1 Tradename

LUTATHERA® 0.37 GBq/mL solution for infusion.

2 Description and composition

Pharmaceutical form

Solution for infusion.

Clear, colorless to slightly yellow solution.

pH: 4.5 to 6.0

Active substance

One mL of solution contains 0.37 GBq of lutetium (^{177}Lu) oxodotreotide at the date and time of calibration.

The total amount of radioactivity per single dose vial is 7.4 GBq (200 mCi) ± 10% at the date and time of infusion. Given the fixed volumetric activity of 0.37 GBq/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 beta-emission to stable hafnium-177 with the most abundant beta-minus (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%).

Excipients

Acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), ascorbic acid (2.80 mg/mL), pentetic acid (0.05 mg/mL), sodium chloride (6.85 mg/mL) , sodium hydroxide (0.64 mg/mL), water for injections (ad to 1 mL).

This information might differ in some countries.

3 Indications

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

4 Dosage regimen and administration

Important safety instructions

Lutathera is a radiopharmaceutical and should be handled with appropriate safety measures to minimize radiation exposure in accordance with national regulations and/or institutional guidelines (see section Warnings and precautions). Waterproof gloves and effective radiation shielding should be used when handling Lutathera (see section Pharmaceutical information).

Radiopharmaceuticals, including Lutathera, should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

Pregnancy status of females of reproductive potential must be verified prior to initiating treatment with Lutathera (see section Pregnancy, lactation, females and males of reproductive potential).

Patient identification

Before initiating treatment with Lutathera, presence of somatostatin receptor-positive tumors must be confirmed, preferably by somatostatin receptor imaging.

Dosage regimen

General target population

Adults

The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7.4 GBq each. The recommended interval between each infusion is 8 weeks (±1 week).

Premedications and concomitant medications

Antiemetics

Antiemetics should be administered with sufficient lead time prior to the start of the amino acid solution. Refer to full prescribing information of antiemetics for administration instructions.

In case of severe nausea or vomiting during the infusion of the amino acid solution despite administration of a pre-procedure antiemetic, an antiemetic of a different pharmacological class can be administered.

Amino acid solution

For renal protection, an intravenous amino acid solution containing L-lysine and L-arginine must be administered 30 minutes before the start of the Lutathera infusion (see Tables 4-1 and 4-2). The amino acid solution infusion should continue during, and for at least 3 hours after the completion of the Lutathera infusion. Infusion of the amino acid solution and Lutathera through a separate venous access in each of the patient's arms is the preferred method. However, if two intravenous lines are not possible due to poor venous access or institutional/clinical preference, the amino acid solution and Lutathera may be infused through the same line via a three-way valve, taking into consideration flow rate and maintenance of venous access. The dose of the amino acid solution should not be decreased even if a reduced dose of Lutathera is administered.

An amino acid solution containing just L-lysine and L-arginine in the amounts specified in Table 4-1 (e.g., LysaKare®) is considered the medicinal product of choice, due to the lower total volume to be infused and lower osmolality.

The amino acid solution can be prepared as a compounded product, in compliance with the hospital's good preparation practices for sterile medicinal products and according to the composition specified in Table 4-1.

Table 4-1 Composition of the compounded amino acid solution

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

**equivalent to 20.0 g L-lysine*
*** equivalent to 20.7 g L-arginine*

Commercially available amino acid solutions (e.g., LysaKare®) can be used if compliant with the specification listed in Table 4-2.

Table 4-2 Specification of commercially available amino acid solutions

Characteristic	Specification
L-lysine HCl	Between 18 and 25 g*
L-arginine HCl	Between 18 and 25 g**
Volume	1 to 2 L
Osmolality	<1200 mOsmol/kg

**equivalent to 14.4 to 20 g L-lysine*
***equivalent to 14.9 to 20.7g L-arginine*

Treatment monitoring

Before each administration and during treatment with Lutathera, hematology (platelet count, white blood cell count with differential counts and hemoglobin [Hb]), kidney function test (serum creatinine and creatinine clearance by Cockcroft-Gault formula) and liver function test (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum albumin, INR and bilirubin) should be performed to assess the patient's condition and adapt the therapeutic protocol if necessary (dose, infusion interval, number of infusions) (see Table 4-3).

These laboratory tests should be performed shortly before each administration and between 4 to 6 weeks after each dose of Lutathera. 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 drug reactions (ADRs) (see section Adverse drug reactions). Dosing may need to be modified based on the tests results as described in Table 4-3 Recommended dose modifications for adverse drug reactions.

Dose modifications for adverse drug reactions

Management of severe or intolerable adverse drug reactions may require temporary dose interruption (extension of the dosing interval from 8 weeks up to 16 weeks), dose reduction, or permanent discontinuation of treatment with Lutathera. Recommended dose modifications of Lutathera for adverse drug reactions are provided in Table 4-3.

