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 is adjusted between 20.5 mL and 25.0 mL in order to provide the required amount of radioactivity at the date and time of infusion.

Lutetium (^{177}Lu) has a half-life of 6.647 days. Lutetium (^{177}Lu) decays by β^- emission to stable Hafnium (^{177}Hf) with the most abundant β^- (79.3%) having a maximum energy of 0.497 MeV. 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 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

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.

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 (tumour uptake score ≥ 2).

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 which could be extended up to 16 weeks in case of dose modifying toxicity (DMT) (see Table 5).

For renal protection purpose, an amino acid solution must be administered intravenously during 4 hours. The infusion of the amino acid solution should start 30 minutes prior to start of Lutathera infusion.

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

Table 1. Composition of the standard amino acid solution

Compound	**Amount**
Lysine	25 g
Arginine	25 g
Sodium chloride 9 mg/mL (0.9%) solution for injection	1 L

Alternatively, some 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**
Lysine content	Between 18 and 24 g
Arginine content	Between 18 and 24 g
Volume	1.5 L to 2.2 L
Osmolarity	< 1,050 mOsmol

Considering the high quantity of amino acids and the significant volume that commercially available solutions may require to meet the above specifications, the compounded solution is considered the medicinal product of choice, due to its lower total volume to be infused and lower osmolarity.

Treatment monitoring
Before each administration and during the treatment, biological tests are required to re-assess the patient's condition and adapt the therapeutic protocol if necessary (dose, infusion interval, number of infusions).
The minimum laboratory tests needed before each infusion are:

- Haematology (Haemoglobin [Hb], white blood cell count, platelet count)
- Kidney function (serum creatinine and creatinine clearance)
- Liver function (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], albumin, bilirubin)

These tests should be performed at least once within 2 to 4 weeks prior to administration and shortly before the 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 thereof, in order to be able to detect possible delayed adverse reactions (see section 4.8). Dosing may need to be modified based on the tests results.

Dose modification
In some circumstances, it might be necessary to temporarily discontinue treatment with Lutathera, adapt the dose after the first administration or even discontinue the treatment (see Table 3 - Table 5 and Figure 1).

Table 3. Criteria for permanent discontinuation of treatment with Lutathera

Discontinue Lutathera administrations in patients who have experienced or are at risk of any of the following conditions during treatment:
Severe heart failure (defined as grade III or IV of the New York Heart Association (NYHA) classification)
Pregnancy
Hypersensitivity to the active substance or to any of the excipients of this medicinal product
When specific adverse reactions to this medicinal product persist or reoccur, such as delayed grade 3-4 (G3-G4) hematotoxicity (see Table 5).

Table 4. Criteria for temporary discontinuation treatment with Lutathera

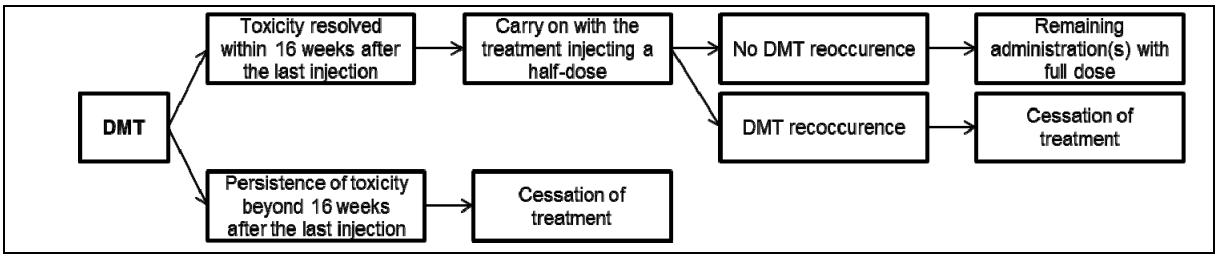
Temporarily discontinue treatment with Lutathera in the following conditions:	
Criterion	**Action**
Occurrence of an intercurrent disease (e.g. urinary tract infection), which according to the physician could increase the risks associated to Lutathera administration.	Temporarily discontinue the treatment until resolution or stabilisation. Treatment can be resumed after resolution or stabilisation.
Major surgery.	Wait 12 weeks after the date of surgery to administer Lutathera.
Major or some specific adverse reactions to Lutathera.	See Table 5.

