6.6 Special precautions for disposal and handling
LutaPol 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 instruction 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)-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 exposure, there is no 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Narodowe Centrum Badań Jądrowych
ul. Andrzeja Sołtana 7
05-400 Otwock
Tel. (22) 718 07 00
Fax (22) 718 03 50

8. MARKETING AUTHORISATION NUMBER
22081

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 08.09.2014
Date of latest renewal: 18.09.2019

10. DATE OF REVISION OF THE TEXT
28.10.2020

11. DOSIMETRY
Recommended doses ^{177}Lu-DOTATATE absorbed by human, are calculated based on rat model.
The radiation dose received by the various organs following intravenous administration of an Lutetium (^{177}Lu)-labelled medicinal product is dependent on the specific medicinal product being radiolabelled. Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation will be available in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.
The dosimetry table below is presented in order to evaluate absorbed dose from ^{177}Lu-DOTATATE.
The dosimetry estimates were based on a rat distribution study and the calculations were effected in accordance with MIRD/ICRP 60 recommendations.

Organ	Rad/mCi	mGy/MBq
Adrenals	5.670 ± 0.86	1.533 ± 0.233
Lower large intestine	3.289 ± 1.17	0.889 ± 0.316
Small intestine	0.172 ± 0.06	0.047 ± 0.015
Stomach	0.461 ± 0.09	0.125 ± 0.023
Upper large intestine	0.440 ± 0.10	0.119 ± 0.028
Heart wall	0.042 ± 0.01	0.011 ± 0.002
Kidneys	2.477 ± 0.17	0.670 ± 0.047
Liver	0.086 ± 0.02	0.023 ± 0.005
Lungs	0.029 ± 0.01	0.008 ± 0.002
Muscle	0.038 ± 0.01	0.010 ± 0.004
Pancreas	11.12 ± 2.07	3.006 ± 0.561
Red marrow	0.360 ± 0.05	0.097 ± 0.014
Bone surfaces	1.926 ± 0.23	0.521 ± 0.061
Spleen	0.074 ± 0.02	0.020 ± 0.004
Bladder wall	1.322 ± 0.16	0.357 ± 0.042
Total body	0.116 ± 0.03	0.031 ± 0.007

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
Before use LutaPol packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber. Lutetium (^{177}Lu) is a beta and gamma pure emitter. Activity measurements using an ionisation chamber are very sensitive to geometric factors and, therefore, should be performed only under geometric conditions which have been appropriately validated.
Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements.
The vial should never be opened and must be kept inside its lead shielding. The product should be aseptically withdrawn through the stopper using sterilised single use needle and syringe after disinfecting the stopper. Before withdrawal the product can be diluted with the solution recommended in the labelling procedure of the product to be radiolabelled.
Appropriate aseptic precautions should be taken complying with radiation safety and pharmaceutical quality requirements, in order to maintain the product and labelling procedure sterility.
Any unused product or waste material should be disposed of in accordance with local requirements.

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LutaPol, radiopharmaceutical precursor, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 vial contains 0.925-37 GBq Lutetium (^{177}Lu) on the reference date and time (corresponding to 1.86 – 74 micrograms of lutetium in volume from 0,010 mL to 2 mL as lutetium chloride in hydrochloric acid solution).
Lutetium (^{177}Lu) decays to stable Hafnium (^{177}Hf). It decays by emission of β^- particles with maximum energy 498 keV (average 149.2 keV) and emission of gamma radiation with prominent energies 208 keV (10.4%) and 113 keV (6.2%). Lutetium (^{177}Lu) has a half-life of 6.65 days.
Lutetium (^{177}Lu) is produced in nuclear reactor by neutron irradiation of Lutetium enriched in isotope (^{176}Lu). Such obtained Lutetium (^{177}Lu) contains stable Lutetium (^{176}Lu) as carrier. The specific activity of Lutetium (^{177}Lu) in pharmaceutical product LutaPol is higher than 500 GBq/mg of Lutetium.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Radiopharmaceutical precursor, solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
To be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide.

Radiopharmaceutical precursor - Not intended for direct use in patients.

4.2 Posology and method of administration
Posology
The quantity of LutaPol 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 the paediatric use of Lutetium (^{177}Lu)-labelled medicinal products refer to the Summary of Products Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

Method of administration
LutaPol is intended for *in vitro* labelling of medicinal products which are subsequently administered by the approved route.
Further information on the preparation of the product is given in section 12.

