ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lutathera 370 MBq/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 370 MBq of lutetium (^{177}Lu) oxodotreotide at the date and time of calibration.

The total amount of radioactivity per single-dose vial is 7 400 MBq at the date and time of infusion. Given the fixed volumetric activity of 370 MBq/mL at the date and time of calibration, the volume of the solution in the vial ranges between 20.5 and 25.0 mL in order to provide the required amount of radioactivity at the date and time of infusion.

Physical characteristics

Lutetium-177 has a half-life of 6.647 days. Lutetium-177 decays by β^- emission to stable hafnium-177 with the most abundant β^- (79.3%) having a maximum energy of 0.498 MeV. The average beta energy is approximately 0.13 MeV. Low gamma energy is also emitted, for instance at 113 keV (6.2%) and 208 keV (11%).

Excipient with known effect

Each mL of solution contains up to 0.14 mmol (3.2 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.

4.2 Posology and method of administration

Important safety instructions

Lutathera should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

Patient identification

Before starting treatment with Lutathera, somatostatin receptor imaging (scintigraphy or positron emission tomography [PET]) must confirm the overexpression of these receptors in the tumour tissue with the tumour uptake at least as high as normal liver uptake.

Posology

Adults
The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7 400 MBq each. The recommended interval between each administration is 8 weeks (±1 week).

Information on dose modifications to manage severe or intolerable adverse drug reactions is given in the respective section below.

Amino acid solution
For renal protection purposes, an amino acid solution containing L-lysine and L-arginine must be administered intravenously over 4 hours (see composition in Tables 1 and 2). The infusion of the amino acid solution should start 30 minutes prior to start of Lutathera infusion. Infusion of the amino acid solution and Lutathera through a separate venous access in each of the patient's arms is the preferred method. However, if two intravenous lines are not possible due to poor venous access or institutional/clinical preference, the amino acid solution and Lutathera may be infused through the same line via a three-way valve, taking into consideration flow rate and maintenance of venous access. The dose of the amino acid solution should not be decreased even if a reduced dose of Lutathera is administered.

An amino acid solution containing just L-lysine and L-arginine in the amounts specified in Table 1 is considered the medicinal product of choice, due to the lower total volume to be infused and lower osmolality.

The amino acid solution can be prepared as a compounded product, in compliance with the hospital's good preparation practices for sterile medicinal products and according to the composition specified in Table 1.

Table 1 Composition of the compounded amino acid solution

Compound	**Amount**
L-lysine HCl	25 g*
L-arginine HCl	25 g**
Sodium chloride 9 mg/mL (0.9%) solution for injection, or water for injections	1 L
* equivalent to 20.0 g L-lysine ** equivalent to 20.7 g L-arginine	

Alternatively, commercially available amino acid solutions can be used if compliant with the specification described in Table 2.

Table 2 Specification of commercially available amino acid solutions

Characteristic	**Specification**
L-lysine HCl	Between 18 and 25 g*
L-arginine HCl	Between 18 and 25 g**
Volume	1 to 2 L
Osmolality	<1 200 mOsmol/kg
* equivalent to 14.4-20 g L-lysine ** equivalent to 14.9-20.7 g L-arginine	

Treatment monitoring
Before each administration and during the treatment with Lutathera, laboratory tests are required to assess the patient's condition and adapt the therapeutic protocol as necessary (dose, infusion interval, number of infusions) (see Table 3).

The minimum laboratory tests needed before each infusion are:

- Haematology (haemoglobin [Hb], white blood cell count with differential counts, platelet count)
- Kidney function (serum creatinine and creatinine clearance by Cockcroft-Gault formula)
- Liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum albumin, international normalised ratio [INR] and bilirubin)

These laboratory tests should be performed at least once in the 2 to 4 weeks prior to administration, and shortly before administration. It is also recommended to perform these tests every 4 weeks for at least 3 months after the last infusion of Lutathera and every 6 months thereafter, in order to be able to detect possible delayed adverse reactions (see section 4.8). Dosing may need to be modified based on the test results (see Table 3).

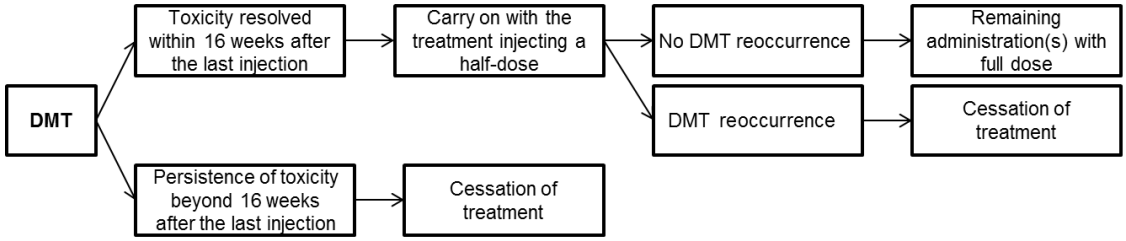
Dose modification
Management of severe or intolerable adverse drug reactions may require temporary dose interruption (extension of the dosing interval from 8 weeks up to 16 weeks), dose reduction, or permanent discontinuation of treatment with Lutathera (see Table 3 and Figure 1).

Table 3 Recommended dose modifications of Lutathera for adverse drug reactions

Adverse drug reaction	Severity of adverse drug reaction	Dose modification
Thrombocytopenia	First occurrence of: Grade 2 (platelets <75-50 x 10^9/L) Grade 3 (platelets <50-25 x 10^9/L) Grade 4 (platelets <25 x 10^9/L)	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume Lutathera at 3 700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer Lutathera at 7 400 MBq (200 mCi) as next dose. Permanently discontinue Lutathera for Grade 2 or higher thrombocytopenia requiring a dosing interval beyond 16 weeks.
	Recurrent Grade 2, 3 or 4	Permanently discontinue Lutathera.
Anaemia and neutropenia	First occurrence of anaemia: Grade 3 (Hb <8.0 g/dL); transfusion indicated Grade 4 (life-threatening consequences) First occurrence of neutropenia: Grade 3 (absolute neutrophil count [ANC] <1.0-0.5 x 10^9/L) Grade 4 (ANC <0.5 x 10^9/L)	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume Lutathera at 3 700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 anaemia or neutropenia, administer Lutathera at 7 400 MBq (200 mCi) as next dose. Permanently discontinue Lutathera for Grade 3 or higher anaemia or neutropenia requiring a dosing interval beyond 16 weeks.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.

Renal toxicity	First occurrence of: • Creatinine clearance less than 40 mL/min; calculated using Cockcroft-Gault formula with actual body weight, or • 40% increase from baseline serum creatinine, or • 40% decrease from baseline creatinine clearance; calculated using Cockcroft-Gault formula with actual body weight.	Withhold dose until resolution or return to baseline. Resume Lutathera at 3 700 MBq (100 mCi) in patients with resolution or return to baseline. If reduced dose does not result in renal toxicity, administer Lutathera at 7 400 MBq (200 mCi) as next dose. Permanently discontinue Lutathera for renal toxicity requiring a dosing interval beyond 16 weeks.
	Recurrent renal toxicity	Permanently discontinue Lutathera.
Hepatotoxicity	First occurrence of: • Bilirubinaemia greater than 3 times the upper limit of normal (Grade 3 or 4), or • Albuminaemia less than 30 g/L with INR >1.5	Withhold dose until resolution or return to baseline. Resume Lutathera at 3 700 MBq (100 mCi) in patients with resolution or return to baseline. If reduced Lutathera dose does not result in hepatotoxicity, administer Lutathera at 7 400 MBq (200 mCi) as next dose. Permanently discontinue Lutathera for hepatotoxicity requiring a dosing interval beyond 16 weeks.
	Recurrent hepatotoxicity	Permanently discontinue Lutathera.
Any other CTCAE* Grade 3 or Grade 4 adverse drug reaction[1]	First occurrence of Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume Lutathera at 3 700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer Lutathera at 7 400 MBq (200 mCi) as next dose. Permanently discontinue Lutathera for Grade 3 or higher adverse drug reaction requiring a dosing interval beyond 16 weeks.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.
[1] No dose modification required for haematological toxicities Grade 3 or Grade 4 solely due to lymphopenia. * CTCAE: Common Terminology Criteria for Adverse Events, National Cancer Institute		

Figure 1 Overview of instructions for dose modifications



DMT: Dose-modifying toxicity

Other reasons to consider temporary dose interruption of Lutathera include occurrence of an intercurrent disease (e.g. urinary tract infection) which the physician considers could increase the risks associated with Lutathera administration and which should be resolved or stabilised for treatment to resume, or major surgery, in the event of which treatment should be withheld for 12 weeks after the date of surgery.

Special populations

Elderly

No dose adjustment is required in patients aged 65 years or above as clinical experience has not identified differences in responses between the elderly and younger patients. However, since increased risk of presenting with haematotoxicity has been described in elderly patients (≥70 years old), close follow-up allowing for prompt dose adaptation (DMT) in this population is advisable.

Renal impairment

Careful consideration of the activity to be administered to patients with renal impairment is required since an increased radiation exposure is possible in these patients. The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with baseline severe renal impairment (creatinine clearance <30 mL/min by Cockcroft-Gault formula) or end-stage renal disease have not been studied. Treatment with Lutathera in patients with kidney failure with creatinine clearance <30 mL/min is contraindicated (see section 4.3). Treatment with Lutathera in patients with baseline creatinine clearance <40 mL/min (using Cockcroft-Gault formula) is not recommended. No dose adjustment is recommended for renally impaired patients with baseline creatinine clearance ≥40 mL/min. However, as this medicinal product is known to be substantially excreted by the kidneys, renal function should be more frequently monitored during treatment as these patients may be at greater risk of toxicity. For additional details about the treatment of patients with renal toxicity, see Table 3 in section 4.2 and section 4.4.

Hepatic impairment

Careful consideration of the activity to be administered to patients with hepatic impairment is required since an increased radiation exposure is possible in these patients. The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with baseline severe hepatic impairment (total bilirubin >3 times upper limit of normal, regardless of AST level) have not been studied. Patients with baseline hepatic impairment with either total bilirubin >3 times the upper limit of normal or albuminaemia <30 g/L and INR >1.5 should only be treated with Lutathera after a careful benefit-risk assessment. No dose adjustment is recommended for patients with baseline mild or moderate hepatic impairment.

For additional details about the treatment of patients with hepatotoxicity, see Table 3 in section 4.2 and section 4.4.

Paediatric population

The safety and efficacy of Lutathera in paediatric patients aged below 18 years have not been established. Currently available data in paediatric patients aged 12 years and older are described in sections 4.8, 5.1, 5.2 and 11 but no recommendation on a posology can be made.

Method of administration

Lutathera is for intravenous use. It is a ready-to-use radiopharmaceutical medicinal product for single use only.

Administration instructions

The gravity method, the peristaltic pump method or the syringe pump method may be used for administration of the recommended dose. Treating healthcare professionals may use other methods deemed appropriate and safe, particularly when dose reduction is required.

When using the gravity method or the peristaltic pump method, Lutathera should be infused directly from its original container. The peristaltic pump method or the syringe pump method should be used when administering a reduced dose of Lutathera following dose modification for an adverse reaction (see Table 3 in section 4.2). Using the gravity method to administer a reduced dose of Lutathera may result in the delivery of the incorrect volume of Lutathera if the dose is not adjusted prior to administration. Radiation safety precautions must be considered regardless of the administration method used (see section 6.6).

The following table summarises the whole administration procedure for Lutathera:

Table 4 Procedure for administration of antiemetic, amino acid solution and Lutathera

Administered agents	**Start time (min)**	**Infusion rate (mL/h)**	**Duration**
Antiemetic	At least 30 minutes prior to amino acid solution	As per prescribing information	As per prescribing information
Amino acid solution, either extemporaneously compounded (1 L) or commercial (1 to 2 L)	0	250-500 depending on volume	4 hours
Lutathera with sodium chloride 9 mg/mL (0.9%) solution for injection	30	Up to 400	30 ± 10 minutes

For instructions on the method of preparation and intravenous methods of administration, see section 12.

For recommendations in case of extravasation, see section 4.4.

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).
- Kidney failure with creatinine clearance <30 mL/min.

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.

Given the mechanism of action and the tolerance profile of Lutathera, it is not recommended to start treatment with Lutathera in patients with somatostatin receptor-negative or mixed visceral lesions according to somatostatin receptor imaging.

Myelosuppression

Because of the potential for undesirable haematological effects, blood counts must be monitored at baseline and prior to each dose of Lutathera during treatment and until resolution of any eventual toxicity (see section 4.2). Patients with impaired bone marrow function and patients who have received prior chemotherapy or external beam radiotherapy (involving more than 25% of the bone marrow) may be at higher risk of haematological toxicity during Lutathera treatment. Treatment of patients with severely impaired haematological function at baseline and during treatment (e.g. Hb <4.9 mmol/L or 8 g/dL, platelets <75 x 10^9/L, or leukocytes <2 x 10^9/L) is not recommended unless solely due to lymphopenia.