Table 5. Instructions for dose modifications

Adjust Lutathera dosing for the following severe adverse reactions:	
Severe adverse reactions **Dose-modifying toxicity (DMT) criteria**	**Action**
Thrombocytopenia of grade 2 or superior (CTCAE)**.	1. Temporarily discontinue the treatment. 2. Monitor biological parameters every 2 weeks, and treat appropriately if needed; in case of renal failure, good hydration is recommended if not otherwise contraindicated. a. **<u>If the observed toxicity continues</u>** beyond 16 weeks after the last infusion, treatment with Lutathera must be definitively stopped. b. **<u>If the observed toxicity resolves</u>** within 16 weeks after the last infusion, it is possible to continue the treatment with Lutathera by infusing a half dose (3,700 MBq)*. 3. If the half dose is well tolerated (i.e. no DMT reoccurrence), the next remaining treatment administration(s) should continue with full dose (i.e. 7,400 MBq); but, if DMT recurs after treatment with a half dose, treatment with Lutathera must be definitively stopped.
Any haematological toxicity of grade 3 or superior (CTCAE)**, except lymphopenia.	
Renal toxicity defined as an estimated creatinine clearance < 40 mL/min, or a 40% increase compare to the baseline serum creatinine level with a decrease of over 40% compared to the baseline creatinine clearance.	
Liver toxicity defined as either: • Bilirubinemia > 3 times the upper limit of normal, • Or hypoalbuminemia < 30 g/L with a decreased prothrombin ratio < 70%.	
Any other CTCAE grade 3 or grade 4 toxicity** possibly related to Lutathera.	

* The concomitant amino acids infusion is always administered at full dose (see section 4.4).
** CTCAE: Common Terminology Criteria for Adverse Events, National Cancer Institute

Figure 1. Scheme of instructions for dose modifications



Special populations

Elderly

Clinical experience has not identified differences in responses between the elderly and younger patients. However, since increased risk of presenting haematotoxicity has been described in elderly patients (≥ 70 years old), a close follow up allowing for prompt dose adaptation (DMT) in this population is advisable.

Renal impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. The pharmacokinetic profile of lutetium (^{177}Lu) oxodotreotide in patients with severe renal impairment (creatinine clearance < 30 mL/min) has not been studied, therefore treatment with Lutathera in those patients is contraindicated (see section 4.3). As this medicinal product is known to be substantially excreted by the kidneys, patients with mild to moderate impaired renal function should be more frequently monitored during the treatment.
For additional details about the treatment of patient with renal impairment see Table 5 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 of lutetium (^{177}Lu) oxodotreotide in patients with severe hepatic impairment has not been studied, therefore treatment with Lutathera in those patients is not recommended.
For additional details about the treatment of patient with mild to moderate hepatic impairment, see Table 5 and section 4.4.

Paediatric population

Lutathera is not indicated for paediatric population
There is no relevant use of Lutathera in the paediatric population in the indication of treatment of GEP-NETs (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma).

Method of administration

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

Lutathera must be administered by slow intravenous infusion over approximately 30 minutes, concomitantly with amino acid solution administered by contralateral intravenous infusion. This medicinal product must not be injected as a bolus.
Premedication with antiemetics should be injected 30 minutes before the start of amino acid solution infusion.

The recommended infusion method for administration of Lutathera is the gravity method. During the administration the recommended precaution measures should be undertaken (see section 6.6).

Lutathera should be infused directly from its original container. The vial must not be opened or the solution transferred to another container. During the administration only disposable materials should be used.

The medicinal product should be infused through an intravenous catheter placed in the vein exclusively for its infusion.

Requirements
Storage of the vial
- Either in a container made of polymethyl methacrylate (PMMA), a transparent radioprotection container that allows a direct visual inspection of the vial,
- Or in the lead container in which Lutathera is delivered.

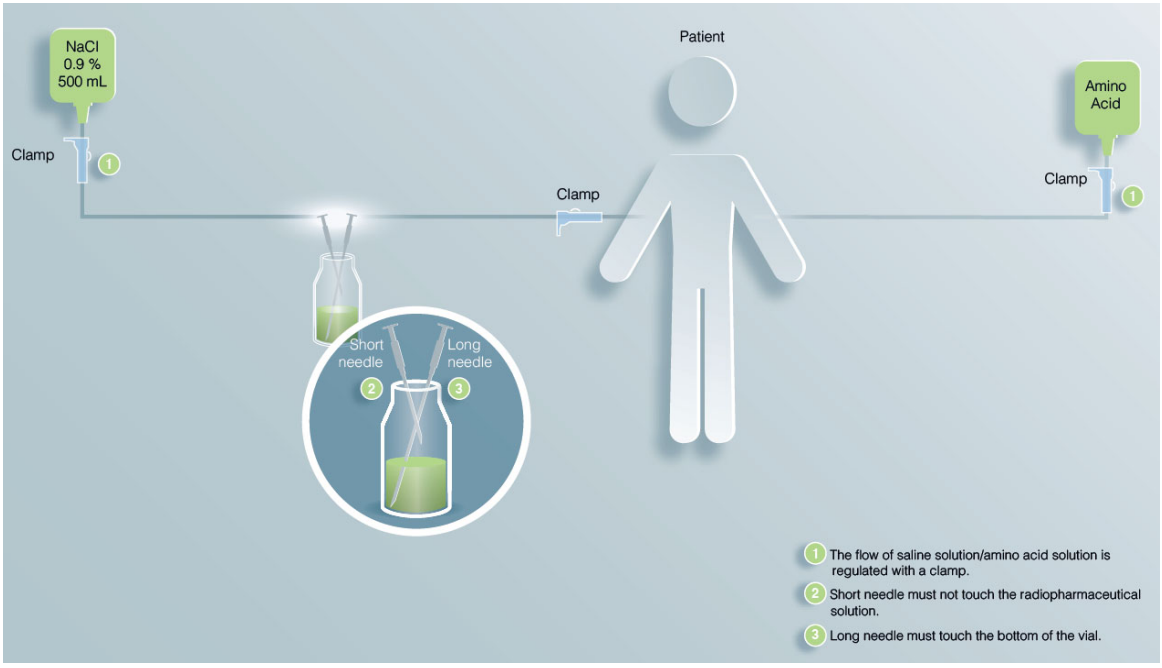
Room and equipment preparation:
- Administration room:
  - The floor and the furniture should be covered with tissue paper to avoid any accidental contamination