4.3 Contraindications
Do not administer LutaPol directly to the patient.
LutaPol is contraindicated in the following cases:
- Hypersensitivity to Lutetium (^{177}Lu) chloride or to any of the excipients listed in section 6.1
- Established or suspected pregnancy, breast-feeding, planning pregnancy
- When pregnancy cas not bee excluded (see section 4.6)

For information on contraindications to particular Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with LutaPol refer 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
The contents of the vial of LutaPol 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.
For each patient, the radiation exposure must be justifiable by the likely benefit from the pharmaceutical procedure with use of this pharmaceutical. The quantity of LutaPol required for radiolabelling and the quantity of Lutetium (^{177}Lu)-labelled medicinal product that is administered to patient, should be as low as reasonably achievable to obtain the required therapeutic effect.
For information concerning special warnings and special precautions for use of Lutetium (^{177}Lu)-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.
Precautions with respect to relatives, carers and hospital staff are provided in section 6.6.

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 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 (177Lu) 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 (177Lu) 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.

Extravasation
There have been reports of extravasation of Lutetium-177 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.

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.

Paediatric population
Particular care should be taken when administering radioactive medicinal products to children and adolescents (from 2 to 16 years old).

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, because LutaPol is a precursor solution for radiolabelling medicinal products.
For information concerning interactions associated with the use of Lutetium (^{177}Lu) –labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential
Women of childbearing potential have to use effective contraception during and shortly after treatment. 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.

Pregnancy
Lutetium (^{177}Lu)-labelled medicinal products are contraindicated in established or suspected pregnancy or when pregnancy has not been excluded, when breast-feeding or when pregnancy is planning (see section 4.3).

Breast-feeding
Before administering a radioactive medicinal product to a mother who is breast-feeding, consideration should be given to whether the investigation could be reasonably delayed until the mother has ceased breast-feeding. If the administration cannot be delayed, a lactating mother should be advised to stop breast-feeding.
Further information concerning the use of a Lutetium (^{177}Lu) -labelled medicinal products in pregnancy and breast-feeding is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

Fertility
Further information concerning the use of a 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
Possible adverse reactions following the intravenous administration Lutetium (^{177}Lu)-labelled medicinal product prepared by radiolabelling with LutaPol, 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. For each patient, exposure to ionising radiation must be justifiable on the basis of likely clinical benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended therapeutic result.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.
The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself.

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).

Blood and lymphatic system disorders
very common: Anaemia, thrombocytopenia, leukopenia and lymphopenia
common: Neutropenia
not known: Pancytopenia

Endocrine disorders
frequency unknown: Carcinoid crisis

Gastrointestinal disorders
very common: Nausea, vomiting
not known: Dry mouth

Neoplasms benign, malignant and unspecified (including cysts and polyps):
common: Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (see section 4.4)
uncommon: Acute myeloid leukaemia (see section 4.4)

Skin and subcutaneous tissue disorders:
very common: 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.
Alopecia, described as mild and temporary, has been observed among patients receiving Lutetium 177 peptide receptor radionuclide therapy for neuroendocrine tumours.

Metabolism and nutrition disorders:
not known: Tumour lysis syndrome

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.
Adverse reactions may be reported to marketing authorization holder.

4.9 Overdose
The presence of free Lutetium (^{177}Lu) chloride in the body after an inadvertent administration of LutaPol will lead to increased bone marrow toxicity and haematopoietic stem cells damage.
Therefore, in case of an inadvertent administration of LutaPol, 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 LutaPol labelling of carrier molecules for therapeutic purposes:
- Ca-DTPA (Trisodium calcium diethylenetriaminepentaacetate) or
- Ca-EDTA (Calcium disodium ethylenediaminetetraacetate)
These chelating agents suppress yttrium radiotoxicity by an exchange between the calcium ion and the lutetium due to their capacity of forming water soluble complexes with the chelating ligands (DTPA, EDTA). These complexes are rapidly eliminated by the kidneys.
1 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 dextrose, or normal saline).
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 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 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 LutaPol, 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of the studies with products containing lutetium (^{177}Lu) chloride as an active in all subsets of the paediatric population on grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population and on grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for the paediatric patients. This waiver does however not extend to any diagnostic or 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 LutaPol, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

5.3 Preclinical safety data
The toxicological properties of Lutetium (^{177}Lu)-labelled, medicinal products prepared by radiolabelling with LutaPol prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.
There are no data available on the toxicity of Lutetium (^{177}Lu) chloride nor on its effects on reproduction in animals or its mutagenic or carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Hydrochloric acid concentrated
Water for injection

6.2 Incompatibilities
Radiolabelling of medicinal products, such as monoclonal antibodies, peptides or other substrates, with Lutetium (^{177}Lu) 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.

6.3 Shelf life
7 days from the date of manufacture.

6.4 Special precautions for storage
Store below 25°C.
Store in the original package.
Storage should be in accordance with national regulation on radioactive material.

6.5 Nature and contents of container
Colourless type I glass vial of 2 mL sealed with rubber stopper and an aluminium crimp cap, placed in lead shielding container.
Pack size: 1 vial

During storage, due to ionizing radiation, the vial may change colour into yellow-brown. This discoloration has no influence into the product quality.