Myelodysplastic syndrome and acute leukaemia

Late-onset myelodysplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with Lutathera (see section 4.8), occurring approximately 29 months (9-45) for MDS and 55 months (32-125) for AL after the first Lutathera infusion. The aetiology of these therapy-related secondary myeloid neoplasms (t-MNs) is unclear. Factors such as age >70 years, impaired renal function, baseline cytopenias, prior number of therapies, prior exposure to chemotherapeutic agents (specifically alkylating agents), and prior radiotherapy are suggested as potential risks and/or predictive factors for MDS/AL.

Renal toxicity

Because lutetium (^{177}Lu) oxodotreotide is almost exclusively eliminated through the renal system, it is mandatory to concomitantly administer an amino acid solution containing the amino acids L-lysine and L-arginine. The amino acid solution will help to decrease reabsorption of lutetium (^{177}Lu) oxodotreotide through the proximal tubules, resulting in a significant reduction in the kidney absorbed dose (see section 4.2). When the recommended concomitant amino acid solution infusion is delivered over a 4-hour time span, a mean reduction in kidney radiation exposure of about 47% has been reported.

Patients should be encouraged to remain hydrated and to urinate frequently before, on the day of and the day after administration of Lutathera (e.g. 1 glass of water every hour).

Renal function as determined by serum creatinine and calculated creatinine clearance using Cockcroft-Gault formula must be assessed at baseline, during and for at least the first year after treatment (see section 4.2).

Patients with renal impairment at baseline or with renal or urinary tract abnormalities, may be at increased risk of toxicity due to increased radiation exposure (see section 4.2).

For patients with creatinine clearance <50 mL/min, an increased risk for transient hyperkalaemia due to the amino acid solution should also be taken into consideration (see Warning and precaution regarding the co-administered renal protective amino acid solution).

Hepatotoxicity

Since many patients referred for Lutathera therapy have hepatic metastasis, it may be common to observe patients with altered baseline liver function. Patients with hepatic metastasis or pre-existing advanced hepatic impairment may be at increased risk of hepatotoxicity due to radiation exposure. Therefore, it is recommended to monitor ALT, AST, bilirubin, serum albumin and INR during treatment (see section 4.2).

Hypersensitivity

Cases of hypersensitivity reactions (including isolated angioedema events) have been reported in the post-marketing setting in patients treated with Lutathera (see section 4.8). In the event of serious hypersensitivity reactions, the ongoing Lutathera infusion should be discontinued immediately. Appropriate medicinal products and equipment to manage such reactions should be available for immediate use.

Nausea and vomiting

To prevent treatment-related nausea and vomiting, an intravenous bolus of an antiemetic medicinal product should be injected at least 30 minutes prior to the start of amino acid solution infusion to reach the full antiemetic efficacy (see section 4.2).

Concomitant use of somatostatin analogues

Somatostatin and its analogues competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera (see section 4.5).

Neuroendocrine hormonal crises

Crises due to excessive release of hormones or bioactive substances may occur following treatment with Lutathera, therefore observation of patients by overnight hospitalisation should be considered in some cases (e.g. patients with poor pharmacological control of symptoms). In case of hormonal crises, recommended treatments are: 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 therapy with medicinal products containing lutetium-177. 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 and electrolyte balance should be assessed at baseline and during treatment.

Radioprotection rules

Patients under treatment with Lutathera should be kept away from others during administration and until the radiation emission limits stipulated by the applicable laws are reached, usually within the 4-5 hours following medicinal product administration. The healthcare professional should determine when the patient can leave the controlled area of the hospital, i.e. when the radiation exposure to third parties does not exceed regulatory thresholds.

Patients should be encouraged to remain hydrated and to urinate frequently before, on the day of and the day after administration of Lutathera (e.g. 1 glass of water every hour) to facilitate elimination. They should also be encouraged to defecate every day and to use a laxative if needed. Urine and faeces should be disposed of according to the national regulations.

Provided the patient's skin is not contaminated, such as from the leakage of the infusion system or because of urinary incontinence, radioactivity contamination is not expected on the skin and in the vomited mass. However, it is recommended that when conducting standard care or examinations with medical devices or other instruments which come into contact with the skin (e.g. electrocardiogram [ECG]), basic protection measures should be observed such as wearing gloves, installing the material/electrode before the start of radiopharmaceutical infusion, changing the material/electrode after measurement, and eventually monitoring the radioactivity of equipment after use.

Before being discharged, the patient should be instructed in the necessary radioprotection rules for interacting with other members of the same household and the general public, and the general precautions the patient must follow during daily activities after treatment (as given in the next paragraph and the package leaflet) to minimise radiation exposure to others.

After each administration, the following general recommendations can be considered along with national, local and institutional procedures and regulations:

- Close contact (less than 1 metre) with other people should be limited for 7 days.
- For children and/or pregnant women, close contact (less than 1 metre) should be limited to less than 15 minutes per day for 7 days.
- Patients should sleep in a separate bedroom from other people for 7 days.
- Patients should sleep in a separate bedroom from children and/or pregnant women for 15 days.

Recommended measures in case of extravasation

Disposable waterproof gloves should be worn. The infusion of the medicinal product must be immediately ceased and the administration device (catheter, etc.) removed. The nuclear medicine physician and the radiopharmacist should be informed.

All the administration device materials should be kept in order to measure the residual radioactivity and the activity actually administered and the absorbed dose should be determined. The extravasation area should be delimited with an indelible pen and a picture should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated.

To continue Lutathera infusion, it is mandatory to use a new catheter, possibly placing it in a contralateral venous access.

No additional medicinal product can be administered to the same side where the extravasation occurred.

In order to accelerate medicinal product dispersion and to prevent its stagnation in tissue, it is recommended to increase blood flow by elevating the affected arm. Depending on the case, aspiration of extravasation fluid, flush injection of sodium chloride 9 mg/mL (0.9%) solution for injection, or application of warm compresses or a heating pad to the infusion site to accelerate vasodilation should be considered.

Symptoms, especially inflammation and/or pain, should be treated. Depending on the situation, the nuclear medicine physician should inform the patient about the risks linked to extravasation injury and give advice about potential treatment and necessary follow-up requirements. The extravasation area must be monitored until the patient is discharged from the hospital. Depending on its severity, this event should be declared as an adverse reaction.

Patients with urinary incontinence

During the first 2 days following administration of this medicinal product, special precautions should be taken with patients with urinary incontinence to avoid spread of radioactive contamination. This includes the handling of any materials possibly contaminated with urine.

Patients with brain metastases

There are no efficacy data in patients with known brain metastases, therefore individual benefit-risk must be assessed in these patients.

Secondary malignant neoplasms

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 exposure are less than from the disease itself.

Other patients with risk factors

Patients presenting with any of the conditions below are more prone to develop adverse reactions. Therefore, it is recommended to monitor such patients more frequently during the treatment. Please see Table 3 in case of dose modifying toxicity.

- Bone metastasis;
- Previous oncological radiometabolic therapies with ^{131}I compounds or any other therapy using unshielded radioactive sources;
- History of other malignant tumours unless the patient is considered to have been in remission for at least 5 years.

Contraception in males and females

Female patients of reproductive potential should be advised to use effective contraception during treatment and for 7 months after the last dose of Lutathera (see section 4.6).

Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for 4 months after the last dose of Lutathera (see section 4.6).

Specific warnings and precautions regarding the co-administered renal protective amino acid solution

Hyperkalaemia
A transient increase in serum potassium levels may occur in patients receiving arginine and lysine, usually returning to normal levels within 24 hours from the start of the amino acid solution infusion. Patients with reduced creatinine clearance may be at increased risk for transient hyperkalaemia (see "Renal toxicity" in section 4.4).

Serum potassium levels must be tested before each administration of amino acid solution. In case of hyperkalaemia, the patient's history of hyperkalaemia and concomitant medicinal product should be checked. Hyperkalaemia must be corrected accordingly before starting the infusion.

In case of pre-existing clinically significant hyperkalaemia, a second monitoring prior to amino acid solution infusion must confirm that hyperkalaemia has been successfully corrected. The patient should be monitored closely for signs and symptoms of hyperkalaemia, e.g. dyspnoea, weakness, numbness, chest pain and cardiac manifestations (conduction abnormalities and cardiac arrhythmias). An electrocardiogram (ECG) should be performed prior to discharging the patient.

Vital signs should be monitored during the infusion regardless of baseline serum potassium levels. Patients should be encouraged to remain hydrated and to urinate frequently before, on the day of and the day after administration (e.g. 1 glass of water every hour) to facilitate elimination of excess serum potassium.

In case hyperkalaemia symptoms develop during amino acid solution infusion, appropriate corrective measures must be taken. In case of severe symptomatic hyperkalaemia, discontinuation of amino acid solution infusion should be considered, taking into consideration the benefit-risk of renal protection versus acute hyperkalaemia.

Heart failure
Due to potential for clinical complications related to volume overload, care should be taken with use of arginine and lysine in patients with severe heart failure defined as class III or class IV in the NYHA (New York Heart Association) classification. Patients with severe heart failure defined as class III or class IV in the NYHA classification should only be treated after a careful benefit-risk assessment, taking into consideration the volume and osmolality of the amino acid solution.

Metabolic acidosis
Metabolic acidosis has been observed with complex amino acid solutions administered as part of total parenteral nutrition (TPN) protocols. Shifts in acid-base balance alter the balance of extracellular-intracellular potassium and the development of acidosis may be associated with rapid increases in plasma potassium.

Specific warnings

Sodium content
This medicinal product contains up to 3.5 mmol (81.1 mg) sodium per vial, equivalent to 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Somatostatin analogues

Somatostatin and its analogues competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera. Therefore, administration of long-acting somatostatin analogues should be avoided within 30 days prior to the administration of this medicinal product. If necessary, patients may be treated with short-acting somatostatin analogues up to 24 hours preceding Lutathera administration.

Glucocorticoids

There is some evidence that glucocorticoids can induce down-regulation of subtype 2 somatostatin receptors (SSTR2). Therefore, as a matter of caution, repeated administration of high doses of glucocorticoids should be avoided during Lutathera treatment. Patients with a history of chronic use of glucocorticoids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known whether the intermittent use of glucocorticoids for the prevention of nausea and vomiting during Lutathera administration could induce SSTR2 down-regulation. As a matter of caution, glucocorticoids should also be avoided as preventive antiemetic treatment. In the event that the treatment administered for the prevention of nausea and vomiting before the amino acid solution infusion proves insufficient, a single glucocorticoid dose can be used, provided it is not given before initiating or within one hour after the end of Lutathera infusion.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in any 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 Lutathera, pregnancy should be excluded using an adequate/validated test.

Contraception in males and females

Lutathera can cause foetal harm when administered to a pregnant woman.

Female patients of reproductive potential should be advised to use effective contraception during treatment and for 7 months after the last dose of Lutathera.

Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for 4 months after the last dose of Lutathera.

Pregnancy

No studies on animal reproductive function have been conducted with lutetium (^{177}Lu) oxodotreotide.

Radionuclide procedures carried out on pregnant women also involve a radiation dose to the foetus. The use of Lutathera is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk associated with the ionising radiation (see section 4.3). Pregnant women should be advised of the risk to a foetus.

Breast-feeding

It is unknown whether lutetium (^{177}Lu) oxodotreotide is excreted in breast milk. A risk to the breast-fed child associated with ionising radiation cannot be excluded. Breast-feeding should be avoided

during treatment with this medicinal product. If treatment with Lutathera during breast-feeding is necessary, the child must be weaned.

Fertility

No animal studies have been performed to determine the effects of lutetium (^{177}Lu) oxodotreotide on male and female fertility. Ionising radiations of lutetium (^{177}Lu) oxodotreotide may potentially have temporary toxic effects on female and male gonads. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm or eggs can be discussed as an option for patients before treatment.

4.7 Effects on ability to drive and use machines

Lutathera has no or negligible influence on the ability to drive and use machines. Nevertheless, the general condition of the patient and the possible adverse reactions to treatment must be taken into account before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Lutathera is based on pooled data from patients from clinical studies (NETTER-1 phase III and Erasmus phase I/II Dutch patients), as well as data from the NETTER-P phase II study and from compassionate use programmes.

The most common adverse reactions in patients receiving Lutathera treatment were nausea and vomiting, which occurred at the beginning of the infusion in 58.9% and 45.5% of patients, respectively. The causality of nausea/vomiting is confounded by the emetic effect of the concomitant amino acid solution administered for renal protection.