- Medicinal products to be administered:
  - One vial of Lutathera
  - One bag of sodium chloride 9 mg/mL (0.9%) solution for injection (500 mL)
  - Amino acid solution bag(s)
  - Antiemetics

- Care supplies and equipment:
  - Two infusion poles
  - One Long needle (90 – 100 mm)
  - One Short needle
  - Two gravity intravenous infusion sets with a clamp to regulate or stop the flow (one for Lutathera, one for amino acid solution administration)
  - Two peripheral intravenous plastic catheters
  - One sterile tubing line with a clamp to regulate or stop the flow
  - A pair of tongs (for Lutathera vial handling)
  - Calibrated radioactivity measurement system and Geiger counter to monitor the radioactivity of Lutathera

Lutathera vial tubing connections procedure (see Figure 2):
- The tubing line should be pre-filled with sodium chloride 9 mg/mL (0.9%) solution for injection and then connected with a venous catheter previously inserted to the patient's arm.
- The infusion set should be connected to the bag of sodium chloride 9 mg/mL (0.9%) solution for injection and pre-filled by opening the clamp.
- The short needle should be inserted into the Lutathera vial, so that it does not touch the radiopharmaceutical solution. This will equilibrate pressure thus reducing any risk of leakage.
- The short needle should be then connected to the pre-filled infusion set.
- The long needle should be connected to the pre-filled tubing line and then inserted into the Lutathera vial, so that it touches the bottom of the vial. This will allow for the complete extraction of the radiopharmaceutical solution.
- The flow of the radiopharmaceutical solution should be regulated with the clamps.

Figure 2. Gravity infusion method - tubing connection scheme



Administration procedure (gravity method)
During the infusion, the flow of sodium chloride 9 mg/mL (0.9%) solution for injection increases the pressure in the Lutathera vial, facilitating the flow of Lutathera into the catheter inserted in the patient's peripheral vein.
Careful monitoring of the vital signs during the infusion is recommended.

1. Two intravenous plastic catheters should be inserted into patient's peripheral veins, one on each arm.
2. The catheters should be connected to the infusion sets (one for Lutathera, one for amino acid solution).
3. Antiemetic premedication should be administered 30 minutes before start of amino acid solution infusion (see section 4.2).
4. Administration of the amino acid solution should be initiated 30 minutes before Lutathera infusion, with an infusion rate of 250 to 550 mL/h (depending on the solution type). Amino acid solution should be administered over 4 hour time span. Rates lower than 320 mL/h are not recommended for commercial solutions. In case of severe nausea or vomiting during amino acid solution infusion, an antiemetic of a different pharmacological class can be administered.
5. Radioactivity in the Lutathera vial should be measured immediately before infusion using a calibrated radioactivity measurement system.
6. Lutathera infusion should start 30 minutes after the beginning of the amino acid solution infusion, with the infusion rate of approximately 400 mL/h (this infusion rate is the reference rate and can be adapted depending on the patient's venous status). Lutathera should be administered over 20 to 30 minute time span. Constant intra-vial pressure should be maintained during the entire infusion.
7. Lutathera administration should be initiated by opening first the tubing line connected to the patient's peripheral vein, and then, by opening the infusion set connected to the bag of sodium chloride 9 mg/mL (0.9%) solution for injection. The pole height should be adjusted in order to compensate any increase or reduction of pressure inside the vial. Moving the patient's arm position should be avoided if possible (extreme flexion or extension which could lead to vein compression).
8. The flow of Lutathera from the vial to the patient should be monitored during the entire infusion. Soon after the start of the infusion, the radioactivity emission over the patient's thorax should be measured using Geiger counter to verify the presence of Lutathera in the bloodstream. Subsequent checks of the radioactivity emission should be performed approximately every 5 minutes at the level of the patient's thorax and vial. During the infusion, the radioactivity

emission from the patient's thorax should steadily increase while the one from the Lutathera vial should decrease.