Table 4-3 Recommended dose modifications of Lutathera for adverse drug reactions

ADR	Severity of ADR	Dose modification
Thrombocytopenia	First occurrence of: Grade 2 (Platelets <75 to 50 x 10^9/L) Grade 3 (Platelets <50 to 25 x 10^9/L) Grade 4 (Platelets <25 x 10^9/L)	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer Lutathera at 7.4 GBq (200 mCi) as next dose. Permanently discontinue Lutathera for Grade 2 or higher thrombocytopenia requiring a dosing interval beyond 16 weeks.
	Recurrent Grade 2, 3 or 4	Permanently discontinue Lutathera.
Anemia and neutropenia	First occurrence of anemia: Grade 3 (Hb <8.0 g/dL)[1]; transfusion indicated Grade 4 (life threatening consequences) First occurrence of neutropenia: Grade 3 (absolute neutrophil count (ANC) <1.0 to 0.5 x 10^9/L) Grade 4 (ANC <0.5 x 10^9/L)	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 anemia or neutropenia, administer Lutathera at 7.4 GBq (200 mCi) as next dose. Permanently discontinue Lutathera for Grade 3 or higher anemia or neutropenia requiring a dosing interval beyond 16 weeks.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.
Renal toxicity	First occurrence of: • Creatinine clearance less than 40 mL/min; calculated using Cockcroft-Gault formula with actual body weight, or • 40% increase from baseline serum creatinine, or • 40% decrease from baseline creatinine clearance; calculated using Cockcroft-Gault formula with actual body weight.	Withhold dose until resolution or return to baseline. Resume Lutathera at 3.7 GBq (100 mCi) in patients with resolution or return to baseline. If reduced dose does not result in renal toxicity, administer Lutathera at 7.4 GBq (200 mCi) as next dose. Permanently discontinue Lutathera for renal toxicity requiring a dosing interval beyond 16 weeks.
	Recurrent renal toxicity	Permanently discontinue Lutathera.
Hepatotoxicity	First occurrence of: • Bilirubinemia >3 times the upper limit of normal (Grade 3 or 4), or • Albuminemia less than 30 g/L with international normalized ratio (INR) >1.5.	Withhold dose until resolution or return to baseline. Resume Lutathera at 3.7 GBq (100 mCi) in patients with resolution or return to baseline. If reduced Lutathera dose does not result in hepatotoxicity, administer Lutathera at 7.4 GBq (200 mCi) as next dose. Permanently discontinue Lutathera for hepatotoxicity requiring a dosing interval beyond 16 weeks.
	Recurrent hepatotoxicity.	Permanently discontinue Lutathera.
Any other CTCAE* Grade 3 or Grade 4 ADR[1]	First occurrence of Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer Lutathera at 7.4 GBq (200

ADR	Severity of ADR	Dose modification
		mCi) as next dose. Permanently discontinue Lutathera for Grade 3 or higher ADR requiring a dosing interval beyond 16 weeks.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.

[1]No dose modification required for hematological toxicities Grade 3 or Grade 4 solely due to lymphopenia

** CTCAE: Common Terminology Criteria for Adverse Events, National Cancer Institute*

Special populations

Renal impairment

Lutathera is substantially excreted by the kidneys, thus patients with renal impairment may be at increased risk of toxicity due to increased radiation exposure. The pharmacokinetic profile and safety of Lutathera in patients with baseline severe renal impairment (creatinine clearance <30 mL/min by Cockcroft-Gault formula) or end-stage renal disease have not been studied, and treatment with Lutathera in those patients is contraindicated. Treatment with Lutathera in patients with baseline creatinine clearance <40 mL/min is not recommended. No dose adjustment is recommended for renally impaired patients with baseline creatinine clearance ≥40 mL/min. However, renal function should be monitored more frequently during treatment as these patients may be at greater risk of toxicity.

Hepatic impairment

Patients with hepatic impairment may be at increased risk of hepatotoxicity due to radiation exposure.

The pharmacokinetic profile and safety of Lutathera in patients with baseline severe hepatic impairment (total bilirubin >3 times upper limit of normal regardless of AST level) have not been studied.

Patients with baseline hepatic impairment with either total bilirubin >3 times the upper limit of normal or albuminemia <30 g/L and INR >1.5, should only be treated with Lutathera after careful benefit-risk assessment. No dose adjustment is recommended for patients with baseline mild or moderate hepatic impairment.

Pediatric patients (below 18 years)

The safety and efficacy of Lutathera have not been established in pediatric patients.

Geriatric patients (65 years of age or above)

No dosage adjustment is required in patients 65 years of age or above as clinical experience has not identified differences in responses between geriatric and younger patients.

Method of administration

Preparation instructions

- Use aseptic technique and radiation shielding when administering the Lutathera solution. Use tongs when handling the vial to minimize radiation exposure.

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

Administration instructions

The gravity method, the peristaltic pump method or the syringe pump method may be used for administration of the recommended dose. Treating healthcare professionals may use other methods deemed appropriate and safe, particularly when dose reduction is required. When using the gravity method or the peristaltic pump method, Lutathera should be infused directly from its original container. The peristaltic pump method or the syringe pump method should be used when administering a reduced dose of Lutathera following a dose modification for an adverse drug reaction (see Table 4-3 Recommended dose modifications for adverse drug reactions). Using the gravity method to administer a reduced dose of Lutathera may result in the delivery of the incorrect volume of Lutathera if the dose is not adjusted prior to administration. Radiation safety precautions must be considered regardless of the administration method used (see section Warnings and precautions).