Due to the bone marrow toxicity of Lutathera, the most expected adverse reactions were related to haematological toxicity: thrombocytopenia (25%), lymphopenia (22.3%), anaemia (13.4%), pancytopenia (10.2%).

Other very common adverse reactions reported include fatigue (27.7%) and decreased appetite (13.4%).

At the time of the NETTER-1 final analysis, after a median follow-up duration of 76 months in each study arm, the safety profile remained consistent with that previously reported.

Tabulated list of adverse reactions

The adverse reactions are listed in Table 5 according to frequency and MedDRA System Organ Class (SOC). The frequencies are categorised as follows: 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).

Table 5 Frequency of adverse reactions reported from clinical studies and post-marketing surveillance

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Not known
Infections and infestations			Conjunctivitis Respiratory tract infection Cystitis Pneumonia Herpes zoster Ophthalmic herpes zoster Influenza Staphylococcal infections Streptococcal bacteraemia	
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (myelodysplastic syndrome)	Acute myeloid leukaemia Acute leukaemia Chronic myelomonocytic leukaemia	
Blood and lymphatic system disorders	Thrombocytopenia[2] Lymphopenia[3] Anaemia[4] Pancytopenia	Leukopenia[5] Neutropenia[6]	Refractory cytopenia with unilineage dysplasia Nephrogenic anaemia Bone marrow failure Thrombocytopenic purpura	
Immune system disorders			Hypersensitivity	Angioedema
Endocrine disorders		Secondary hypothyroidism	Hypothyroidism Diabetes mellitus Carcinoid crisis Hyperparathyroidism	
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia Dehydration Hypomagnesaemia Hyponatraemia	Hypoglycaemia Hypernatraemia Hypophosphataemia Tumour lysis syndrome Hypercalcaemia Hypocalcaemia Hypoalbuminaemia Metabolic acidosis	
Psychiatric disorders		Sleep disorders	Anxiety Hallucination Disorientation	
Nervous system disorders		Dizziness Dysgeusia Headache[10] Lethargy Syncope	Formication Hepatic encephalopathy Paraesthesia Parosmia Somnolence Spinal cord compression	
Eye disorders			Eye disorders	
Ear and labyrinth disorders			Vertigo	
Cardiac disorders		Electrocardiogram QT prolonged	Atrial fibrillation Palpitations Myocardial infarction Angina pectoris Cardiogenic shock	
Vascular disorders		Hypertension[7] Flushing Hot flush Hypotension	Vasodilatation Peripheral coldness Pallor Orthostatic hypotension Phlebitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Oropharyngeal pain Pleural effusion Sputum increased Choking sensation	

Gastrointestinal disorders	Nausea Vomiting	Abdominal distension Diarrhoea Abdominal pain Constipation Abdominal pain upper Dyspepsia Gastritis	Dry mouth Flatulence Ascites Gastrointestinal pain Stomatitis Haematochezia Abdominal discomfort Intestinal obstruction Colitis Pancreatitis acute Rectal haemorrhage Melaena Abdominal pain lower Haematemesis Haemorrhagic ascites Ileus	
Hepatobiliary disorders		Hyperbilirubinaemia[9]	Pancreatic enzymes decreased Hepatocellular injury Cholestasis Hepatic congestion Hepatic failure	
Skin and subcutaneous tissue disorders		Alopecia	Rash Dry skin Swelling face Hyperhidrosis Pruritus generalised	
Musculoskeletal and connective tissue disorders		Musculoskeletal pain[8] Muscle spasms		
Renal and urinary disorders		Acute kidney injury Haematuria Renal failure Proteinuria	Leukocyturia Urinary incontinence Glomerular filtration rate decreased Renal disorder Acute pre-renal failure Renal impairment	
General disorders and administration site conditions	Fatigue[1]	Injection site reaction[11] Oedema peripheral Administration site pain Chills Influenza-like illness	Injection site mass Chest discomfort Chest pain Pyrexia Malaise Pain Death Feeling abnormal	
Investigations		Blood creatinine increased GGT* increased ALT** increased AST*** increased Blood ALP**** increased	Blood potassium decreased Blood urea increased Glycosylated haemoglobin increased Haematocrit decreased Protein urine Weight decreased Blood creatine phosphokinase increased Blood lactate dehydrogenase increased Blood catecholamines C-reactive protein increased	
Injury, poisoning and procedural complications			Clavicle fracture	

Surgical and medical procedures		Transfusion	Abdominal cavity drainage Dialysis Gastrointestinal tube insertion Stent placement Abscess drainage Bone marrow harvest Polypectomy	
Social circumstances			Physical disability	

[1] Includes asthenia and fatigue
[2] Includes thrombocytopenia and platelet count decreased
[3] Includes lymphopenia and lymphocyte count decreased
[4] Includes anaemia and haemoglobin decreased
[5] Includes leukopenia and white blood cell count decreased
[6] Includes neutropenia and neutrophil count decreased
[7] Includes hypertension and hypertensive crisis
[8] Includes arthralgia, pain in extremity, back pain, bone pain, flank pain, musculoskeletal chest pain and neck pain
[9] Includes blood bilirubin increased and hyperbilirubinaemia
[10] Includes headache and migraine
[11] Includes injection site reaction, injection site hypersensibility, injection site induration, injection site swelling
*Gamma-glutamyltransferase
**Alanine aminotransferase
***Aspartate aminotransferase
****Alkaline phosphatase

Description of selected adverse reactions

Myelosuppression
Mostly mild/moderate bone marrow toxicity (myelo-/haematotoxicity) manifested with reversible/transient reductions in blood counts affecting all lineages (cytopenias in all combinations, i.e. pancytopenia, bicytopenias, isolated monocytopenias - anaemia, neutropenia, lymphocytopenia and thrombocytopenia). In spite of an observed significant selective B-cell depletion, no increase in the rate of infectious complications occurs after peptide receptor radionuclide therapy (PRRT). Cases of irreversible haematological pathologies, i.e. premalignant and malignant blood neoplasms (i.e. myelodysplastic syndrome and acute myeloid leukaemia, respectively) have been reported following Lutathera treatment.

In NETTER-1, platelet nadir occurred at a median of 5.1 months following the first dose. Of the 59 patients who developed thrombocytopenia, 68% had platelet recovery to baseline or normal levels. The median time to platelet recovery was 2 months. Fifteen of the nineteen patients in whom platelet recovery was not documented had post-nadir platelet counts.

Renal toxicity
Lutetium (^{177}Lu) oxodotreotide is excreted by the kidney.

The long-term trend of progressive glomerular filtration function deterioration demonstrated in the clinical studies confirms that Lutathera-related nephropathy is a chronic kidney disease that develops progressively over months or years after exposure. An individual benefit-risk assessment is recommended prior to treatment with Lutathera in patients with mild or moderate renal impairment. For additional details see section 4.2 (Table 3 and “Renal impairment” subsection) and section 4.4. The use of Lutathera is contraindicated in patients with kidney failure with creatinine clearance <30 mL/min (see section 4.3).

Neuroendocrine hormonal crises
Hormonal crises related to release of bioactive substances (probably due to lysis of the neuroendocrine tumour cells) have rarely been observed and resolved after appropriate medical treatment (see section 4.4).

Paediatric population

Based on published literature and on clinical data from 11 adolescents with somatostatin receptor-positive GEP-NET or phaeochromocytoma or paraganglioma (PPGL) enrolled in NETTER-P, no new safety signals were reported.

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

Overdose is unlikely with Lutathera as this medicinal product is supplied as a single-dose and ready-to-use product containing a predefined amount of radioactivity and it is administered by persons authorised to handle radiopharmaceuticals after evaluation of the patient by a qualified physician. In the event of overdose, an increase in the frequency of the adverse reactions related to radiotoxicity is expected.

In the event of administration of a radiation overdose with Lutathera, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding during the first 48 hours after infusion. It might be helpful to estimate the effective dose that was applied.

The following laboratory tests should be carried out every week, for the next 10 weeks:
- Haematological monitoring: white blood cell count with differential counts, platelets and haemoglobin
- Blood chemistry monitoring: serum creatinine and glycaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Therapeutic radiopharmaceuticals, Other therapeutic radiopharmaceuticals, ATC code: V10XX04

Mechanism of action

Lutetium (^{177}Lu) oxodotreotide has a high affinity for subtype 2 somatostatin receptors (SSTR2). It binds to malignant cells which overexpress SSTR2.

Lutetium-177 is a β^- emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), causing death of the targeted tumour cells with a limited effect on neighbouring normal cells.

Pharmacodynamic effects

At the concentration used (about 10 µg/mL in total, for both free and radiolabelled forms), the peptide oxodotreotide does not exert any clinically relevant pharmacodynamic effect.

Clinical efficacy and safety

NETTER-1

The NETTER-1 phase III study was a multicentre, stratified, open-label, randomised, comparator-controlled, parallel-group study comparing treatment with Lutathera (4 doses of 7 400 MBq, one dose every 8 weeks [±1 week]) co-administered with an amino acid solution and best supportive care (octreotide long-acting release [LAR] 30 mg after each Lutathera dose and every 4 weeks after completion of Lutathera treatment for symptom control, replaced by short-acting octreotide in the 4-week interval before Lutathera administration) to high-dose octreotide LAR (60 mg every 4 weeks) in patients with inoperable, progressive, somatostatin receptor-positive, midgut carcinoid tumours. The primary endpoint for the study was progression-free survival (PFS) evaluated by response evaluation criteria in solid tumours (RECIST v1.1), based on blinded independent review committee (BIRC) assessment. Secondary efficacy endpoints included objective response rate (ORR), overall survival (OS), time to tumour progression (TTP), safety and tolerability of the medicinal product, and health-related quality of life (HRQoL).

At the time of the primary analysis, 229 patients were randomised to receive either Lutathera (n=116) or high-dose octreotide LAR (n=113). Demographic and baseline disease characteristics were well balanced between the treatment arms with a median age of 64 years and 82.1% Caucasian in the general population.

At the time of the primary PFS analysis (cut-off date 24 July 2015), the number of centrally confirmed disease progressions or deaths was 21 events in the Lutathera arm and 70 events in the high-dose octreotide LAR arm (Table 6). PFS differed significantly ($p<0.0001$) between the treatment arms. The median PFS for the Lutathera arm was not reached at the cut-off date, whereas the median PFS for the high-dose octreotide LAR arm was 8.5 months. The hazard ratio (HR) for the Lutathera arm compared to the high-dose octreotide LAR arm was 0.18 (95% CI: 0.11; 0.29), indicating 82% reduction in the risk of disease progression or death in favour of the Lutathera arm.

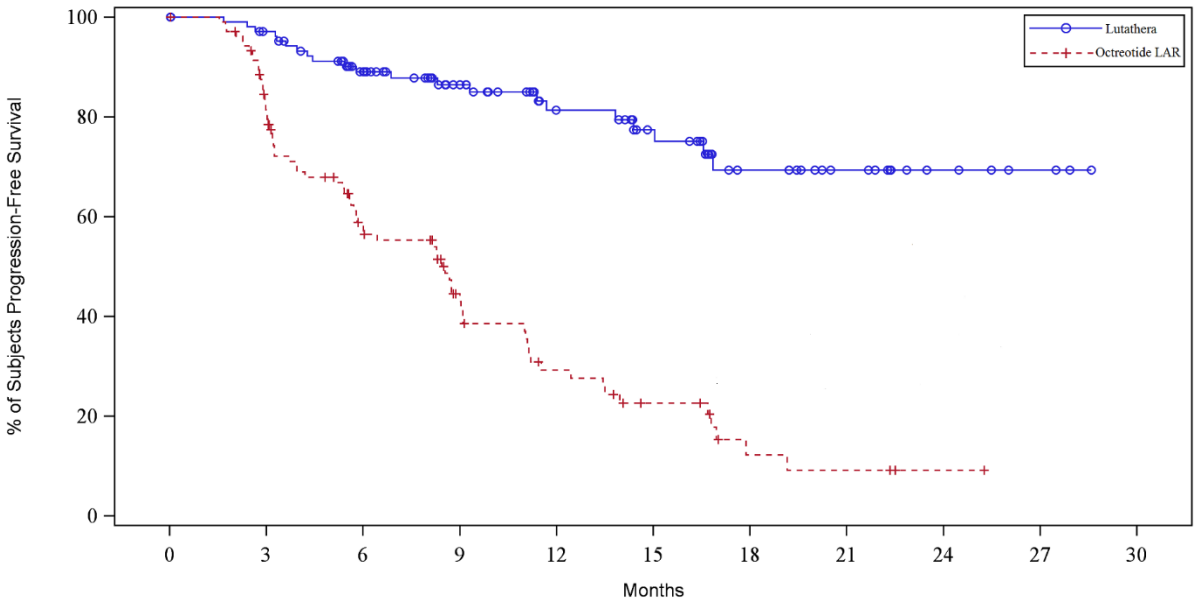
Table 6 PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumours – cut-off date 24 July 2015 (full analysis set [FAS], N=229)

	Treatment	
	Lutathera and octreotide LAR	**High-dose octreotide LAR**
N	116	113
Patients with events	21	70
Censored patients	95	43
Median in months (95% CI)	Not reached	8.5 (5.8; 9.1)
p-value of Log-rank test	<0.0001	
Hazard ratio (95% CI)	0.177 (0.108; 0.289)	

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut-off date 24 July 2015 is depicted in Figure 2.