9. To ensure complete administration, the Lutathera vial should be kept under even pressure. The level of solution in the vial should remain constant during the entire infusion.
   Visual controls of the solution levels should be repeated during the administration by direct visual control (when PMMA container is used) or using a pair of tongs to handle the vial when the lead shipping container is used.
10. The infusion should be stopped once the radioactivity emission from the vial becomes stable for several minutes (or during two consecutive measurements). This is the only parameter to determine the procedure completion. The volume of sodium chloride 9 mg/mL (0.9%) solution for injection necessary to complete the infusion may vary.
11. Total activity administered is equal to the activity in the vial before infusion minus the activity remaining in the vial after the infusion. The measurements should be performed using a calibrated system.

The following table summarises the required procedures during a treatment course with Lutathera using the gravity method:

Table 6. Administration procedure of antiemetic amino acid solution and Lutathera

Administered agents	**Start time (min)**	**Infusion rate (mL/h)**	**Duration**
Antiemetic	0	-	bolus
Amino acid solution, either extemporaneously compounded (1 L) or commercial (1.5 L to 2.2 L)	30	250 – 550 (not < 320 mL/h for commercial solutions)	4 hours
Lutathera with sodium chloride 9 mg/mL (0.9%) solution for injection	60	400	20 to 30 minutes

For instructions on the medicinal product before administration, see section 10.
For patient preparation, see section 4.4.
For recommendations in case of extravasation, see section 4.4.

4.3 Contraindications

- Hypersensitivity to the active substance, 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 effects, blood counts must be monitored at baseline and during treatment and until resolution of any eventual toxicity (see section 4.2). Patients with impaired

haematological 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 initiation is not recommended in patients with severely impaired haematological function at baseline (e.g. Hb < 4.9 mmol/L or 8 g/dL, platelets < 75 g/L or 75 x 10^3/mm^3, or leukocytes < 2 g/L or 2000/mm^3) (except lymphopenia).

Myelodisplastic syndrome and acute leukaemia

Late-onset myelodisplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with Lutathera (see section 4.8), occurring approximately 28 months (9 – 41) for MDS and 55 months (32 - 125) for AL after the end of treatment. Etiology of this 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 acids solution will help to decrease reabsorption of lutetium (^{177}Lu) oxodotreotide through the proximal tubules, resulting in a significant reduction in the kidney radiation dose (see section 4.2). When the recommended concomitant amino acids infusion is delivered over a 4 hour time span, a mean reduction in kidney radiation exposure of about 47% has been reported.
It is not recommended to decrease the amount of amino acid solution in case of Lutathera dose adaptation.
Patients should be encouraged to empty their bladder as frequently as possible during the administration of amino acids and the hours after administration.
Renal function as determined by serum creatinine and calculated creatinine clearance must be assessed at baseline, during and at least for the first year after treatment (see section 4.2).
Patients with renal impairment at baseline, or with renal or urinary tract morphological abnormalities may be at greater risk of toxicity. Treatment with Lutathera in patients with creatinine clearance < 40 mL/min (using Cockcroft Gault) at baseline is not recommended. More frequent monitoring of renal function is recommended in renally impaired patients with creatinine clearance > 40 mL/min (see section 4.2).
For patients with creatinine clearance < 50 mL/min, an increased risk for transient hyperkalemia 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).

Hepatic toxicity

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 ALAT, ASAT, bilirubin and albumin serum during treatment (see section 4.2).
Patients with baseline liver impairment with either total bilirubinemia > 3 times the upper limit of normal or albuminemia < 30 g/L and prothrombin ratio decreased < 70%, should only be treated with Lutathera after careful benefit-risk assessment (see section 4.2).

Nausea and vomiting

To avoid 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 pharmacologic 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 medicines containing lutetium (^{177}Lu). Patients with a history of renal insufficiency and high tumour burden may be at greater risk and should be treated with increased caution. Renal function as well as electrolyte balance should be assessed at baseline and during treatment.

Radioprotection rules
Lutathera should always be infused through an intravenous catheter placed exclusively for its infusion. The adequate position of the catheter should be checked before and during infusion.

The patient treated with Lutathera should be kept away from others during the administration and up to reaching the radiation emission limits stipulated by applicable laws, usually within the 4-5 hours following medicinal product administration. The nuclear medicine physician 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.

The patient should be encouraged to urinate as much as possible after Lutathera administration. Patients should be instructed to drink substantial quantities of water (1 glass every hour) on the day of infusion and the day after to facilitate elimination. The patient should also be encouraged to defecate every day and to use laxative if needed. Urine and faeces should be disposed according to the national regulations.