The following table summarizes the whole administration procedure for Lutathera:

Table 4-1 Procedure for administration of antiemetic, amino acid solution and Lutathera

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

Intravenous methods of administration

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

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

Instructions for the peristaltic pump method:

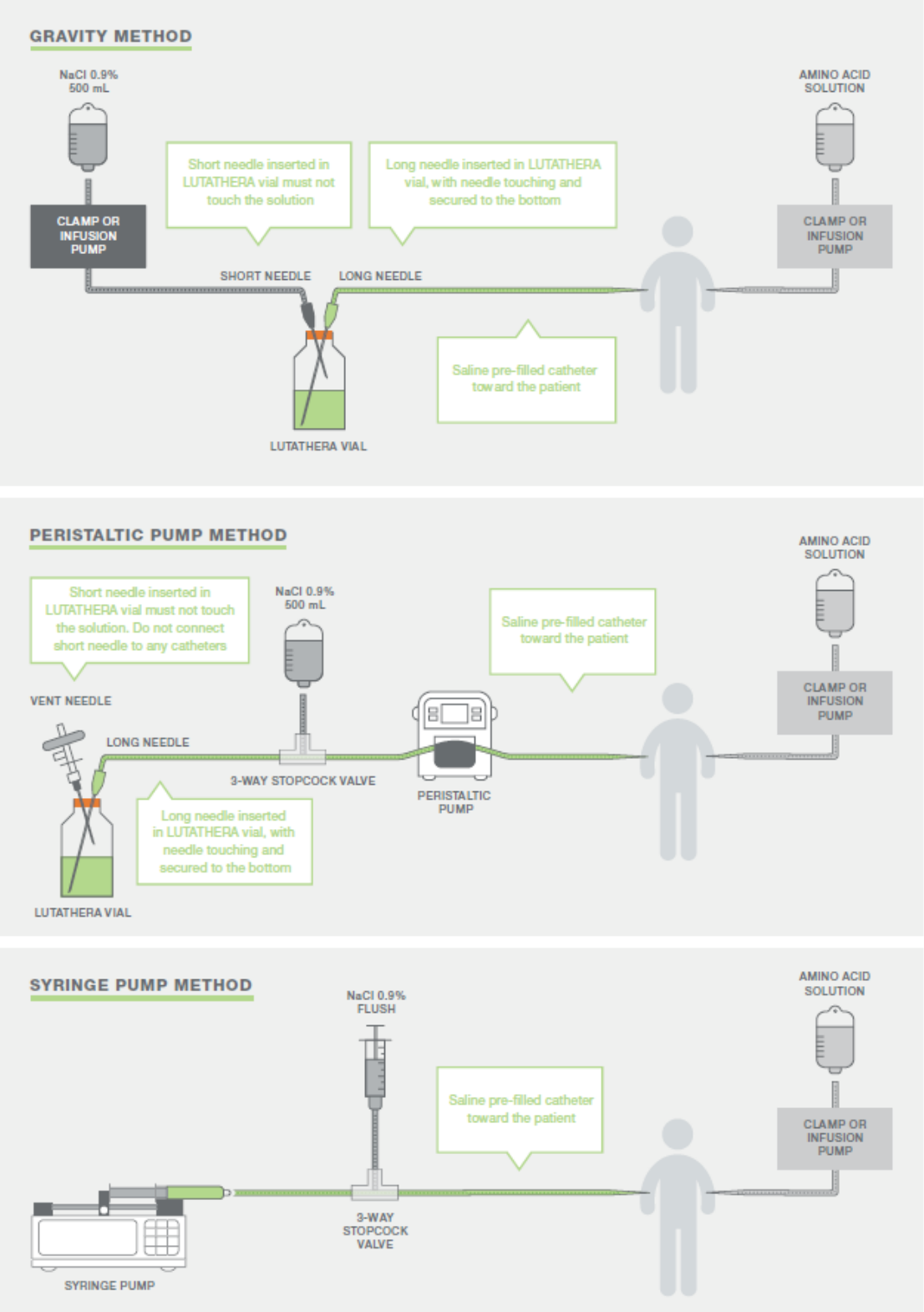
- Insert a filtered 2.5 cm, 20 gauge needle (short venting needle) into the Lutathera vial. Ensure that the short needle does not touch the Lutathera solution in the vial and do not connect the short needle directly to the patient or to the peristaltic pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Lutathera vial, ensuring that the long needle touches and is secured to the bottom of the Lutathera vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic pump following the pump manufacturer's instructions.
- Prime the line by opening the 3-way stopcock valve and pumping the Lutathera solution through the tubing until it reaches the exit of the valve.