Figure 2 **PFS Kaplan-Meier curves for patients with progressive midgut carcinoid tumours – cut-off date 24 July 2015 (NETTER-1 phase III study; FAS, N=229)**



At the cut-off date for post-hoc statistical analysis (cut-off date 30 June 2016) including two additional randomised patients (N=231), the number of centrally confirmed disease progressions or deaths was 30 events in the Lutathera arm and 78 events in the high-dose octreotide LAR arm (Table 7). PFS differed significantly (p<0.0001) between the treatment arms. The median PFS for the Lutathera arm was 28.4 months whereas the median PFS for the high-dose octreotide LAR arm was 8.5 months. The hazard ratio for the Lutathera arm compared to the high-dose octreotide LAR arm was 0.21 (95% CI: 0.14; 0.33), indicating 79% reduction in the risk of disease progression or death in favour of the Lutathera arm.

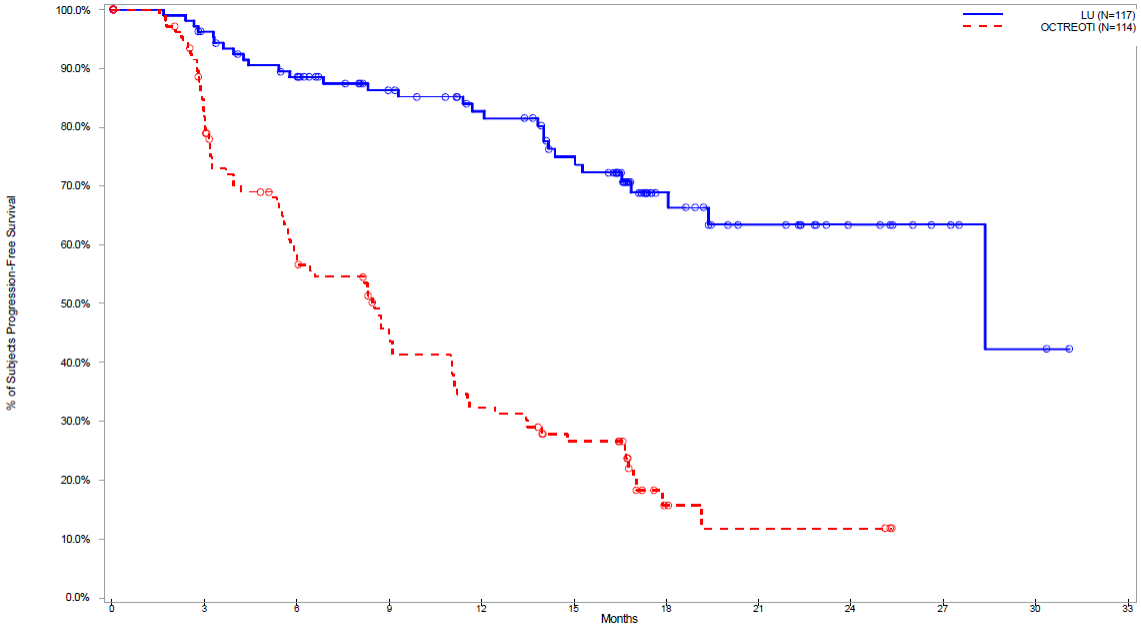
Table 7 **PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumours - cut-off date 30 June 2016 (FAS, N=231)**

	Treatment	
	Lutathera and octreotide LAR	**High-dose octreotide LAR**
N	117	114
Patients with events	30	78
Censored patients	87	36
Median in months (95% CI)	28.4 (28.4; NE)	8.5 (5.8; 11.0)
p-value of Log-rank test	<0.0001	
Hazard ratio (95% CI)	0.214 (0.139; 0.330)	

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the FAS at the cut-off date 30 June 2016 is depicted in Figure 3.

Figure 3 PFS Kaplan-Meier curves for patients with progressive midgut carcinoid tumours – cut-off date 30 June 2016 (NETTER-1 phase III study; FAS, N=231)

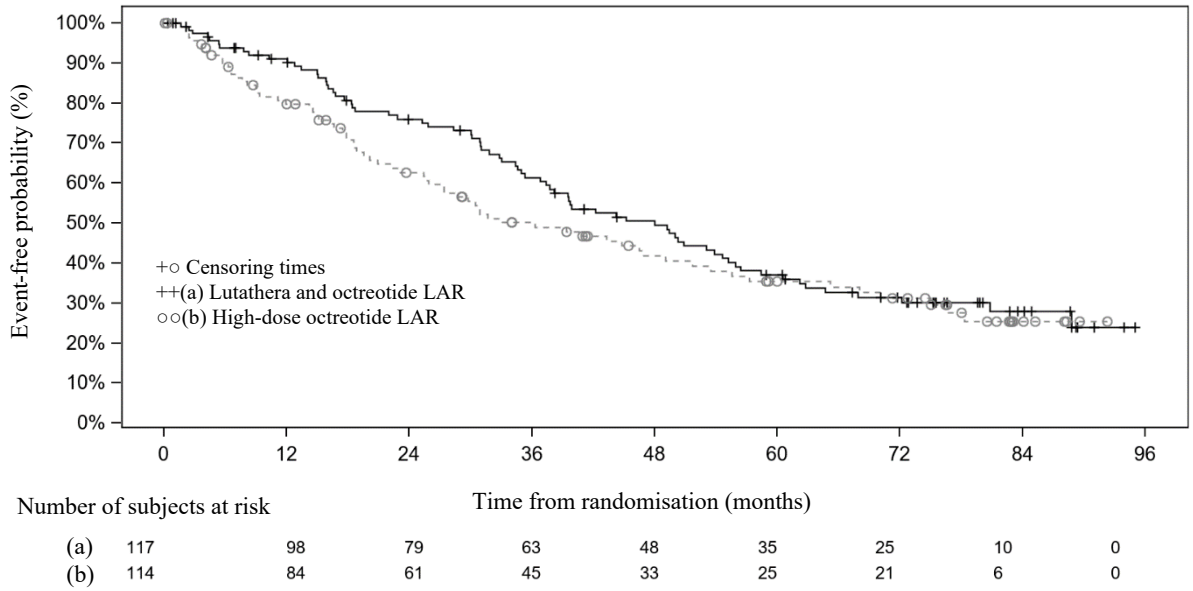


At the time of the interim OS analysis (cut-off date 24 July 2015), there were 17 deaths in the Lutathera arm and 31 deaths in the high-dose octreotide LAR arm, yielding a HR of 0.459 (99.9915% CI: 0.140; 1.506) in favour of the Lutathera arm. The median OS was not reached in the Lutathera arm at the cut-off date, while it was 27.4 months in the high-dose octreotide LAR arm. The interim OS results did not reach statistical significance. An update conducted about one year later (cut-off date 30 June 2016) including two additional randomised patients (N=231) showed a similar trend, with 28 deaths in the Lutathera arm and 43 deaths in the high-dose octreotide LAR arm, yielding a HR of 0.536 in favour of the Lutathera arm. The median OS was still not reached in the Lutathera arm at the cut-off date, while it was 27.4 months in the high-dose octreotide LAR arm.

At the time of the final OS analysis, which occurred 5 years after the last patient was randomised (N=231, cut-off date 18 January 2021), the median follow-up duration was 76 months in each study arm. There were 73 deaths in the Lutathera arm (62.4%) and 69 deaths in the high-dose octreotide LAR arm (60.5%), yielding a HR of 0.84 (95% CI: 0.60; 1.17; unstratified Log-rank test p=0.3039, two-sided) in favour of the Lutathera arm. The median OS was prolonged by a clinically relevant extent of 11.7 months in patients randomised to the Lutathera arm compared to patients randomised to high-dose octreotide LAR, with a median OS of 48.0 months (95% CI: 37.4; 55.2) and 36.3 months (95% CI: 25.9; 51.7), respectively. The final OS results did not reach statistical significance. In the high-dose octreotide LAR arm, 22.8% of patients received subsequent radioligand therapy (including lutetium (^{177}Lu) oxodotreotide) within 24 months of randomisation, and 36% of patients received subsequent radioligand therapy by the final OS cut-off date, which along with other factors may have influenced the OS in this subset of patients.

The OS Kaplan-Meier graph for the FAS at the cut-off date 18 January 2021 is depicted in Figure 4.

Figure 4 OS Kaplan-Meier curves for patients with progressive midgut carcinoid tumours – cut-off date 18 January 2021 (NETTER-1 phase III study; FAS, N=231)



In presence of non-proportional hazards, an additional sensitivity analysis (Restricted mean survival time) was performed at the time of the final OS analysis to further estimate the treatment effect (Table 8). At 60 months after randomisation, the average OS benefit was 5.1 months (95% CI: -0.5; 10.7) longer in the Lutathera arm compared to the high-dose octreotide LAR arm.

Table 8 OS by restricted mean survival time (RMST) observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumours (FAS, N=231)

		Lutathera and octreotide LAR N=117	**High-dose octreotide LAR N=114**
24 months	Deaths, n (%)	26 (22.2)	39 (34.2)
	RMST (95% CI)	21.2 (20.2; 22.3)	19.3 (18.0; 20.7)
	Difference (95% CI)	1.9 (0.1; 3.6)	
36 months	Deaths, n (%)	41 (35.0)	51 (44.7)
	RMST (95% CI)	29.7 (27.7; 31.6)	26.0 (23.7; 28.3)
	Difference (95% CI)	3.7 (0.7; 6.7)	
48 months	Deaths, n (%)	53 (45.3)	58 (50.9)
	RMST (95% CI)	36.2 (33.4; 39.0)	31.5 (28.3; 34.8)
	Difference (95% CI)	4.6 (0.3; 8.9)	
60 months	Deaths, n (%)	65 (55.6)	63 (55.3)
	RMST (95% CI)	41.2 (37.6; 44.9)	36.1 (31.9; 40.4)
	Difference (95% CI)	5.1 (-0.5; 10.7)	

Health-Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (generic instrument) and its neuroendocrine tumour module (EORTC QLQ-GI.NET-21).

The results indicate an improvement in the overall global health-related quality of life up to week 84, for patients in the Lutathera treatment arm as compared to patients in the high-dose octreotide LAR arm.

ERASMUS

The Erasmus phase I/II study was a monocentric single-arm open-label study to evaluate the efficacy of Lutathera (4 doses of 7 400 MBq each, one dose every 8 weeks) co-administered with amino acid solution in patients with somatostatin receptor-positive tumours. The median age of patients enrolled in the study was 59 years. Most patients were Dutch (811) with the remaining (403) residents of various European and non-European countries. The main analysis included 811 Dutch patients with different somatostatin receptor-positive neuroendocrine tumour types (NETs). The ORR (including complete response [CR] and partial response [PR] according to RECIST criteria) and duration of response (DoR) for the FAS Dutch population with gastroenteropancreatic (GEP) and bronchial NETs (360 patients) as well as per tumour type are presented in Table 9.

Table 9 Best response, ORR and DoR observed in the Erasmus phase I/II study in Dutch patients with GEP and bronchial NETs – (FAS, N=360)

	N	CR		PR		SD		ORR				DoR (months)		
Tumour type		**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**	**95%CI**		**Median**	**95%CI**	
All NETs*	360	11	3%	151	42%	183	51%	162	45%	40%	50%	16.3	12.2	17.8
Bronchial	19	0	0%	7	37%	11	58%	7	37%	16%	62%	23.9	1.7	30.0
Pancreatic	133	7	5%	74	56%	47	35%	81	61%	52%	69%	16.3	12.1	21.8
Foregut**	12	1	8%	6	50%	4	33%	7	58%	28%	85%	22.3	0.0	38.0
Midgut	183	3	2%	58	32%	115	63%	61	33%	27%	41%	15.3	10.5	17.7
Hindgut	13	0	0%	6	46%	6	46%	6	46%	19%	75%	17.8	6.2	29.9

CR = Complete response; PR = Partial response; SD = Stable disease; ORR = Objective response rate (CR+PR); DoR = Duration of response

* Includes foregut, midgut and hindgut; **Foregut NETs other than bronchial and pancreatic

The overall median PFS and OS for the FAS Dutch population with GEP and bronchial NETs as well as per tumour type are presented in Table 10.