As long as 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 exams with medical devices or other instruments which contact 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 the patient is released, the nuclear physician should explain the necessary radioprotection rules of interacting with family members and third parties, and the general precautions the patient must follow during daily activities after treatment (as given in next paragraph) to minimize radiation exposure to others.
Close contact (less than 1 meter) with other people should be limited for 7 days following an administration of Lutathera. For children and/or pregnant women, close contact (less than 1 meter) 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 following an administration of Lutathera. Patients should sleep in separate bedrooms 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 eventually 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, sodium chloride 9 mg/mL (0.9%) solution for injection flush injection, or applying 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 upon its seriousness, 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 is 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
A patient presenting with any of the conditions below is more prone to develop adverse reactions. Therefore, it is recommended to monitor those patients more frequently during the treatment. Please see Table 5 in case of dose modifying toxicity.

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

Specific warnings
This medicinal product contains up to 3.5 mmol (81.1 mg) sodium per dose, 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.

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

Hyperkalemia
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 infusion.
Serum potassium levels must be tested before each treatment with amino acid solutions. In case of hyperkalemia, patient's history of hyperkalemia and concomitant medication should be checked. Hyperkalemia must be corrected accordingly before starting the infusion.

In case of pre-existing clinically significant hyperkalemia, a second monitoring prior to amino acid infusion must confirm that hyperkalemia has been successfully corrected. The patient should be monitored closely for signs and symptoms of hyperkalemia, e.g. dyspnea, 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 instructed to drink substantial quantities of water (at least 1 glass every hour) on the day of infusion to remain hydrated and facilitate excretion of excess serum potassium.
In case hyperkalemia symptoms develop during amino acid infusion, appropriate corrective measures must be taken. In case of severe symptomatic hyperkalemia, discontinuation of amino acid solution infusion should be considered, taking into consideration the risk-benefit of renal protection versus acute hyperkalemia.

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 classification (New York Heart Association). Patients with severe heart failure defined as class III or class IV in the NYHA classification should only be treated after careful benefit-risk assessment, taking into consideration 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 until at least 24 hours preceding Lutathera administration.

There is some evidence that corticosteroids can induce down-regulation of SST2 receptors. Therefore, as a matter of cautiousness, repeated administration of high-doses of glucocorticosteroids should be avoided during Lutathera treatment. Patients with a history of chronic use of glucocorticosteroids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known if there is of interaction between glucocorticosteroids used intermittently for the prevention of nausea and vomiting during Lutathera administration. Therefore, glucocorticosteroids should be avoided as preventive anti-emetic treatment. In the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of Lutathera infusion.

The absence of inhibition or significant induction of the human CYP450 enzymes, the absence of specific interaction with P-glycoprotein (efflux transporter) as well as OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and BCRP transporters in pre-clinical studies suggest that Lutathera has a low probability of causing significant other drug-drug interactions.

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 fetal harm when administered to a pregnant woman. During treatment with Lutathera and for a minimum of the following 6 months after the end of the treatment, appropriate measures must be taken to avoid pregnancy; this applies to patients of both genders.

Pregnancy
No studies on animal reproductive function have been conducted with lutetium (^{177}Lu) oxodotreotide. Radionuclide procedures carried out on pregnant women also involve 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 ionizing 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 suckling 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 the fertility of either gender. Ionizing 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 to patients before the 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 safety profile
The overall safety profile of Lutathera is based on pooled data from patients from clinical trials (NETTER-1 phase III and Erasmus phase I/II Dutch patients) and from compassionate use programs.

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 acids infusion 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%).

Tabulated list of adverse reactions
The adverse reactions are listed in Table 7 according to the frequency and the MedDRA System Organ Class (SOC). The frequencies are categorized 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 7. Frequency of adverse reactions reported from clinical trials and from post-marketing surveillance

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
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
Endocrine disorders		Secondary hypothyroidism	Hypothyroidism Diabetes mellitus Carcinoid crisis Hyperparathyroidism
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia Dehydration Hypomagnesaemia Hyponatremia	Hypoglycaemia Hypernatremia Hypophosphatemia Tumor 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	Dry mouth Flatulence Ascities

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
		Constipation Abdominal pain upper Dyspepsia Gastritis	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 generalized
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 prerenal 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 Deaths Feeling abnormal
Investigations		Blood creatinine increased GGT* increased ALAT** increased ASAT*** 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 amino transferase
*** Aspartate amino transferase
**** Alkaline phosphatase

Description of selected adverse reactions

Bone marrow toxicity

Bone marrow toxicity (myelo-/hematotoxicity) manifested with reversible / transient reductions in blood counts affecting all lineages (cytopenias in all combinations, i.e., pancytopenia, bicytopenias, isolated monocytopenias – anemia, neutropenia, lymphocytopenia, and thrombocytopenia). In spite of an observed significant selective B-cell depletion, no increase in the rate of infectious complications occurs after PRRT.

Cases of irreversible hematological pathologies, i.e., premalignant and malignant blood neoplasms (i.e., myelodysplastic syndrome and acute myeloid leukemia, respectively) have been reported following Lutathera treatment.

Nephrotoxicity

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 and moderate renal impairment, for additional details see section 4.2 (Table 3) and section 4.4. The use of Lutathera is contraindicated in patients with severe kidney failure (see section 4.3).

