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 (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).

Amino acid solution
For renal protection purposes, an amino acid solution 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.

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 the lower total volume to be infused and lower osmolarity.

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 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, 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	Between 18 and 24 g
Arginine	Between 18 and 24 g
Volume	1.5 to 2.2 L
Osmolarity	< 1 050 mOsmol

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).

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 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.

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

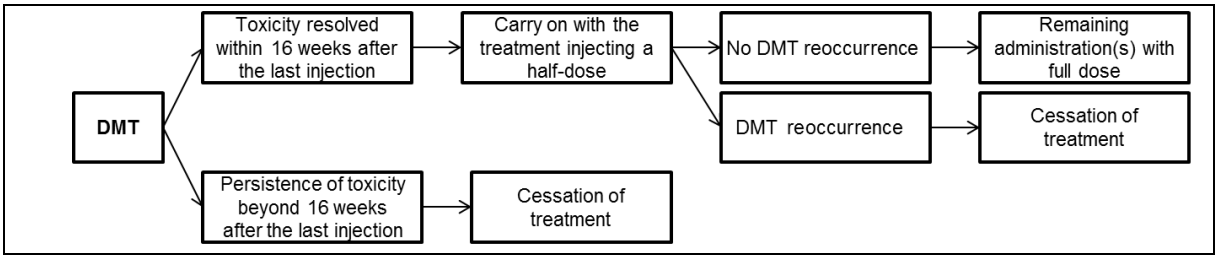
Temporarily discontinue treatment with Lutathera in the following conditions:	
Criterion	**Action**
Occurrence of an intercurrent disease (e.g. urinary tract infection), which according to the physician could increase the risks associated to Lutathera administration.	Temporarily discontinue the treatment 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 Overview of instructions for dose modifications



DMT: Dose-modifying toxicity

Special populations
Elderly
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 of lutetium (^{177}Lu) oxodotreotide in patients with baseline severe renal impairment (creatinine clearance <30 mL/min by Cockcroft-Gault formula) 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 treatment.
For additional details about the treatment of patients with renal toxicity 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 baseline severe hepatic impairment has not been studied, therefore treatment with Lutathera in those patients is not recommended.

For additional details about the treatment of patients with mild to moderate hepatic impairment, see Table 5 in section 4.2 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 and 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 an antiemetic 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 administration the recommended precaution measures should be taken (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 supplied.

Room and equipment preparation

- Administration room:
  - The floor and furniture should be covered with tissue paper to avoid any accidental contamination.

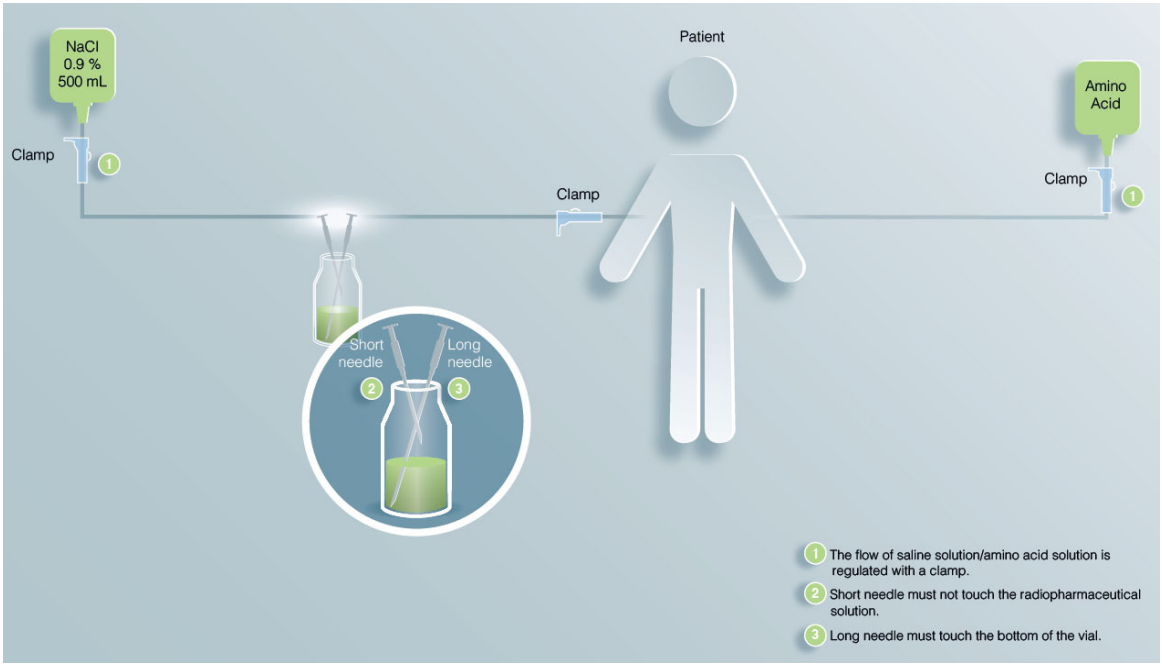
- Medicinal products to be administered:
  - One vial of Lutathera
  - One bag of sodium chloride 9 mg/mL (0.9%) solution for injection (500 mL)
  - Amino acid solution bag(s)
  - Antiemetic

- 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 connection procedure (see also 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 already inserted into 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 method – overview of tubing connection procedure



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 vital signs during the infusion is recommended.