Table 10 PFS and OS observed in the Erasmus phase I/II study in Dutch patients with GEP and bronchial NETs – (FAS, N=360)

		PFS **Time** (months)			**OS** **Time** (months)		
		Median	95%CI		Median	95%CI	
All NETs*	360	28.5	24.8	31.4	61.2	54.8	67.4
Bronchial	19	18.4	10.4	25.5	50.6	31.3	85.4
Pancreatic	133	30.3	24.3	36.3	66.4	57.2	80.9
Foregut**	12	43.9	10.9	ND	NR	21.3	ND
Midgut	183	28.5	23.9	33.3	54.9	47.5	63.2
Hindgut	13	29.4	18.9	35.0	NR	ND	ND

PFS = Progression free survival; OS = Overall survival; ND = Not detected, NR = Not reached

* Includes foregut, midgut and hindgut; **Foregut NETs other than bronchial and pancreatic

In the Erasmus phase I/II study 188 patients (52%) received and 172 (48%) did not receive concomitant octreotide LAR during Lutathera treatment. No statistically significant difference in PFS was observed between the subgroup of patients who did not receive octreotide LAR (25.4 months [95% CI 22.8; 30.6]) and the subgroup of patients who did receive concomitant treatment with octreotide LAR (30.9 months [95% CI 25.6; 34.8]) (p= 0.747).

Paediatric population

NETTER-P

The NETTER-P phase II study was a multicentre, open-label, single-arm study to evaluate the safety and dosimetry of Lutathera in adolescents aged 12 to <18 years with somatostatin receptor-positive GEP-NET or PPGL. The treatment consisted of 4 Lutathera doses of 7 400 MBq (200 mCi), one dose every 8 weeks (±1 week), co-administered with an amino acid solution of 2.5% arginine and 2.5% lysine.

Primary endpoints included the measurement of target organ absorbed radiation doses (see section 11) and the incidence of adverse events and laboratory toxicities after the first Lutathera administration in the pooled population of GEP-NET and PPGL patients. All efficacy endpoints were exploratory.

At the time of the primary analysis (cut-off date 12 March 2024), 11 patients were enrolled with somatostatin receptor-positive tumours, 4 with GEP-NETs and 7 with PPGLs. Patients had a median age of 15 years (range: 13 to 17 years), 6 were female. The mean number of cycles of Lutathera administered was 3.6 (± 0.9), with 9 patients (4 GEP-NET, 5 PPGL) receiving 4 cycles, 1 PPGL patient receiving 3 cycles, and 1 PPGL patient receiving 1 cycle of Lutathera. As per NETTER-P study protocol dose modification criteria, a 50% dose reduction was implemented in 2 PPGL patients after the first cycle due to the estimated cumulative organ absorbed dose for the kidney exceeding 29 Gy.

Out of the 4 GEP-NET patients, two had G1 and two had G2 tumours. All GEP-NET patients had metastatic disease. All 4 patients with GEP-NET underwent surgery and received ≥1 line of prior antineoplastic treatments. All PPGL patients, including 5 patients with extra-adrenal paraganglioma and 2 patients with adrenal pheochromocytoma, had metastatic disease. Two of these patients had prior unilateral nephrectomy. Six of the PPGL patients had received prior antineoplastic treatment.

At the time of the primary analysis (cut-off date 12 March 2024), 9 patients (3 with GEP-NET and 6 with PPGL) had overall response data available, and had stable disease as the best overall response (BOR). One of the three GEP-NET patients had progressive disease 3 months after the last dose was administered and discontinued from the study. The fourth GEP-NET patient had tumour not evaluable by CT/MRI scan. One of the PPGL patients discontinued from the treatment based on physician decision after the first cycle and remained in the study for long-term follow up. Ten of eleven patients remained in the study and were alive without tumour progression.

The overall safety profile of Lutathera in adolescent patients with GEP-NET or PPGL in the NETTER-P study was consistent with that reported in the GEP-NET adult population. However, long-term safety data in adolescent patients from the NETTER-P study are currently not available.

The safety and efficacy of Lutathera have not been established in paediatric patients aged below 18 years. The European Medicines Agency has waived the obligation to submit the results of studies with Lutathera in the paediatric population from birth to less than 12 years of age in the treatment of GEP-NETs (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

This medicinal product is administered intravenously and is immediately and completely bioavailable.

Distribution

An analysis performed with human plasma to determine the extent of plasma protein binding of non-radioactive compound (lutetium (^{175}Lu) oxodotreotide) showed that about 50% of the compound is bound to plasmatic proteins.

Transchelation of lutetium-177 from lutetium (^{175}Lu) oxodotreotide into serum proteins has not been observed.

Organ uptake

Within 4 hours after administration, the distribution pattern of lutetium (^{177}Lu) oxodotreotide shows a rapid uptake in kidneys, tumour lesions, liver, and spleen, and in some patients, in the pituitary gland and in the thyroid. The co-administration of amino acid solution decreases the kidney uptake, enhancing the elimination of radioactivity (see section 4.4). Biodistribution studies show that lutetium (^{177}Lu) oxodotreotide is rapidly cleared from the blood.

Biotransformation

There is evidence, from the analysis of urine samples of 20 patients included in the NETTER-1 phase III dosimetry, pharmacokinetic and ECG sub-study, that lutetium (^{177}Lu) oxodotreotide is poorly metabolised and is excreted mainly as intact compound via the renal route.

The high performance liquid chromatography (HPLC) analyses performed on urine samples collected up to 48 hours post infusion showed unchanged lutetium (^{177}Lu) oxodotreotide close to 100% in most of the analysed samples (with lowest value being greater than 92%), indicating that the compound is eliminated in urine mainly as intact compound.

This evidence confirms what was previously observed in the Erasmus phase I/II study, in which HPLC analysis of a urine specimen collected 1 hour post administration of lutetium (^{177}Lu) oxodotreotide from one patient receiving 1.85 MBq of lutetium (^{177}Lu) oxodotreotide indicated that the main portion (91%) was excreted unchanged.

These findings are supported by *in vitro* metabolism data in human hepatocytes, in which no metabolic degradation of lutetium (^{175}Lu) oxodotreotide was observed.

Elimination

Based on the data collected during the Erasmus phase I/II and NETTER-1 phase III studies, lutetium (^{177}Lu) oxodotreotide is primarily eliminated by renal excretion: about 60% of the medicinal product is eliminated in the urine within 24 hours, and about 65% within 48 hours following the administration.

Elderly

The pharmacokinetic profile in elderly patients (≥75 years) has not been established. No data are available.

Paediatric population (12 years to <18 years of age)

Pharmacokinetic data were collected from 11 adolescents aged 12 years and older with somatostatin receptor-positive GEP-NET or PPGL enrolled in the NETTER-P study using the adult dosage. These data were within the range of values in adults, with a mean AUC_{inf} of 35.8 ng.h/mL (CV 12.5%), a mean CL of 6.0 L/h (CV 11.5%) and a mean C_{max} of 10.3 ng/mL (CV 5.2%), which occurred at the end of the Lutathera infusion.

In vitro evaluation of interaction potential

Metabolic and transporter based interaction
The absence of inhibition or significant induction of the human CYP450 enzymes, and the absence of specific interaction with P-glycoprotein (efflux transporter) or OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and BCRP transporters in preclinical studies, suggest that Lutathera has a low probability of causing significant metabolism- or transporter-mediated interactions.

5.3 Preclinical safety data

Toxicological studies in rats demonstrated that a single intravenous injection of up to 4 550 MBq/kg was well tolerated and no deaths were observed. When testing the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) as a single intravenous injection in rats and dogs at doses up to 20 000 µg/kg (rats) and 3 200 µg/kg (dogs), the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) was well tolerated in both species and no deaths were observed. Toxicity with 4 repeated administrations, once every 2 weeks, of 1 250 µg/kg of the cold compound in rats and 80 µg/kg in dogs was not observed. This medicinal product is not intended for regular or continuous administration.

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.
Non-clinical data on the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Sodium acetate
Gentisic acid
Ascorbic acid
Pentetic acid
Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

72 hours from the date and time of calibration.

6.4 Special precautions for storage

Store below 25°C.

Do not freeze.

Store in the original package to protect from ionising radiation (lead shielding).

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

6.5 Nature and contents of container

Clear, colourless Type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal.

Each vial contains a volume that ranges from 20.5 to 25.0 mL of solution, corresponding to an activity of 7 400 MBq at date and time of infusion.

The vial is enclosed within a lead container for protective shielding.

6.6 Special precautions for disposal and other handling

For single use only.

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

If at any time in the preparation of this medicinal product the integrity of the lead container or the vial 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.

It is necessary to wear waterproof gloves and follow suitable aseptic techniques when handling the medicinal product.

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.

This preparation is likely to result in a relatively high radiation dose to most patients. The administration of 7 400 MBq may result in significant environmental hazard.

This may be of concern to others living in the same household as individuals undergoing treatment or to the general public depending on the level of activity administered, hence radioprotection rules should be followed (see section 4.4). Suitable precautions in accordance with national regulations should be taken concerning the activity eliminated by the patients in order to avoid any contaminations.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Lutetium-177 for Lutathera may be prepared using two different sources of stable nuclides (either lutetium-176 or ytterbium-176) resulting in different waste management. The user must consult the documentation provided before using Lutathera to ensure appropriate waste management.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1226/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017
Date of latest renewal: 08 July 2022

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The following conclusions on treatment with Lutathera were determined from radiation dosimetry evaluations performed in clinical studies:

- The critical organ is the bone marrow. However, with the recommended Lutathera cumulative dose of 29 600 MBq (4 administrations of 7 400 MBq), no correlation between haematological toxicity and the total radioactivity administered or bone marrow absorbed dose has been observed either in the Erasmus phase I/II or in the NETTER-1 phase III study.
- The kidney is not a critical organ if a co-infusion of an appropriate amino acid solution is performed (see section 4.2).

Overall, the results of the dosimetric analysis performed in the NETTER-1 phase III dosimetry sub-study and in the Erasmus phase I/II study are in agreement and indicate that the Lutathera dose regimen (4 administrations of 7 400 MBq) is safe.

Table 11 Absorbed dose estimates for lutetium (^{177}Lu) oxodotreotide from NETTER-1 phase III study (Olinda output)

Organ	**Organ absorbed dose per unit activity (mGy/MBq) (n = 20)**	
	Mean	**SD**
Adrenals	0.037	0.016
Brain	0.027	0.016
Breasts	0.027	0.015
Gallbladder wall	0.042	0.019
Lower large intestine wall	0.029	0.016
Small intestine	0.031	0.015
Stomach wall	0.032	0.015
Upper large intestine wall	0.032	0.015
Heart wall	0.032	0.015
Kidneys	0.654	0.295
Liver*	0.299	0.226
Lungs	0.031	0.015
Muscle	0.029	0.015
Ovaries***	0.031	0.013
Pancreas	0.038	0.016
Red marrow	0.035	0.029
Osteogenic cells	0.151	0.268
Skin	0.027	0.015
Spleen	0.846	0.804
Testes**	0.026	0.018
Thymus	0.028	0.015
Thyroid	0.027	0.016
Urinary bladder wall	0.437	0.176
Uterus***	0.032	0.013
Total body	0.052	0.027

*n=18 (two patients excluded because the liver absorbed dose was biased by the uptake of the liver metastases)
**n=11 (male patients only)
***n=9 (female patients only)

Radiation dose to specific organs, which may not be the target organ of therapy, can be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

Paediatric population

Dosimetry of lutetium (^{177}Lu) oxodotreotide in adolescents has been studied in 4 GEP-NET and 6 PPGL patients (age range: 12 to <18 years) enrolled in the phase II NETTER-P study. Dosimetry was collected to define the biodistribution profile of lutetium (^{177}Lu) oxodotreotide and to calculate whole body and organ radiation dosimetry, with particular focus on the radiation absorbed dose to critical organs (e.g. kidney and bone marrow).

The mean and SD of the estimated radiation absorbed doses for adolescents in the NETTER-P study are shown in Table 12.