- Prime the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the primed intravenous catheter to the patient and set the 3-way stopcock valve such that the Lutathera solution is in line with the peristaltic pump.
- Infuse an appropriate volume of Lutathera solution over a 30±10 minute period to deliver the desired radioactivity.
- When the desired Lutathera radioactivity has been delivered, stop the peristaltic pump, and then change the position of the 3-way stopcock valve so that the peristaltic pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic pump and infuse an intravenous flush of 25 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the syringe pump method:

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

Figure 4-1 Overview of methods of administration



Radiation dosimetry

Dosimetry and pharmacokinetics of lutetium (177Lu) oxodotreotide have been studied in a subset of 20 patients enrolled in the Phase III NETTER-1 sub-study, in order to define the pharmacokinetic profile of lutetium (177Lu) oxodotreotide and to calculate whole body and

organ radiation dosimetry, with particular focus on the absorbed radioactive dose to critical organs (e.g., kidney and bone marrow).

The mean and standard deviation (SD) of the estimated radiation absorbed doses for adults receiving Lutathera are shown in Table 4-4.

Table 4-5 Estimated radiation absorbed dose for Lutathera in NETTER-1

	Absorbed dose per unit activity (Gy/GBq) (N=20)		Calculated absorbed dose for 4 x 7.4 GBq (29.6 GBq cumulative activity) (Gy)	
Organ	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.037	0.016	1.1	0.5
Brain	0.027	0.016	0.8	0.5
Breasts	0.027	0.015	0.8	0.4
Gallbladder wall	0.042	0.019	1.2	0.6
Heart wall	0.032	0.015	0.9	0.4
Kidneys	0.654	0.295	19.4	8.7
Liver*	0.299	0.226	8.9	6.7
Lower large intestine wall	0.029	0.016	0.9	0.5
Lungs	0.031	0.015	0.9	0.4
Muscle	0.029	0.015	0.8	0.4
Osteogenic cells	0.151	0.268	4.5	7.9
Ovaries**	0.031	0.013	0.9	0.4
Pancreas	0.038	0.016	1.1	0.5
Red marrow	0.035	0.029	1.0	0.8
Skin	0.027	0.015	0.8	0.4
Small intestine	0.031	0.015	0.9	0.5
Spleen	0.846	0.804	25.1	23.8
Stomach wall	0.032	0.015	0.9	0.5
Testes***	0.026	0.018	0.8	0.5
Thymus	0.028	0.015	0.8	0.5
Thyroid	0.027	0.016	0.8	0.5
Total body	0.052	0.027	1.6	0.8
Upper large intestine wall	0.032	0.015	0.9	0.4
Urinary bladder wall	0.437	0.176	12.8	5.3
Uterus**	0.032	0.013	1.0	0.4

**N=18 (two patients excluded because the liver absorbed dose was biased by the uptake of the liver metastases)*

***N=9 (female patients only)*

****N=11 (male patients only)*

5 Contraindications

Established or suspected pregnancy or when pregnancy has not been excluded (see section Pregnancy, lactation, females and males of reproductive potential).

Severe renal impairment (creatinine clearance < 30 mL/min)

6 Warnings and precautions

Risk from radiation exposure

Lutathera contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. 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 to 5 hours following Lutathera administration (see section Pharmaceutical information). Radiation exposure should be minimized to patients, medical personnel, and household contacts during and after treatment with Lutathera for at least 7 days (see section Clinical pharmacology) and also consistent with institutional good radiation safety practices and patient management procedures (see section Dosage regimen and administration and section Pharmaceutical information).

Myelosuppression

Myelosuppression was reported in the majority of patients treated with Lutathera (see section Adverse drug reactions).

Most of the hematologic events were mild or moderate and reversible/transient. Patients with impaired bone marrow function, as well as patients who received prior chemotherapy or external beam radiotherapy (involving more than 25% of the bone marrow) may be at higher risk of hematological toxicity during Lutathera treatment.

Hematological evaluation of patients must be performed at baseline and prior to each dose of Lutathera. Based on the severity of myelosuppression, Lutathera may require withholding, dose reduction, or permanent discontinuation as described in Table 4-3 Recommended dose modifications for adverse drug reactions.

Treatment of patients with severely impaired hematological 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.

Secondary myelodysplastic syndrome and acute leukemia

Late-onset myelodysplastic syndrome (MDS) and acute leukemia (AL) have been reported after treatment with Lutathera (see section Adverse drug reactions).

In a phase III study (NETTER-1), with a median follow-up time of 76 months in the main study, MDS was reported in 3 patients (2 patients from the main study and 1 patient from the dosimetry sub-study) (2.3%) receiving Lutathera and long-acting octreotide (LAR) compared to no patients who received high-dose octreotide LAR.

In a phase I/II study (ERASMUS), 16 patients (2%) developed MDS and 4 (0.5%) developed AL. The median time to onset was 29 months (9 to 45 months) for MDS and 55 months (32 to 125 months) for AL.

Renal toxicity

Renal dysfunction can develop during and after treatment with Lutathera. Cases of chronic renal impairment have been reported in patients several years following treatment with Lutathera which were mild in nature and were confirmed by serum/urine analyses (see section Adverse drug reactions).

In ERASMUS, 8 patients (1%) developed renal failure 3 to 36 months following treatment with Lutathera.

Administration of amino acid solution should start 30 minutes before and should continue during and for at least 3 hours after each Lutathera dose (see section Dosage regimen and administration). The amino acid solution helps to decrease reabsorption of lutetium (^{177}Lu) oxodotreotide through the proximal tubules resulting in decrease in the radiation dose to the kidneys. 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).