1. Two intravenous plastic catheters should be inserted into the patient's peripheral veins, one in 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 a 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. The Lutathera infusion should start 30 minutes after the beginning of the amino acid solution infusion, with an 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 throughout the infusion.
7. Lutathera administration should be initiated by first opening the tubing line connected to the patient's peripheral vein, and then, 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 could lead to vein compression).
8. The flow of Lutathera from the vial to the patient should be monitored throughout the infusion. Shortly after the start of the infusion, the radioactivity emission over the patient's thorax should be measured using a 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 that 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 throughout the infusion.
   Visual controls of the solution levels should be repeated during administration by direct visual control (when PMMA container is used) or by 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 has been stable for several minutes (or over two consecutive measurements). This is the only parameter that can be used to determine completion of the procedure. 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 infusion. The measurements should be performed using a calibrated system.

The following table summarises the whole administration procedures for Lutathera as required with the gravity method:

Table 6 Procedure for administration 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 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 preparation of the medicinal product before administration, see section 10.
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.

It is not recommended to decrease the amount of amino acid solution in case of Lutathera dose adjustment.
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).
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 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, and serum albumin during treatment (see section 4.2).
Patients with baseline liver impairment with either total bilirubinemia > 3 times the upper limit of normal or albuminaemia <30 g/L and prothrombin ratio decreased < 70%, should only be treated with Lutathera after careful benefit-risk assessment (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
Lutathera should always be infused through an intravenous catheter placed exclusively for its infusion. The correct positioning of the catheter should be checked before and during infusion.
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) 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 5 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 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) 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 7 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 7 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]	Vasodilatation	

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Not known
		Flushing Hot flush Hypotension	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			Clavicle fracture	

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Not known
complications				
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 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).

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 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) 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 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 8). 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.

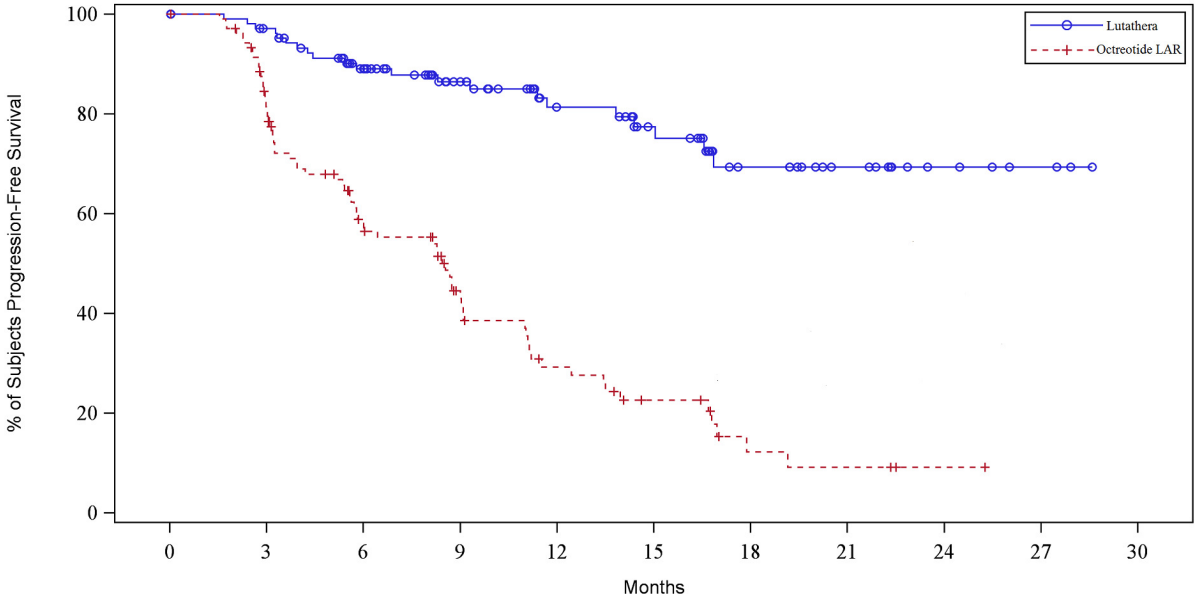
Table 8 PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumours – cut–off date 24 July 2015 (full analysis set [FAS], N=229)

	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 3.

Figure 3 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 9). 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.