Table 12 Absorbed dose estimates for lutetium (^{177}Lu) oxodotreotide in paediatric patients 12 years and older (n=10) in NETTER-P phase II study

Organ	Organ absorbed dose per unit activity (mGy/MBq)		Calculated absorbed dose for 4 x 7.4 GBq (29.6 GBq cumulative activity) (Gy)		Theoretical cumulative absorbed dose (Gy)
	Mean	SD	Mean	SD	Min-Max
Adrenals	0.045	0.011	1.3	0.3	0.64-1.7
Brain	0.020	0.006	0.6	0.2	0.38-0.86
Breasts[a]	0.018	0.005	0.5	0.2	0.37-0.75
Oesophagus	0.023	0.006	0.7	0.2	0.40-0.93
Eyes	0.020	0.006	0.6	0.2	0.38-0.86
Gallbladder wall	0.030	0.010	0.9	0.3	0.48-1.5
Heart wall	0.023	0.006	0.7	0.2	0.40-0.92
Kidneys	0.778	0.280	23.0	8.3	14-40
Left colon	0.273	0.074	8.1	2.2	4.6-12
Liver	0.210	0.205	6.2	6.1	2.4-23
Lungs	0.023	0.006	0.7	0.2	0.40-0.91
Osteogenic cells	0.045	0.017	1.3	0.5	0.64-2.1
Ovaries[b]	0.026	0.007	0.8	0.2	0.49-1.0
Pancreas	0.027	0.006	0.8	0.2	0.46-1.1
Pituitary[c]	1.114	0.425	33.0	12.6	18-56
Prostate[d]	0.025	0.006	0.7	0.2	0.62-0.98
Rectum	0.277	0.076	8.2	2.2	4.8-12
Red marrow (blood)[e]	0.026	0.005	0.8	0.1	0.55-1.0
Red marrow (image)[e]	0.057	0.027	1.7	0.8	0.70-2.8
Right colon	0.156	0.041	4.6	1.2	2.7-6.5
Salivary glands	0.033	0.017	1.0	0.5	0.38-1.7
Small intestine	0.045	0.011	1.3	0.3	0.85-1.9
Spleen	0.742	0.275	22.0	8.1	8.3-34
Stomach wall	0.026	0.006	0.8	0.2	0.44-1.0
Testes[d]	0.020	0.005	0.6	0.1	0.50-0.81
Thymus	0.022	0.006	0.6	0.2	0.39-0.88
Thyroid	0.027	0.017	0.8	0.5	0.38-2.2
Urinary bladder wall	0.552	0.089	16.4	2.6	14-20
Uterus[b]	0.030	0.008	0.9	0.2	0.59-1.2
Total body	0.040	0.010	1.2	0.3	0.66-1.6

[a] n=5 (female patients only).

[b] n=6 (female patients only).

[c] n=9 (3 GEP-NET, 6 PPGL). Pituitary dosimetry estimates were only performed when pituitary uptake was clearly observed on the planar images. Due to the small size of the pituitary gland, availability for quantification only from planar images and interference from activity in the nasal mucosa, estimates can be associated with a large uncertainty.

[d] n=4 (male patients only).

[e] Red marrow dosimetry estimates were determined either using blood radioactivity or by imaging and scaling of a representative region of the lumbar spine.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The user must consult the documentation provided before using Lutathera to ensure appropriate waste management (see section 6.6).

Preparation instructions

- Use aseptic technique and radiation shielding when administering the Lutathera solution. Use tongs when handling the vial to minimise radiation exposure.
- Visually inspect the product under a shielded screen for particulate matter and discolouration prior to administration. Discard the vial if particulates and/or discolouration are present.
- Inspect the package for damage and use a calibrated radioactivity measurement system to determine if any radioactive contamination is present. Do not use the product if the integrity of the vial or the lead container is compromised.
- Do not inject the Lutathera solution directly into any other intravenous solution.
- Confirm the amount of radioactivity of Lutathera delivered to the patient with a calibrated radioactivity measurement system prior to and after each Lutathera administration to confirm that the actual amount of radioactivity administered is equal to the planned amount.
- Do not administer Lutathera as an intravenous bolus.
- Soon after the start of the infusion, monitor the radioactivity emission from the patient using a calibrated radioactivity measurement system to ensure the dose is delivered. During the infusion, the radioactivity emission from the patient should steadily increase, while that from the Lutathera vial should decrease.
- Careful monitoring of the patient's vital signs during the infusion is recommended.

Intravenous methods of administration

Instructions for the gravity method (using a clamp or an infusion pump)

1. Insert a 2.5 cm, 20-gauge needle (short needle) into the Lutathera vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport the Lutathera solution during the infusion). Ensure that the short needle does not touch the Lutathera solution in the vial and do not connect this short needle directly to the patient. Do not allow the sodium chloride solution to flow into the Lutathera vial prior to the initiation of the Lutathera infusion and do not inject the Lutathera solution directly into the sodium chloride solution.
2. Insert a second needle that is 9 cm, 18-gauge (long needle) into the Lutathera vial, ensuring that this long needle touches and is secured to the bottom of the Lutathera vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is pre-filled with 0.9% sterile sodium chloride solution and that is used for the Lutathera infusion into the patient.
3. Use a clamp or an infusion pump to regulate the flow of the sodium chloride solution via the short needle into the Lutathera vial. The sodium chloride solution entering the vial through the short needle will carry the Lutathera solution from the vial to the patient via the intravenous catheter connected to the long needle over a total duration of 30±10 minutes, at an infusion rate of up to 400 mL/h. The infusion should start at a lower rate of <100 mL/h for the first 5 to 10 minutes and should then be increased depending on the patient's venous status. Constant intra-vial pressure should be maintained during the entire infusion.
4. During the infusion, ensure that the level of solution in the Lutathera vial remains constant by repeated direct visual control when transparent shielded container is used, or using a pair of tongs to handle the vial when the lead shipping container is used.
5. Monitor the flow of Lutathera from the vial to the patient during the entire infusion.
6. Disconnect the vial from the long needle line and clamp the sodium chloride solution line once the level of radioactivity is stable for at least five minutes.
7. Follow the infusion with an intravenous flush of 25 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

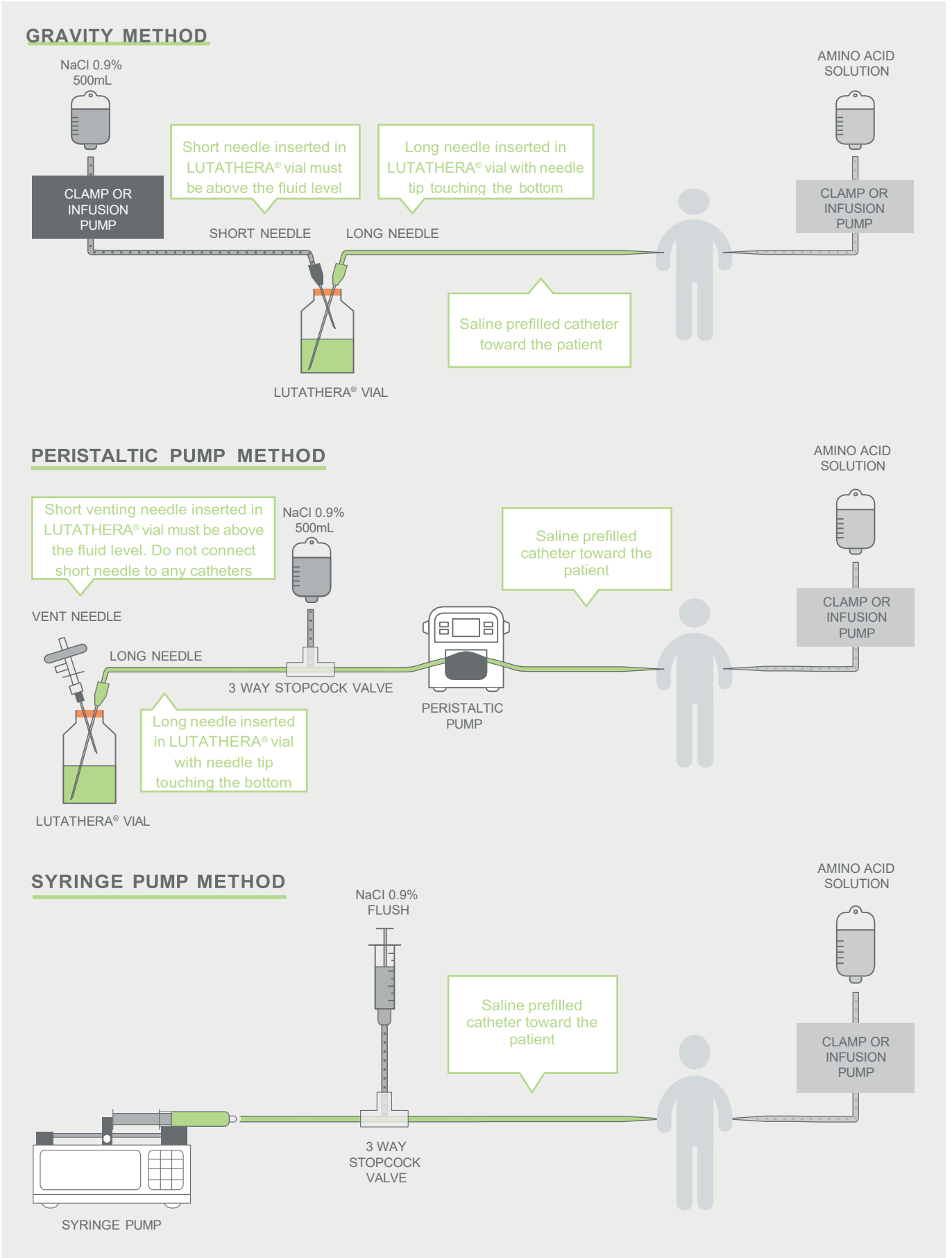
Instructions for the peristaltic pump method

1. Insert a filtered 2.5 cm, 20-gauge needle (short venting needle) into the Lutathera vial. Ensure that the short needle does not touch the Lutathera solution in the vial and do not connect the short needle directly to the patient or to the peristaltic pump.
2. Insert a second needle that is 9 cm, 18-gauge (long needle) into the Lutathera vial, ensuring that the long needle touches and is secured to the bottom of the Lutathera vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
3. Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic pump following the pump manufacturer's instructions.
4. Prime the line by opening the 3-way stopcock valve and pumping the Lutathera solution through the tubing until it reaches the exit of the valve.
5. Prime the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
6. Connect the primed intravenous catheter to the patient and set the 3-way stopcock valve such that the Lutathera solution is in line with the peristaltic pump.
7. Infuse an appropriate volume of Lutathera solution over a 30±10-minute period to deliver the desired radioactivity.
8. When the desired Lutathera radioactivity has been delivered, stop the peristaltic pump, and then change the position of the 3-way stopcock valve so that the peristaltic pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic pump and infuse an intravenous flush of 25 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the syringe pump method

1. Withdraw an appropriate volume of Lutathera solution to deliver the desired radioactivity by using a disposable syringe fitted with a syringe shield and a disposable sterile needle that is 9 cm, 18-gauge (long needle). To aid the withdrawal of the solution, it is possible to use a filtered 2.5 cm, 20-gauge needle (short venting needle) to reduce the resistance from the pressurised vial. Ensure that the short needle does not touch the Lutathera solution in the vial.
2. Fit the syringe into the shielded pump and include a 3-way stopcock valve between the syringe and an intravenous catheter that is pre-filled with 0.9% sterile sodium chloride solution and that is used for Lutathera administration to the patient.
3. Infuse an appropriate volume of Lutathera solution over a 30±10-minute period to deliver the desired radioactivity.
4. When the desired Lutathera radioactivity has been delivered, stop the syringe pump and then change the position of the 3-way stopcock valve so as to flush the syringe with 25 mL of 0.9% sterile sodium chloride solution. Restart the syringe pump.
5. After the flush of the syringe has been completed, perform an intravenous flush with 25 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Figure 5 Overview of methods of administration



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

ANNEX II

A. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Advanced Accelerator Applications Ibérica, S.L.U.
Polígono Industrial la Cuesta – Sector 3
Parcelas 1 y 2 La Almunia de Doña Godina
50100 Zaragoza
Spain

Advanced Accelerator Applications (Italy) S.r.l
Via Ribes 5
10010
Colleretto Giacosa (TO)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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.

- **Additional risk minimisation measures**

Prior to launch of Lutathera in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing patients' awareness on the risk of radiotoxicity by occupational exposure and inadvertent exposure to peptide receptor radionuclide therapy, and at providing information concerning the necessary precautions to take to limit unnecessary exposure to themselves and the people around them.

The MAH shall ensure that in each Member State where Lutathera is marketed, all patients/carers who are expected to be administered Lutathera have access to/are provided with a patient educational material containing:

- The package leaflet
- Patient guide

The patient guide shall contain the following key elements:

- Brief introduction to the treatment and the administration procedure
- Information on the precautions the patient should take before, during and after the administration procedure, at the hospital and at home, to limit unnecessary exposure to radiations of themselves and their entourage.
- Information that PPRT can cause serious side effects during or after treatment and that any side effect should be reported to the physician.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LEAD SHIELDING CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Lutathera 370 MBq/mL solution for infusion
lutetium (^{177}Lu) oxodotreotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One mL contains 370 MBq of lutetium (^{177}Lu) oxodotreotide at calibration time.
Volumetric activity at calibration time: 370 MBq/mL - {DD/MM/YYYY hh:mm UTC}

3. LIST OF EXCIPIENTS

Acetic acid, sodium acetate, gentisic acid, ascorbic acid, pentetic acid, sodium chloride, sodium hydroxide, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

Vial no.: {X}
Volume: {Y} mL
Activity at infusion time: {Z} MBq - {DD/MM/YYYY hh:mm UTC}

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Single-dose vial.
Read the package leaflet before use.