Hormonal crises

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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form *https://sideeffects.health.gov.il*

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. In the case 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 is helpful to estimate the effective dose that was applied.

The following checking should be carried out every week, for the next 10 weeks:

- Hematologic monitoring: white blood cells, platelets, and haemoglobin
- Blood chemistry monitoring: serum creatinine and glycaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10XX04

Mechanism of action
Lutetium (^{177}Lu) oxodotreotide has a high affinity for subtype 2 somatostatin receptors (sst2). It binds to malignant cells which overexpress sst2 receptors.
Lutetium-177 (^{177}Lu) is a β^- emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill 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 radiolabeled forms), the peptide oxodotreotide does not exert any clinically relevant pharmacodynamic effect.

Clinical efficacy and safety
NETTER-1 phase III study was a multicentre stratified, open labelled, randomized, comparator-controlled, parallel-group study comparing treatment with Lutathera (4 doses of 7,400 MBq every 8 weeks) co-administered with amino acid solution plus best supportive care (BSC; octreotide long acting release [LAR] 30 mg every 4 weeks for symptoms control, replaced by short acting octreotide in the 4 weeks 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 1.1), based on independent radiology assessment. Secondary endpoints included objective response rate (ORR), overall survival (OS), time to tumour progression (TTP), safety and tolerability of the medicinal product and quality of life (QoL). Two hundred twenty-nine (229) patients have been randomized to receive either Lutathera (n=116) or high dose 60 mg octreotide LAR (n=113). Demographics as well as patients and disease characteristics were well balanced between groups with a median age of 64 years and 82.1% Caucasian in the general population.

At the time of final per-protocol PFS statistical 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 octreotide LAR arm (Table 8). PFS differed significantly ($p<0.0001$) between the treatment groups. The median PFS for Lutathera was not reached at the time of analysis whereas the one of octreotide LAR was 8.5 months. The hazard ratio for Lutathera was 0.18 (95% CI: 0.11 - 0.29), indicating 82% reduction in the risk for a patient to progress or die under Lutathera compared to octreotide LAR.

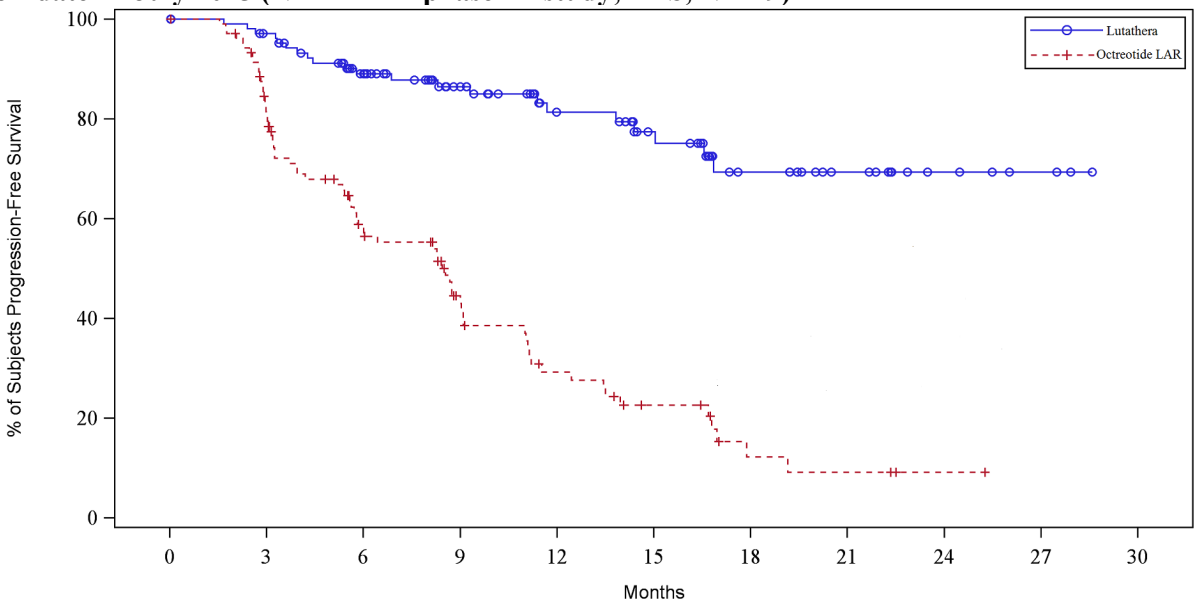
Table 8. PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumour – cut–off date 24 July 2015 (full analyses set (FAS), N=229)

	Treatment	
	Lutathera	**Octreotide LAR**
N	116	113
Patients with events	21	70
Censored patients	95	43
Median 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 3.