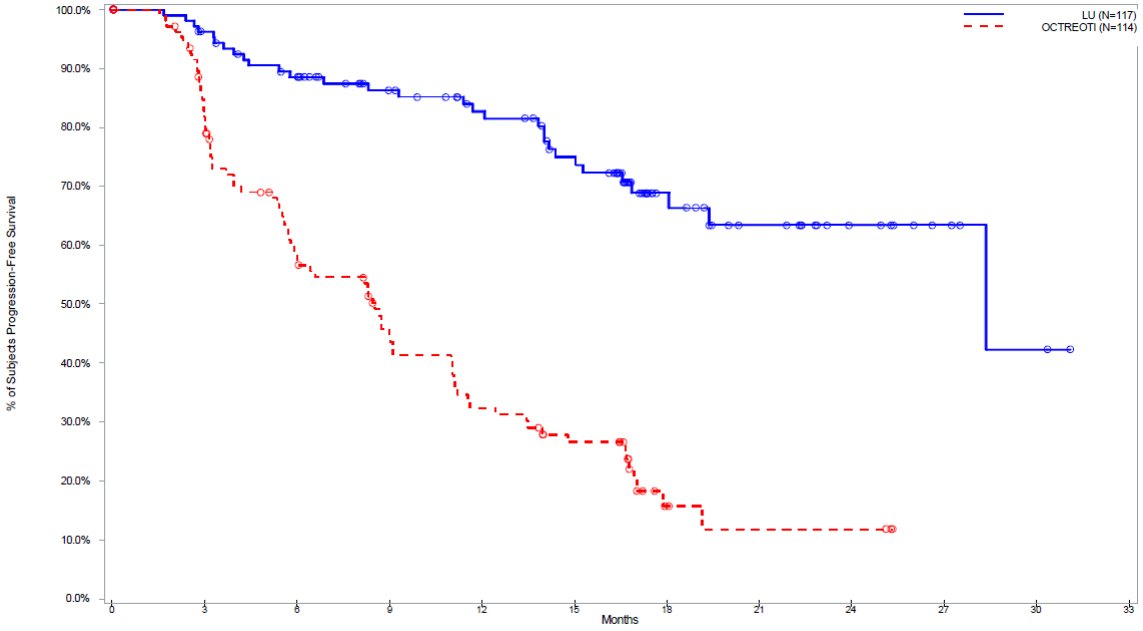
Table 9 PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumours - cut-off date 30 June 2016 (FAS, N=231)

	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 4.

Figure 4 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)



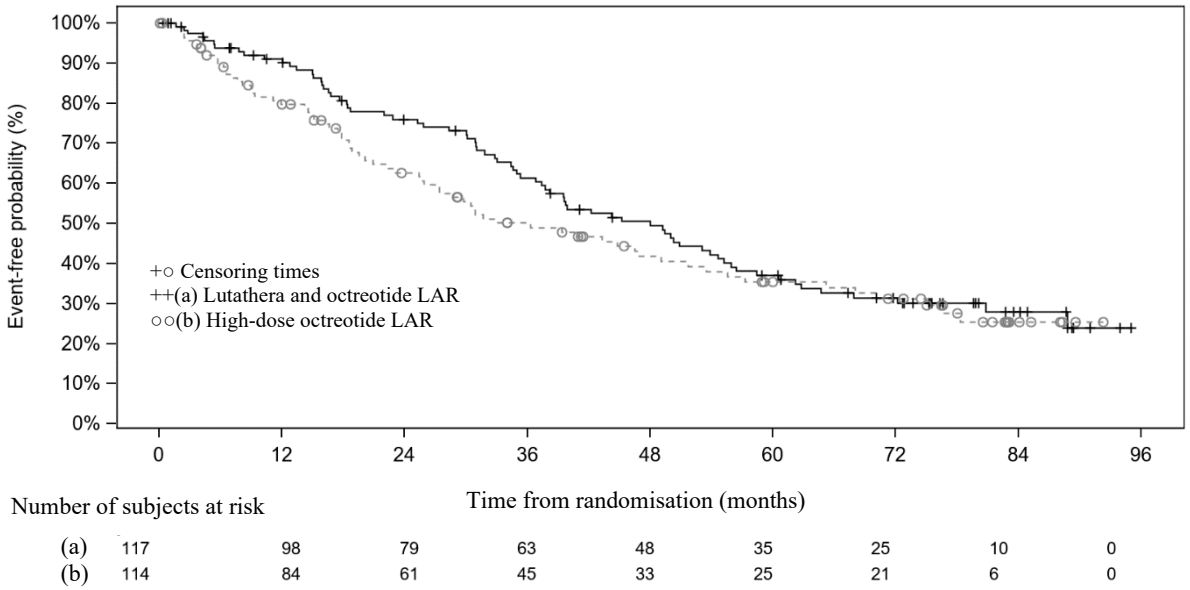
At the time of the interim OS analysis (cut-off date 24 July 2015), there were 17 deaths in the Lutathera arm and 31 deaths in the high-dose octreotide LAR arm, yielding a HR of 0.459 (99.9915% CI: 0.140; 1.506) in favour of the Lutathera arm. The median OS was not reached in the Lutathera arm at the 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 5.

Figure 5 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 10). 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 10 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 11.

Table 11 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 12.

Table 12 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).

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.

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 pre-clinical 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

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.

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 10.

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.

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 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 13 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

Organ	Organ absorbed dose per unit activity (mGy/MBq) (n = 20)	
	Mean	**SD**
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.

10. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Quality control
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 the lead container or the 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 June 2023 according to MoH guidelines.