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:mm UTC}

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Do not freeze.
Store in the original package to protect from ionising radiation (lead shielding).

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 should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1226/001

13. BATCH NUMBER

Batch:

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

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

Lutathera 370 MBq/mL solution for infusion
lutetium (^{177}Lu) oxodotreotide
Intravenous use

2. METHOD OF ADMINISTRATION

Single-dose vial.

3. EXPIRY DATE

EXP: {DD/MM/YYYY hh:mm UTC}

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Vial no.: {X}
Volume: {Y} mL
Volumetric activity at calibration time: 370 MBq/mL - {DD/MM/YYYY hh:mm UTC}
Activity at infusion time: {Z} MBq - {DD/MM/YYYY hh:mm UTC}

6. OTHER



Manufacturer
Advanced Accelerator Applications Ibérica, S.L.U.
Polígono Industrial la Cuesta – Sector 3
Parcelas 1 y 2 La Almunia de Doña Godina
50100 Zaragoza
Spain

Advanced Accelerator Applications (Italy) S.r.l
Via Ribes 5
10010
Colleretto Giacosa (TO)
Italy

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lutathera 370 MBq/mL solution for infusion
lutetium (^{177}Lu) oxodotreotide

Read all of this leaflet carefully before you are given this medicine 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 doctor or other healthcare professional who will supervise the procedure.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lutathera is and what it is used for
2. What you need to know before Lutathera is used
3. How Lutathera is used
4. Possible side effects
5. How Lutathera is stored
6. Contents of the pack and other information

1. What Lutathera is and what it is used for

What Lutathera is
Lutathera contains lutetium (^{177}Lu) oxodotreotide. This medicine is a radiopharmaceutical product for therapy only.

What Lutathera is used for
Lutathera is used for the treatment of adults with certain tumours (gastroenteropancreatic neuroendocrine tumours), which cannot be completely removed from your body by surgery, have spread in your body (metastatic) and do not respond any more to your current treatment.

How Lutathera works
The tumour needs to have somatostatin receptors on the surface of its cells in order for the medicine to be effective. Lutathera binds with these receptors and emits radioactivity directly into the tumour cells, causing their death.

The use of Lutathera involves exposure to amounts of 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.

2. What you need to know before Lutathera is used

Lutathera must not be used
- if you are allergic to lutetium (^{177}Lu) oxodotreotide or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant, think you may be pregnant or if it has not been confirmed that you are not pregnant.
- if your kidneys are seriously impaired.

Warnings and precautions
Talk to your doctor before you are given Lutathera as it may cause:
- secondary blood cancer (myelodysplastic syndrome or acute leukaemia), which can occur in rare cases several years after completion of Lutathera treatment.

If any of these apply to you before or during treatment with Lutathera, tell your doctor or other healthcare professional:
- if you have or have had weakness, tiredness, shortness of breath, poor concentration, infections, fever, bleeding or bruising more easily than normal or difficulty to stop bleeding (signs and symptoms of myelosuppression).
- if you have had any other type of cancer in the last 5 years, bone metastasis, or previous anti-cancer treatment (chemotherapy) or radiation therapy.
- if you have or have had swollen feet and ankles, too much urine or not enough urine, itching or trouble catching your breath (signs and symptoms of chronic kidney disease).
- if you have or have had itchy yellow skin, yellowing of the whites of your eyes, nausea or vomiting, tiredness, loss of appetite, pain in the upper right side of your stomach area (abdomen), dark or brown urine, or bleeding or bruising more easily than normal (signs and symptoms of liver disease).
- if you have breathlessness, weakness, numbness, chest pain, palpitations or abnormal heart rhythm (signs and symptoms of high potassium levels in blood, also known as hyperkalaemia).
- if you have breathlessness, difficulty breathing when lying down or swelling of the feet or legs (signs and symptoms of heart failure).
- if your kidney or urinary tract is not correctly developed.
- if you suffer from urinary incontinence.

Tell your doctor or other healthcare professional right away if you experience any of the following after the start of Lutathera treatment:
- facial/throat swelling and/or difficulty breathing (signs and symptoms of angioedema).
- flushing, diarrhoea, difficulty breathing with wheezing or coughing, dizziness, light-headedness (signs and symptoms of neuroendocrine hormone crisis), which may appear within the first 24 hours after Lutathera administration.
- tiredness, loss of appetite, changes in your heartbeat, trouble thinking clearly (signs and symptoms of metabolic acidosis).
- muscle cramping, muscle weakness, confusion or shortness of breath (signs and symptoms of tumour lysis syndrome). Treatment with Lutathera (lutetium (^{177}Lu) oxodotreotide) 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 order blood tests to monitor you for this syndrome.

Unless your doctor considers that the clinical benefit of the treatment outweighs the possible risks, you will not be given this medicine:
- if you have ever received external radiation therapy on more than 25% of your bone marrow.
- if your heart is seriously impaired.
- if you have seriously affected blood cell counts.
- if your liver is seriously impaired.
- if it appears that your tumour does not have sufficient somatostatin receptors.

Before administration of Lutathera you should
- drink plenty of water in order to urinate as often as possible during the first hours after the infusion.

Children and adolescents
The safety and efficacy of this medicine have not been established in children and adolescents under 18 years of age. Talk to your doctor or nuclear medicine doctor if you are under 18 years old.

Other medicines and Lutathera
Tell your doctor or nuclear medicine doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, since they may interfere with your treatment. This includes in particular somatostatin analogues or glucocorticoids (also called corticosteroids). If you are taking somatostatin analogues you might be asked to stop and/or adapt your treatment for a short period of time.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines mentioned above.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nuclear medicine doctor for advice before you are given this medicine.

Lutathera must not be given to pregnant women as ionising radiation is dangerous for the unborn baby. Breast-feeding must be stopped during treatment with this medicine. If treatment with Lutathera during breast-feeding is necessary, the child must be weaned.

You must inform your doctor and/or the nuclear medicine doctor before the administration of Lutathera if there is a possibility you might be pregnant or if you have missed your period or if you are breast-feeding.

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

Female patients should use effective birth control during Lutathera treatment and for 7 months after completing the treatment.

Male patients should use effective birth control during treatment and for 4 months after completing the treatment.

If you are a woman who could become pregnant, your doctor or other healthcare professional will check if you are pregnant and perform a pregnancy test, if necessary, before starting treatment with Lutathera.

If you become pregnant or think you are pregnant after starting treatment with Lutathera, tell your doctor and/or nuclear medicine doctor right away.

The radiation coming from the medicine may potentially decrease your fertility. A consultation with a genetic counsellor is recommended if you wish to have children after treatment. Preservation of sperm or eggs may be offered to you before the treatment.

Driving and using machines
It is considered unlikely that Lutathera will affect your ability to drive or to use machines. However, your general condition and the possible adverse reactions to treatment must be taken into account before driving or using machines.

Lutathera contains sodium
This medicine contains up to 81.1 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Lutathera is used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Lutathera 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.

How much Lutathera is given
The recommended dose is 7 400 MBq (megabecquerel, the unit used to express radioactivity), which is given as a single infusion once approximately every 8 weeks for a total of 4 times.

Administration of Lutathera and conduct of the procedure
Lutathera is administered directly into a vein.

Due to the radiation emitted by this medicine, during the administration procedure you should be isolated from other patients who are not receiving the same treatment. The doctor or other healthcare professional will inform you when you can leave the controlled area of the hospital.

In addition to Lutathera, you will be given an infusion with amino acids in order to protect your kidneys. This might cause nausea and vomiting and before the start of treatment you will therefore also receive an injection with a medicine that will help to reduce these symptoms.

Duration of the administration procedure
Your nuclear medicine doctor or other healthcare professional will inform you about the usual duration of the procedure.
The infusion of Lutathera takes 30 ±10 minutes, but the complete administration procedure will take approximately 5 hours. Your doctor will regularly monitor your condition during the administration.

Treatment monitoring
Treatment with Lutathera can have an impact on blood cells, liver and kidneys (see section 4). Your doctor will therefore ask you to have regular blood tests in order to check whether it is appropriate for you to receive this treatment and during treatment to detect any side effects as early as possible. If necessary, the electrical activity of your heart will also be checked before you are discharged from the hospital (with a test called an electrocardiogram or ECG). Based on the results, your doctor may decide to delay, modify or stop your treatment with this medicine if necessary.

After administration of Lutathera
You will be asked to drink enough water (e.g. 1 glass of water every hour) to enable you to urinate as often as possible on the day of infusion and the day after, and to try to empty your bowels every day, in order to eliminate the medicine from your body.
Because this medicine is radioactive, you will have to follow the instructions described below to minimise radiation exposure to others unless otherwise instructed by your doctor.
Based on current knowledge and experience in this field and on the properties of the medicine, it is estimated that the health risks to the people who live with you and the general public are low.

<u>Contact with other members of your household</u>
You should limit close contact (less than 1 metre) with people who live with you for 7 days after you receive Lutathera. You should sleep in a separate bedroom from other people for 7 days after you receive Lutathera.

<u>Contact with children and/or pregnant women</u>
After you receive Lutathera, it is strongly recommended that you limit close contact (less than 1 metre) with children and/or pregnant women to less than 15 minutes per day for 7 days. You should sleep in a separate bedroom from children and/or pregnant women for 15 days after you receive Lutathera.

<u>Use of toilets</u>
It is strongly recommended to empty your bowels every day and use a laxative if necessary. Furthermore, drink frequently and try to urinate as often as possible on the day you receive treatment and on the day after. Follow the advice of your doctor or other healthcare professional on how much fluid to drink.

Take special precautions to avoid contamination during the 7 days after treatment (these apply to all patients, regardless of gender):
- You must always sit when using the toilet.
- It is essential that you use toilet paper every time you use the toilet.
- Always wash your hands well after using the toilet.
- Flush all wipes and/or toilet paper down the toilet immediately after use.

- Flush any tissues or any other items that contain bodily waste, such as blood, urine and faeces down the toilet. Items that cannot be flushed down the toilet, such as sanitary pads and bandages, must be placed in separate plastic waste disposal bags (according to "Waste disposal recommendations" below).

Showering and laundry
Take special precautions during the 7 days after treatment:
- Take a shower every day,
- Wash your underwear, pyjamas, sheets and any clothes that contain sweat, blood or urine separately from the laundry of other members of your household, using a standard washing cycle. You do not need to use bleach and do not need extra rinses.

People with reduced mobility
People who are confined to bed or have reduced mobility will preferably receive assistance from a care provider. It is recommended that when providing assistance in the bathroom, the care provider wears disposable gloves for the 7 days after administration. Any special medical equipment that could be contaminated by your bodily fluids (e.g. catheters, colostomy bags, bedpans, water nozzles) must be emptied immediately into the toilet and then cleaned. Carers who clean up vomit, blood, urine or faeces should wear plastic gloves, which should be disposed of in a separate plastic waste disposal bag (see "Waste disposal recommendations" below).

Waste disposal recommendations
All items to be thrown away should be discarded in a separate plastic waste disposal bag to be used only for this purpose. Keep the plastic waste disposal bags separate from other household waste and away from children and animals.

A member of the hospital staff will tell you how and when to get rid of these waste disposal bags.

Hospitalisation and emergency care
If for any reason you require emergency medical assistance or are unexpectedly admitted to the hospital during the 3 months after your treatment, you should inform the healthcare professionals about the nature, date and dose of your radioactive treatment. To facilitate this, carry your discharge letter with you at all times.

Travel
Keep your discharge letter with you whenever you are travelling for at least 3 months after treatment.

Other precautions
The doctor or other healthcare professional will inform you if you need to take any other special precautions after receiving this medicine. Contact your doctor or nuclear medicine doctor if you have any questions.

If you have been given more Lutathera than you should
An overdose is unlikely because you will only receive a single dose of Lutathera precisely controlled by the nuclear medicine doctor or other healthcare professional supervising the procedure. However, in the event of an overdose, you will receive the appropriate treatment.

Should you have any further questions on the use of Lutathera, please ask the nuclear medicine doctor or other healthcare professional who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Lutathera side effects are mainly linked to radioactivity.
The most common side effect seen in patients being treated with Lutathera is the impact on the bone marrow. This can lead to a decrease in the different types of blood cells, most importantly red blood cells (responsible for transporting oxygen from the lungs to the different organs), platelets (special cells which help the blood to clot), and other blood cells such as white blood cells (help to fight infection). This happens in many patients and is frequently temporary. However, in rare cases the decrease in blood cells may be long-standing and/or permanent.
As a consequence, a decrease in the various blood cell types may put you at risk for bleeding, tiredness, shortness of breath, and infection. If this does occur to you, your doctor may decide to delay, modify or stop the treatment administration.

