 5 minutes.

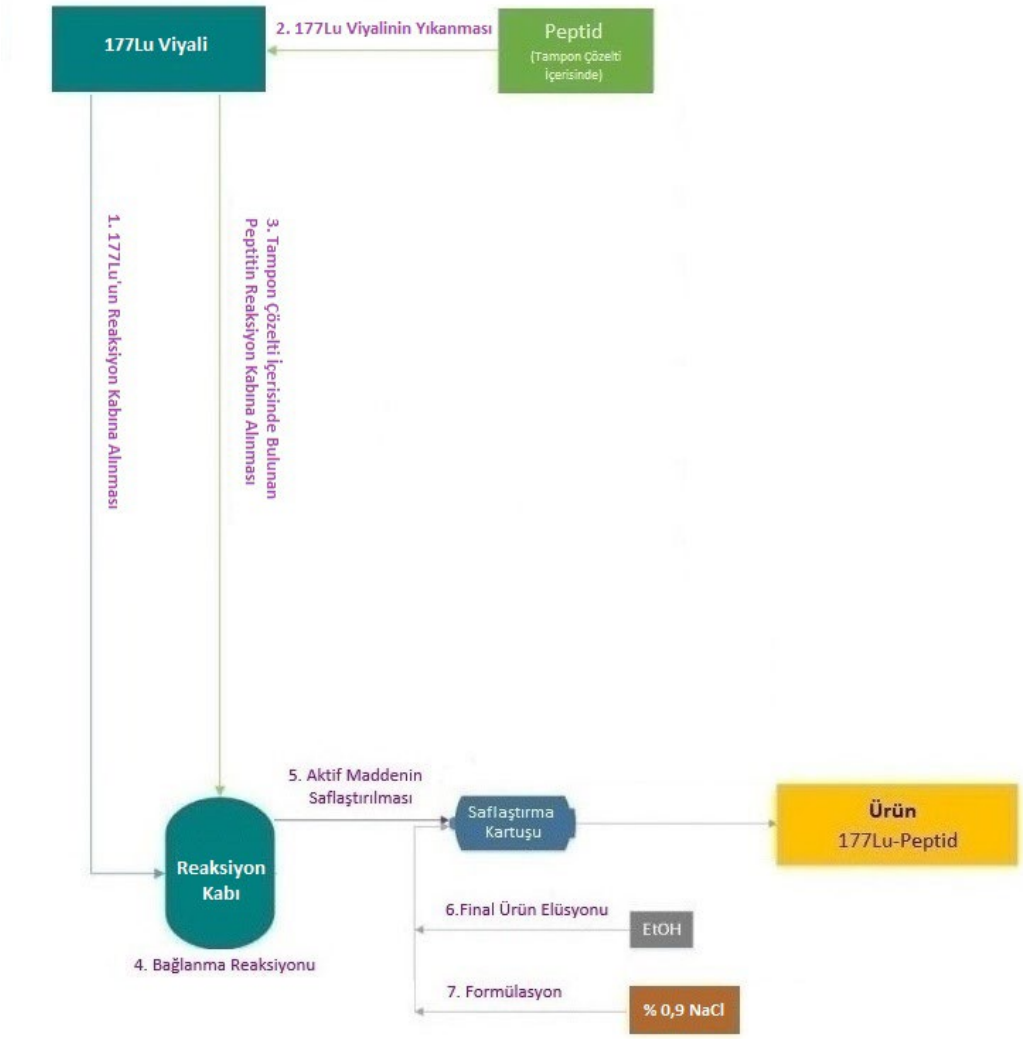
*** ^{177}Lu labeled PSMA and DOTA peptide compounds, can optionally be purified at this step with the C18 Light cartridge.**

C18 Light Cartridge Pre-conditioning

C18 Light cartridge conditioned with 2 mL Ethanol and dry with air. Then conditioned with 10 mL water for injection and dried with approx. 20 mL air to dryness.

The ^{177}Lu bound peptide compound is passed through the pre-conditioned C18 Light cartridge. The labeled product remains in the C18 Light cartridge and unbound ^{177}Lu goes to waste. Afterwards 2 ml 50% EtOH-water for injection solution passes through C18 Light cartridge and carries bound lutetium to the final product vial.

- Adjust the final volume to 10 ml with 0.9 % saline.
- 0.3 mg DTPA which is dissolved in 0.1 mL ultra-pure water added to the final product.
- Pass the solution through 0.22 µm sterile filter.
- Perform quality control analysis.



Quality Control Procedures:

Procedure for HPLC Analysis

Materials Required for HPLC

1. HPLC Column; C18 5 µm, 4.6 x 250 mm
2. Trifluoroacetic acid (Ultra-pure)
3. Acetonitrile (HPLC grade)
4. Water (Ultra-pure)

Column

Size: l = 0.25 m, Ø = 4.6 mm

Stationary phase: C18 - Reversed phase (5 µm)

Mobile phase
Mobile phase A: trifluoroacetic acid R, water for chromatography R (1:99 v/v)
Mobile phase B: trifluoroacetic acid R, acetonitrile R (1:99 v/v)

Wavelength: 220 nm

PSMA
Flow Rate: 1 ml/min
Analysis Time: 16 min.

Minutes	%A	%B
0-8	100	0
8-12	25	75
12-12.01	25	75
12.01-16	100	0

DOTA
Flow Rate: 1.3 ml/min
Duration of Analysis: 20 min

Minutes	%A	%B
0-8	76	24
8-9	40	60
9-14	40	60
14-14.01	76	24
14.01-20	76	24

Procedure for TLC Analysis

Materials Required for TLC
1. Ammonium Acetate (Ultra-pure)
2. Methyl Alcohol (99.9%)
3. Water (Ultra-pure)
4. TLC Paper & Chromatography Chamber

Mobile Phase Preparation for TLC:
Ammonium Acetate, Methyl Alcohol (50:50, v/v)
- Weigh 7.7 g of Ammonium Acetate, dissolve it with 100 ml ultra-pure water.
- Add 100 ml of Methyl Alcohol to the Ammonium Acetate solution and mix it well.

Analysis Procedure

- Cut ITLC-SG paper of size 10.0 cm X 2.0 cm.
- Pour about 7-8 mm of mobile phase to TLC chamber.
- Cover the TLC chamber with glass plate or stretch film and leave it for 10 minutes.
- Apply the quality control sample 1.5 cm above from the bottom edge of the ITLC plate.
- Let the solvent to run approximately 9.5 cm from the starting point.
- Labelled product will migrate with the solvent front (Rf = 0.9 - 1) and on contrary free Free ^{177}Lu will not run in the chromatogram. Labeled product will run to between Rf=0.9-1.
- Since background retention is high in ITLC strips, “% of ROI” values should be accepted.