Monitor serum creatinine and creatinine clearance (see Treatment monitoring under section Dosage regimen and administration). Based on the creatinine clearance, Lutathera may require withholding, dose reduction, or permanent discontinuation as described in Table 4-3 Recommended dose modifications for adverse drug reactions.

Patients with renal impairment at baseline may be at increased risk of toxicity due to increased radiation exposure (see section Dosage regimen and administration). For patients with creatinine clearance <50mL/min, an increased risk for transient hyperkalemia due to the amino acid solution should also be taken into consideration (see Hyperkalemia under section Warnings and precautions).

Hepatotoxicity

In ERASMUS, 2 patients (0.25%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with 1 patient (0.12%) experiencing intrahepatic congestion and cholestasis (see section Adverse drug reactions).

Patients with hepatic metastasis or pre-existing advanced hepatic impairment may be at increased risk of hepatotoxicity due to radiation exposure.

Transaminases, bilirubin, serum albumin and INR should be monitored during treatment with Lutathera (see Treatment monitoring under section Dosage regimen and administration). Based on the severity of hepatotoxicity, Lutathera may require withholding, dose reduction, or permanent discontinuation as described in Table 4-3 Recommended dose modifications for adverse drug reactions.

Hypersensitivity

Cases of hypersensitivity reactions (including isolated angioedema events) have been reported in the post-marketing setting in patients treated with Lutathera (see section Adverse drug reactions). In the event of serious hypersensitivity reactions, the ongoing Lutathera infusion should be discontinued immediately. Appropriate medications and equipment to manage such reactions should be available for immediate use. Patients with a history of hypersensitivity reactions to Lutathera should be premedicated before subsequent doses. Based on the severity and recurrency of hypersensitivity reactions, Lutathera may require permanent discontinuation as described in Table 4-3 Recommended dose modifications for adverse drug reactions (under "Any other CTCAE Grade 3 or Grade 4 ADR").

Neuroendocrine hormonal crisis

Neuroendocrine hormonal crises, manifesting with flushing, diarrhea, bronchospasm and hypotension, occurred in 1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose.

Patients should be monitored for signs and symptoms of tumor-related hormonal release. Somatostatin analogs, fluids, corticosteroids, and electrolytes should be administered as clinically indicated. Overnight hospitalization of patients should be considered in some cases for observation (e.g. patients with poor pharmacologic control of symptoms).

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 solution infusion. Patients with reduced creatinine clearance may be at increased risk for transient hyperkalemia (see Renal toxicity under section Warnings and precautions).

Serum potassium levels must be tested before each administration of amino acid solutions. In case of hyperkalemia, the 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 solution 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 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 hyperkalemia symptoms develop during amino acid solution 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 benefit-risk 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 (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.

7 Adverse drug reactions

Summary of the safety profile

The overall safety profile of Lutathera is based on data from patients from clinical studies (NETTER-1 phase III and ERASMUS phase I/II) and from compassionate use programs.

The safety data and frequency of the adverse drug reactions reported below are based on NETTER-1 (n=111) and ERASMUS (n=811).

Very common ADRs (at frequency ≥10%) were: nausea (58.9%), vomiting (45.5%) fatigue (27.7%), thrombocytopenia (25%), lymphopenia (22.3%), anaemia (13.4%), decreased appetite (13.4%) and pancytopenia (10.2%).

Nausea and vomiting occurred mainly at the beginning of the infusion. The causality of nausea/vomiting is confounded by the emetic effect of the concomitant amino acid solution administered for renal protection.

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 summary of adverse drug reactions from clinical studies

Adverse drug reactions from clinical studies (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 7-1 Frequency of adverse drug reactions reported from clinical studies

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

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia Dehydration Hypomagnesaemia Hyponatraemia	Hypoglycaemia Hypernatraemia Hypophosphataemia Tumour lysis syndrome Hypercalcaemia Hypocalcaemia Hypoalbuminaemia Metabolic acidosis
Psychiatric disorders		Sleep disorders	Anxiety Hallucination Disorientation
Nervous system disorders		Dizziness Dysgeusia Headache[10] Lethargy Syncope	Formication Hepatic encephalopathy Paraesthesia Parosmia Somnolence Spinal cord compression
Eye disorders			Eye disorders
Ear and labyrinth disorders			Vertigo
Cardiac disorders		Electrocardiogram QT prolonged	Atrial fibrillation Palpitations Myocardial infarction Angina pectoris Cardiogenic shock
Vascular disorders		Hypertension[7] Flushing Hot flush Hypotension	Vasodilatation Peripheral coldness Pallor Orthostatic hypotension Phlebitis
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Oropharyngeal pain Pleural effusion Sputum increased Choking sensation
Gastrointestinal disorders	Nausea Vomiting	Abdominal distension Diarrhoea Abdominal pain Constipation Abdominal pain upper Dyspepsia Gastritis	Dry mouth Flatulence Ascites Gastrointestinal pain Stomatitis Haematochezia Abdominal discomfort

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
			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	Blood potassium decreased Blood urea increased Glycosylated haemoglobin increased

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
		AST*** increased Blood ALP**** 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 hypersensitivity, injection site induration, injection site swelling
** Gamma-glutamyltransferase*
***Alanine amino-transferase*
**** Aspartate amino-transferase*
***** Alkaline phosphatase*

Adverse drug reactions from spontaneous reports (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Lutathera via spontaneous case reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from spontaneous reports (frequency not known)

Immune system disorders
Angioedema

Description of selected adverse drug reactions

Myelosuppression

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. Among these 15 patients, 5 improved to Grade 1, 9 to Grade 2, and 1 to Grade 3.