Figure 3. PFS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - cut–off date 24 July 2015 (NETTER-1 phase III study; FAS, N=229)



At the cut-off date for post-hoc statistical analysis (30 June 2016), the number of centrally confirmed disease progressions or deaths was 30 events in the Lutathera arm and 78 events in the octreotide LAR arm (Table 9). PFS differed significantly (p<0.0001) between the treatment groups. The median PFS for Lutathera was 28.4 months whereas the one of octreotide LAR was 8.5 months. The hazard ratio for Lutathera was 0.21 (95% CI: 0.14 - 0.33), indicating 79% reduction in the risk for a patient to progress or die under Lutathera compared to octreotide LAR.

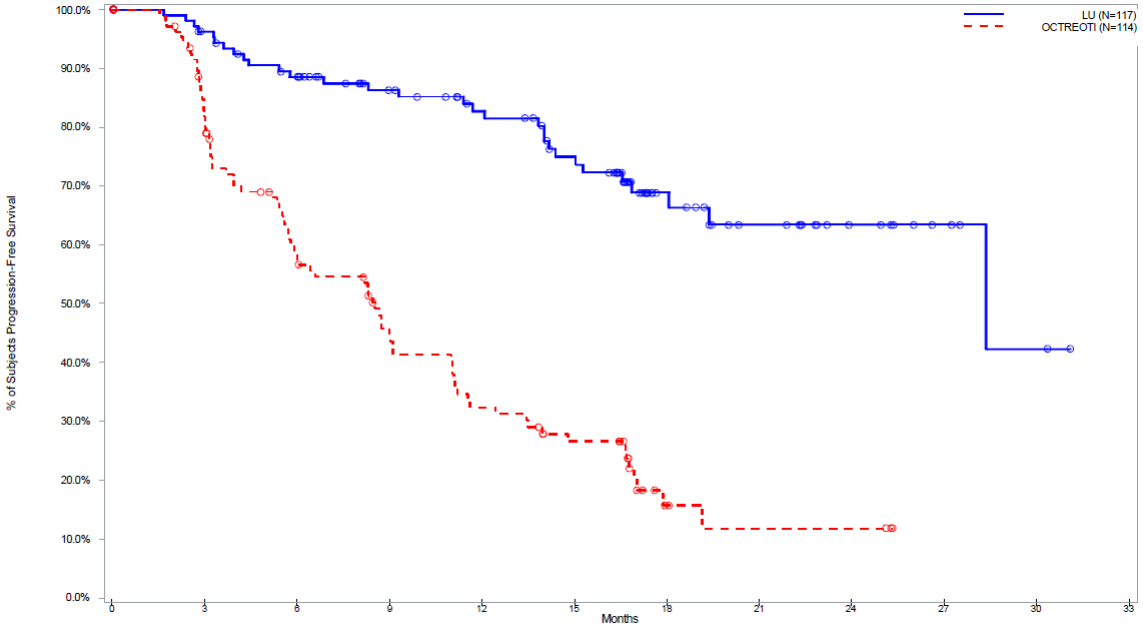
Table 9. PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumour - cut-off date 30 June 2016 (full analyses set (FAS), N=231)

	Treatment	
	Lutathera	**Octreotide LAR**
N	117	114
Patients with events	30	78
Censored patients	87	36
Median 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 ; 0.331)	

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut-off date 30 June 2016 is depicted in Figure 4.

Figure 4. PFS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - cut-off date 30 June 2016 (NETTER-1 phase III study; FAS, N=231)



With respect to overall survival OS, at the time of interim analysis (24 July 2015), there were 17 deaths in the Lutathera arm and 31 in octreotide LAR 60 mg arm and the hazard ratio was 0.459 in favour of Lutathera, but did not reach the level of significance for interim analysis (HR 99.9915% CI: 0.140, 1.506). OS median was 27.4 months in octreotide LAR arm and was not reached in Lutathera arm. An update conducted about one year after (30 June 2016) showed similar trend with 28 deaths in the Lutathera arm and 43 in octreotide LAR 60 mg arm, an HR of 0.536, and a median OS of 27.4 months in octreotide LAR arm and still not reached in Lutathera arm. The final OS analysis is foreseen after 158 cumulative deaths.

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 on Lutathera treatment as compared to patients on Octreotide LAR.

Erasmus phase I/II study was a monocentric single arm open-label study to evaluate the efficacy of Lutathera (7,400 MBq administered for 4 times every 8 weeks) co-administered with amino acid solution in patients with somatostatin receptor positive tumours. The mean age of patients enrolled in the study was 60 years. Most patients were Dutch (811) with the remaining (403) residents of various European and non-European countries. The main analysis has been conducted on 811 Dutch patients with different somatostatin receptor positive tumour types. 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 10.

Table 10. 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*	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 (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 (360 patients) as well as per tumour type are presented in Table 11.

Table 11. PFS and OS observed in the Erasmus phase I/II study in Dutch patients with GEP and bronchial NET – (FAS, N=360)

		PFS **Time** (months)			**OS** **Time** (months)		
		Median	95%CI		Median	95%CI	
All*	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			21.3	
Midgut	183	28.5	23.9	33.3	54.9	47.5	63.2
Hindgut	13	29.4	18.9	35.0			

PFS = Progression free survival; OS = Overall survival
* 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]) versus the subgroup who did receive concomitant treatment with octreotide LAR (30.9 months [95% CI 25.6-34.8]) (p= 0.747).