Some side effects could be serious
If you experience any serious side effects, **tell your doctor right away**.

Very common: may affect more than 1 in 10 people
- Bleeding or bruising more easily than normal or difficulty to stop bleeding (possible signs of low level of blood platelets) (thrombocytopenia)
- Infections with signs such as fever, sore throat or mouth ulcers (possible signs of low level of white blood cells) (lymphopenia)
- Tiredness, weakness, pale skin or shortness of breath (possible signs of low level of red blood cells) (anaemia)
- Tiredness, weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or difficulty to stop bleeding and infections with signs such as fever, chills, sore throat or mouth ulcers (possible signs of low level of blood cells) (pancytopenia)

Common: may affect up to 1 in every 10 people
- Bone marrow cancer resulting in poorly formed blood cells or blood cells that do not work properly, with signs and symptoms of anaemia, lymphopenia, neutropenia and/or thrombocytopenia (myelodysplastic syndrome)
- Infections with signs such as fever, sore throat or mouth ulcers (possible signs of low level of white blood cells) (leukopenia and neutropenia)
- Weight gain, tiredness, hair loss, muscle weakness, feeling cold (possible signs of underactive thyroid gland) (secondary hypothyroidism)
- Thirst, low urine output, weight loss, dry flushed skin, irritability (possible signs of dehydration)
- Transient, self-limited loss of consciousness followed by spontaneous recovery (syncope)
- Irregular heartbeat (change in the electrical activity of the heart) (electrocardiogram QT prolonged)
- Dizziness, light-headedness (possible signs of low blood pressure) (hypotension)
- Passing urine less often than usual or passing much smaller amounts of urine than usual (possible signs of kidney problems) (renal failure and acute kidney injury)

Uncommon: may affect up to 1 in every 100 people
- Sore throat, runny nose, difficult or painful breathing and fever (possible signs of a respiratory tract infection)
- Cough, difficult or painful breathing, wheezing, pain in chest when breathing, fever (possible symptoms of lower respiratory tract infection) (pneumonia)
- Rash of small fluid-filled blisters, appearing on reddened skin, signs of viral infection that can be potentially severe (herpes zoster)
- Viral infection of the eyes (ophthalmic herpes zoster)
- Staphylococcal infections
- Presence of bacteria in the blood (streptococcal bacteraemia)

- Persistent tiredness, frequent or severe infections, easy bleeding, weight loss (possible symptoms of bone marrow cancer) (acute myeloid leukaemia, acute leukaemia and chronic myelomonocytic leukaemia)
- Bone marrow cancer resulting in poorly formed blood cells or ones that do not work properly, with signs and symptoms of anaemia (refractory cytopenia with unilineage dysplasia)
- Anaemia caused by kidney problems (nephrogenic anaemia)
- Bone pain or fractures, tiredness, increased infections, changes in urination frequency, confusion, thirst, nausea or vomiting, weight loss (possible symptoms of bone marrow failure)
- Bleeding and/or bruising underneath the skin (possible signs of low level of blood platelets) (thrombocytopenic purpura)
- Rash, itching, hives, breathlessness or difficult breathing, wheezing or coughing, light-headedness, dizziness, changes in levels of consciousness, hypotension, with or without mild generalised itching, skin reddening, facial/throat swelling, blue discoloration of the lips, tongue or skin (signs of severe allergic reaction) (hypersensitivity)
- Excessive thirst, high urine output, increased appetite with weight loss, tiredness (signs of high level of sugar in blood) (diabetes mellitus)
- Facial flushing, redness, and a sudden rush of warmth in the face that is sometimes confused with the hot flashes of menopause, diarrhoea, a fast heartbeat, wheezing, a sudden drop in blood pressure (possible signs of carcinoid crisis)
- Nausea, sweating, weakness, dizziness, trembling, headache (sign of low level of sugar in the blood) (hypoglycaemia)
- Rapid and shallow breathing, confusion, tiredness, headache, sleepiness, lack of appetite, jaundice, increased heart rate, possible signs of metabolic acidosis that occurs when the body produces excessive quantities of acid or when the kidneys are not removing enough acid from the body (metabolic acidosis)
- Seeing, feeling or hearing things that are not there (hallucination)
- Altered level of consciousness as a result of liver failure (possible signs of hepatic encephalopathy)
- Pressure on the spinal cord nerves which can be caused by a tumour or other lesion (spinal cord compression)
- Irregular heartbeat (atrial fibrillation)
- Sudden and crushing chest pain, tiredness, irregular heartbeat (possible symptoms of heart attack) (myocardial infarction)
- Crushing chest pain (possible symptoms of problem in the heart) (angina pectoris)
- Collapse caused by a heart problem, during which you may become breathless, pale, experience cold sweat and dry mouth (cardiogenic shock)
- Dizziness, fainting on standing up, fall in blood pressure upon standing (orthostatic hypotension)
- Swelling and reddening of a vein (sign of phlebitis)
- Chest pain, cough, hiccups, rapid breathing (signs of fluid collection between the layers of tissue that line the lungs and chest cavity) (pleural effusion)
- Swelling of the abdomen due to accumulation of fluid (ascites)
- Constipation, swollen abdomen, abdominal pain (intestinal obstruction)
- Diarrhoea, abdominal pain, fever (possible signs of inflammation of the colon) (colitis)
- Vomiting, belching, abdominal pain upper and lower, with or without nausea and vomiting (possible signs of inflammation of the pancreas) (acute pancreatitis)
- Blood vomiting (haematemesis)
- Acute pain and swelling of the abdomen due to accumulation of fluid (haemorrhagic ascites)
- Abdominal pain, general feeling of being unwell (ileus)
- Decreased blood levels of pancreatic enzymes (pancreatic enzymes decreased)
- Yellow skin and eyes, nausea, loss of appetite, dark urine (signs of liver problems) (hepatocellular injury)
- Yellow eyes or skin (signs of liver problems) (cholestasis)
- Liver congestion (hepatic congestion)
- Liver failure (hepatic failure)

- Acute pre-renal failure
- Death
- Clavicle fracture

Not known: frequency cannot be estimated from available data
- Facial/throat swelling and/or difficulty breathing (signs and symptoms of angioedema)

Other possible side effects
Other side effects include the following listed below. If these side effects become severe, tell your doctor or other healthcare professional.

Very common: may affect more than 1 in 10 people
- Loss of appetite
- Nausea
- Vomiting
- Tiredness (fatigue)

Common: may affect up to 1 in every 10 people
- Excessive thirst, high urine output, increase appetite with weight loss (signs of high level of sugar in the blood) (hyperglycaemia)
- Sleep disturbance
- Dizziness
- Disturbed sense of taste (dysgeusia)
- Headache
- Feeling of having little energy, tiredness (lethargy)
- Headache, dizziness (sign of high blood pressure) (hypertension)
- Flushing and hot flushes
- Shortness of breath, laboured breathing (dyspnoea)
- Swelling, feeling of fullness in the abdomen
- Diarrhoea
- Stomach pain
- Constipation
- Upper stomach pain
- Indigestion, pain or an uncomfortable feeling in the upper middle part of your stomach (dyspepsia)
- Stomach pain, nausea (gastritis)
- Yellow skin and eyes, possible symptoms of high amounts of bile pigment (bilirubin) in the blood
- Hair loss (alopecia)
- Pain in muscles, bones or joints
- Muscle spasm
- Blood in urine
- Abnormal results of urine test (presence of serum proteins)
- Skin reaction such as redness or swelling and pain at the site of injection
- Swollen hands, ankles or feet (oedema peripheral)
- Pain in the site of injection
- Chills
- Tiredness, chills, sore throat, joint or muscles aching (influenza-like illness)

Uncommon: may affect up to 1 in every 100 people
- Discharge from the eye with itching, redness and swelling (signs of conjunctivitis)
- Painful and frequent urination (possible symptoms of bladder inflammation) (cystitis)
- Flu symptoms such as tiredness, chills, sore throat, joint or muscles aching (influenza)

- Weight gain, tiredness, hair loss, muscle weakness, feeling cold (signs of underactive thyroid gland) (hypothyroidism)
- Bone and joint pain, excessive urination, abdominal pain, weakness, tiredness (signs of overactive parathyroid gland) (hyperparathyroidism)
- Nausea, shortness of breath, irregular heartbeat, clouding of urine, tiredness and/or joint discomfort associated with abnormal blood test results – high levels of potassium, uric acid and phosphorous, and low levels of calcium (signs of dying tumour cells) (tumour lysis syndrome)
- Excessive emotional distress, troubled (anxiety)
- Disorientation
- A sensation like insects crawling over the skin (formication)
- Sensation of pins and needles (pricking, burning, tingling or numbing sensation) (paraesthesia)
- A distorted sense of smell (parosmia)
- Drowsiness (somnolence)
- Eye problems
- Dizziness, with spinning sensation (vertigo)
- Rapid or irregular heartbeat (palpitations)
- Redness and/or facial flushing due to widening of blood vessels (vasodilation)
- Coldness of hands and feet
- Pale skin (pallor)
- Sore throat (oropharyngeal pain)
- Increased sputum
- Choking sensation
- Dry mouth
- Flatulence
- Gastrointestinal pain
- Mouth sores with gum inflammation (stomatitis)
- Bright red blood in the faeces (haematochezia)
- Belly discomfort (abdominal discomfort)
- Bleeding from the anus (rectal haemorrhage)
- Black faeces (melaena)
- Lower abdominal pain
- Rash
- Dry skin
- Swelling face
- Excessive sweating (hyperhidrosis)
- Generalised itching (pruritus generalised)
- Abnormal results of urine test (presence of leukocytes)
- Involuntary leakage of urine (urinary incontinence)
- Test result that indicates kidney problems (glomerular filtration rate decreased)
- Kidney problem
- Renal impairment
- Abnormal hardening, swelling or lump in the skin at the site of the injection (injection site mass)
- Tiredness, chest discomfort, pain, palpitations (possible signs of heart problems) (chest discomfort)
- Chest pain
- Fever (pyrexia)
- Generally feeling unwell (malaise)
- Pain
- Feeling abnormal
- Loss of weight
- Physical disability

During Lutathera treatment, you may also have side effects of abnormal blood test results, which can give your doctor information on the functioning of some parts of your body

Common: may affect up to 1 in every 10 people
- High level of the following enzymes:
  - Gamma-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase
- High level of blood creatinine
- Low levels of magnesium and sodium in the blood

Uncommon: may affect up to 1 in every 100 people
- High level of the following enzymes:
  - Creatine phosphokinase in the blood that may indicate muscle damage, such as of the heart
  - Lactate dehydrogenase in the blood that gives information about the health of certain organs
- Low levels of potassium, phosphate, calcium and albumin in the blood
- High levels of sodium, calcium, urea, glycosylated haemoglobin, catecholamines and c-reactive protein in the blood
- Low level of red blood cells (haematocrit decreased)
- Presence of protein in urine

During Lutathera treatment, you may also have surgical/medical procedures

Common
- Blood transfusion

Uncommon
- To drain fluid from the peritoneal cavity, the space between the abdominal wall and organs (abdominal cavity drainage)
- To filter your blood to rid your body of harmful wastes, extra salt, and water (dialysis)
- To place a stent
- To drain abscess
- For gastrointestinal tube insertion
- To harvest (collect) stem cells from your bone marrow (bone marrow harvest)
- To remove polyps from the inside of the colon, also called the large intestine (polypectomy)

Reporting of side effects
If you get any side effects, talk to your doctor or 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 Lutathera 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 regulations on radioactive materials.
The following information is intended for the specialist only:
- Keep this medicine out of the sight and reach of children.
- Lutathera must not be used after the expiry date and time which are stated on the label after EXP.
- Store below 25 ºC. Do not freeze.
- Store in the original package to protect from ionising radiation (lead shielding).

6. Contents of the pack and other information

What Lutathera contains
- The active substance is lutetium (^{177}Lu) oxodotreotide. One mL of solution for infusion contains 370 MBq lutetium (^{177}Lu) oxodotreotide at the date and time of calibration.
- The other ingredients are: acetic acid, sodium acetate, gentisic acid, ascorbic acid, pentetic acid, sodium chloride, sodium hydroxide, water for injections (see section 2 “Lutathera contains sodium”).

What Lutathera looks like and contents of the pack
Lutathera is a clear, colourless to slightly yellow solution for infusion, supplied in a clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and sealed with an aluminium seal.
Each vial contains a volume that ranges from 20.5 to 25.0 mL of solution corresponding to an activity of 7 400 MBq at the date and time of infusion.
The vial is enclosed within a lead container for protective shielding.

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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 Lutathera 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.