8 Interactions

Somatostatin analogs

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera. Therefore, administration of long-acting somatostatin analogs should be discontinued at least 4 weeks prior to the administration of Lutathera. If necessary, patients may be treated with short-acting somatostatin analogs up to 24 hours preceding Lutathera administration.

Glucocorticoids

There is some evidence that glucocorticoids can induce down-regulation of subtype 2 somatostatin receptors (SST2). Repeated administration of high doses of glucocorticoids should be avoided during treatment with Lutathera. Patients with history of chronic use of glucocorticoids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known if there is interaction between glucocorticoids used intermittently for the prevention of nausea and vomiting during Lutathera administration. Therefore, glucocorticoids should be avoided as preventive anti-emetic treatment.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

Lutathera is contraindicated in patients with established or suspected pregnancy or when pregnancy has not been excluded (see section Contraindications). Based on its mechanism of action, Lutathera can cause fetal harm (see section Non-clinical safety data) when administered to a pregnant woman.

There are no available data on Lutathera use in pregnant women. No animal studies using lutetium (^{177}Lu) oxodotreotide have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, Lutathera being a radiopharmaceutical has the potential to cause fetal harm. Pregnant women should be advised of the potential risk to a fetus.

9.2 Lactation

Risk summary

There are no data on the presence of lutetium (^{177}Lu) oxodotreotide in human milk, or its effects on the breast-fed child or milk production. No lactation studies in animals were conducted. Because of the potential risk for serious adverse drug reactions in breast-fed

children, women receiving Lutathera should be advised to not breast-feed. If Lutathera treatment is started during breast-feeding, breast-feeding should be discontinued permanently.

9.3 Females and males of reproductive potential

Pregnancy testing

The pregnancy status of females of reproductive potential must be verified prior to initiating treatment with Lutathera (see section Dosage regimen and administration).

Contraception

Females:

Lutathera can cause fetal 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.

Males:

Based on its mechanism of action, 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.

Infertility

No animal studies were conducted to determine the effects of lutetium (^{177}Lu) oxodotreotide on male and female fertility. Ionizing radiations of lutetium (^{177}Lu) oxodotreotide may cause temporary infertility in males and females.

10 Overdosage

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 should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals. In the event of overdose, an increase in the frequency of the adverse drug reactions related to radiotoxicity is expected.

In the event of administration of a radiation overdose with Lutathera, the radiation 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 radiation dose that was applied.

Hematological monitoring, including white blood cells counts (with differential counts), platelets, and hemoglobin, and blood chemistry monitoring, including serum creatinine and blood glucose should be performed every week for the next 10 weeks.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

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

Lutetium (^{177}Lu) is a beta-minus 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 tumor cells with a limited effect on neighboring normal cells.

Pharmacodynamics (PD)

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

Cardiac electrophysiology

The ability of Lutathera to prolong the QTc interval at the recommended dose was assessed in an open-label study in 20 patients with somatostatin receptor-positive midgut carcinoid tumors. Single doses of Lutathera resulted in mean QTcF change from baseline of 2.8 msec during the first 2 hours, 4.2 msec at 4 hours, 10 msec at 8 hours and 11.1 msec at 24 hours. No subject had a QTcF value exceeding 480 msec or ΔQTcF >60 msec. A concentration dependent increase in QTc was not detected. No clinically relevant changes in the mean QTc interval (i.e., >20 msec) were detected.

Pharmacokinetics (PK)

The pharmacokinetics of lutetium (^{177}Lu) oxodotreotide have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors.

Absorption

The mean blood exposure (AUC) of lutetium (^{177}Lu) oxodotreotide at the recommended dose is 41 ng.h/mL [coefficient of variation (CV) 36%]. The mean maximum blood concentration (C_{max}) for lutetium (177Lu) oxodotreotide is 10 ng/mL (CV 50%), which generally occurred at the end of the Lutathera infusion.

Distribution

The mean volume of distribution (V_z) for lutetium (^{177}Lu) oxodotreotide is 460 L (CV 54%).

The non-radioactive form (lutetium (^{175}Lu) oxodotreotide) is 43% bound to human plasma proteins.

Organ uptake

Within 4 hours after administration, lutetium (^{177}Lu) oxodotreotide distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid. The co-administration of amino acids reduced the median radiation dose to the kidneys by 47% (34% to 59%) and increased the mean beta-phase blood clearance of lutetium (177Lu) oxodotreotide by 36%.