5.2 Pharmacokinetic properties

Absorption
The medicinal product is administered intravenously and is immediately and completely bioavailable.

Organ uptake
At 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.
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 from lutetium (^{175}Lu) oxodotreotide into serum proteins has not been observed.

Biotransformation
There is evidence, from the analysis of urine samples of 20 patients included in the NETTER-1 phase III Dosimetry, pharmacokinetic and ECG substudy, that lutetium (^{177}Lu) oxodotreotide is poorly metabolized and is excreted mainly as intact compound by renal route.
The high performance liquid chromatography (HPLC) analyses performed on urine samples collected up to 48 hours post infusion showed lutetium (^{177}Lu) oxodotreotide radiochemical purity close to 100% in most of the analysed samples (with lowest radiochemical purity value being greater than 92%), indicating that the compound is eliminated in urine mainly as intact compound.

This evidence confirms what has been 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 finding 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 pharmacokinetics profile in elderly patients (≥ 75 years) has not been established. No data are available.

5.3 Preclinical safety data

Toxicological studies with rats have 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 compound was well tolerated in both species and no deaths were observed. Toxicity with four 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 und 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, genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Ascorbic acid
Sodium acetate
Sodium hydroxide
Gentisic acid
Acetic acid
Diethylene triamine pentaacetic acid (DTPA)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

72 hours from the date and time of calibration.
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.
Store in the original package to protect from ionizing radiation (lead shielding).

Storage of radiopharmaceuticals should be in accordance with national regulation 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 varying 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 instruction on preparation of the medicinal product before administration, see section 10.

If at any time in the preparation of this medicinal product the integrity of this container and 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 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.

The surface dose rates and the accumulated dose depend on many factors. Measurements on the location and during work are critical and should be practiced for more precise and instructive determination of overall radiation dose to the staff. Healthcare personnel are advised to limit the time of close contact with patients injected with Lutathera. The use of television monitor systems to monitor the patients is recommended. Given the half-life of ^{177}Lu it is specially recommended to avoid internal contamination. It is necessary to use protective high quality (latex/nitrile) gloves to avoid direct contact with the radiopharmaceutical (vial/syringe). For minimising radiation exposure, always use the principles of time, distance and shielding (reducing the manipulation of the vial and using the material already supplied par the manufacturer).

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 the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered, hence radioprotection rules should be followed (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 according to local requirements.

7. REGISTRATION NUMBER

162-24-35598

8. REGISTRATION HOLDER AND IMPORTER AND ITS ADDRESS

Novartis Israel Ltd., P.O.B 7126, Tel-Aviv.

9. 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 hematologic toxicity and the total radioactivity administered or bone marrow absorbed dose has been observed either in Erasmus phase I/II or in NETTER-1 phase III study.
- Kidney is not a critical organ if a co-infusion of an appropriate amino acids solution is performed.

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

Table 12. Absorbed dose estimates for lutetium (^{177}Lu) oxodotreotide from NETTER-1 phase III study (Olinda output)

Organ	**Organ absorbed dose (mGy/MBq) (n = 20)**	
	Mean	**SD**
Adrenals	0.04	0.02
Brain	0.03	0.02
Breasts	0.03	0.01
Gallbladder Wall	0.04	0.02
Lower Large Intestine Wall	0.03	0.02
Small Intestine	0.03	0.02
Stomach Wall	0.03	0.02
Upper Large Intestine Wall	0.03	0.02
Heart Wall	0.03	0.02
Kidneys	0.65	0.29
Liver	0.49	0.62
Lungs	0.03	0.01
Muscle	0.03	0.02
Ovaries**	0.03	0.01
Pancreas	0.04	0.02
Red Marrow	0.03	0.03
Osteogenic Cells	0.15	0.27
Skin	0.03	0.01
Spleen	0.85	0.80
Testes*	0.03	0.02

Organ	**Organ absorbed dose (mGy/MBq) (n = 20)**	
	Mean	**SD**
Thymus	0.03	0.02
Thyroid	0.03	0.02
Urinary Bladder Wall	0.45	0.18
Uterus**	0.03	0.01
Total Body	0.05	0.03

*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.

10. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Quality controls
The solution should be visually inspected for damage and contamination before use, and only clear solutions free of visible particles should be used. The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes. The vial must not be opened.

If at any time in the preparation of this medicinal product the integrity of this vial is compromised, it should not be used.

The amount of radioactivity in the vial must be measured prior to infusion using a suitable radioactivity calibration system in order to confirm that the actual amount of radioactivity to be administered is equal to the planned amount at the infusion time.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 6.6).

Revised in December 2021 according to MoH guidelines.