Biotransformation/metabolism

Lutetium (^{177}Lu) oxodotreotide does not undergo hepatic metabolism.

Based on the analysis of urine samples of 20 patients included in the NETTER 1 phase III Dosimetry, pharmacokinetic and ECG sub-study, lutetium (^{177}Lu) oxodotreotide is poorly metabolized and is excreted mainly as intact compound by renal route.

Elimination

The mean clearance (CL) is 4.5 L/h (CV 31%) for lutetium (^{177}Lu) oxodotreotide.

Half-life

The mean terminal blood elimination half-life is 71 (±28) hours for lutetium (^{177}Lu) oxodotreotide.

Excretion

Lutetium (^{177}Lu) oxodotreotide is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following Lutathera administration. Prolonged elimination of lutetium (^{177}Lu) oxodotreotide in the urine is expected; however, based on the half-life of lutetium-177 and terminal blood elimination half-life of lutetium (^{177}Lu) oxodotreotide, greater than 99% of the administered radioactivity will be eliminated within 14 days after administration of Lutathera (see section Warnings and precautions).

Special populations

Geriatric patients (75 years of age or above)

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

In vitro evaluation of drug interaction potential

Metabolic and transporter based interaction

In vitro drug interaction studies performed with lutetium (^{175}Lu) oxodotreotide showed an absence of significant inhibitory or induction effects on human CYP450 enzymes (CYP1A2, 2B6, 2C9, 2C19 or 2D6), no potential interactions with P-glycoprotein (efflux transporter), as well as OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, and BCRP transporters. Therefore, Lutathera has a low probability of causing clinically relevant metabolism- or transporter-mediated interactions.

12 Clinical studies

NETTER-1 study

The NETTER-1 phase III study was a multicenter stratified, open label, randomized, comparator-controlled study comparing treatment with Lutathera (4 doses of 7.4 GBq [200 mCi] , one dose every 8 weeks [±1 week]) co-administered with an amino acid solution and best supportive care (octreotide long acting release [LAR] 30 mg after each Lutathera dose and every 4 weeks after completion of Lutathera treatment for symptoms control) to high dose octreotide LAR (60 mg every 4 weeks) in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors. The primary endpoint for the study was progression-free survival (PFS) evaluated by response evaluation criteria in solid tumors (RECIST v1.1), based on blinded independent review committee (IRC) assessment.

Secondary efficacy endpoints included objective response rate (ORR), overall survival (OS), and health-related quality of life (HRQoL).

At the time of the primary analysis, 229 patients were randomized (1:1). Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤6 or >6 months).

Demographic and baseline disease characteristics were balanced between the treatment arms. Of the 208 patients, whose race/ethnicity was reported, 90% were White, 5% were Black, and 4% were Hispanic or Latino. The median age was 64 years (28 to 87 years); 51% were male, and 96% had metastatic disease in the liver. The median Karnofsky performance score was 90 (60 to 100), 74% received a constant dose of octreotide for >6 months and 12% received prior treatment with everolimus. Sixty-nine percent (69%) of patients had Ki67 expression in ≤2% of tumor cells, 77% had CgA >2 times the upper limit of normal (ULN), 65% had 5-HIAA >2 times ULN, and 65% had alkaline phosphatase ≤ULN.

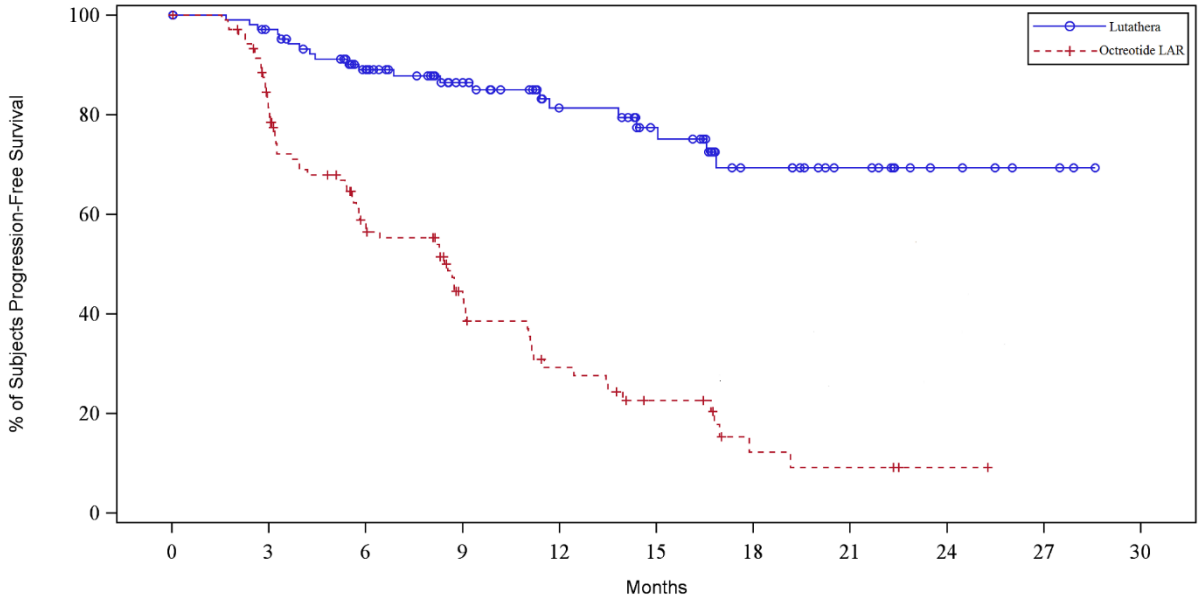
At the time of the primary PFS analysis (cut-off date 24 July 2015), the number of centrally confirmed disease progressions or deaths was 21 events in the Lutathera arm and 70 events in the high-dose octreotide LAR arm (Table 12-1). PFS differed significantly ($p<0.0001$) between the treatment arms. 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 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 favor of the Lutathera arm.

Table 12-1 PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumors, cut-off date 24 July 2015 (full analysis set [FAS], N=229)

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

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut–off date 24 July 2015 is depicted in Figure 12-1.

Figure 12-1 **PFS Kaplan-Meier curves for patients with progressive midgut carcinoid tumors - cut-off date 24 July 2015 (NETTER-1 phase III study; FAS, N=229)**



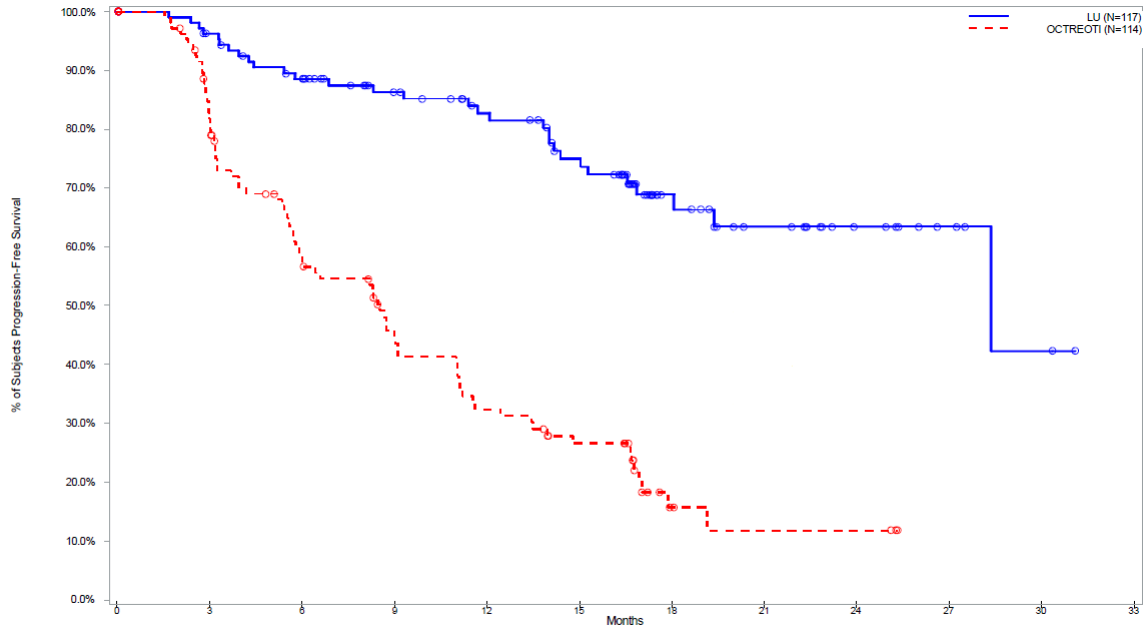
At the cut-off date for post-hoc statistical analysis (cut-off date 30 June 2016) including two additional randomized patients (N=231), the number of centrally confirmed disease progressions or deaths was 30 events in the Lutathera arm and 78 events in the high-dose octreotide LAR arm (Table 12-2). The 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 favor of the Lutathera arm.

Table 12-2 **PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumors, cut-off date 30 June 2016 (FAS, N=231) [21]**

	LUTATHERA and octreotide LAR N=117	High-dose octreotide LAR N=114
PFS by IRC		
Patients with events	30	78
Censored patients	87	36
Median in months (95 %CI)	28.4 (28.4; NE)	8.5 (5.8; 11)
Hazard ratio (95 %CI)	0.214 (0.139; 0.330)	

The PFS Kaplan-Meier graph for the FAS at the cut–off date 30 June 2016 is depicted in Figure 12-2.

Figure 12-2 **PFS Kaplan-Meier curves for patients with progressive midgut carcinoid tumors - cut-off date 30 June 2016 (NETTER-1 phase III study; FAS, N=231)**



At the time of primary PFS analysis (cut-off date 25 July 2015), the ORR was 14.7% (95% CI: 7.8, 21.6) in the Lutathera arm and 4.0% (95% CI: 0.2, 7.8) in the high-dose octreotide LAR arm.

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 favor of the Lutathera arm (Table 12-3). 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 randomized 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 favor 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 randomized (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 favor of the Lutathera arm (Table 12-3). The median OS was prolonged by a clinically relevant extent of 11.7 months in patients randomized to the Lutathera arm compared to patients randomized 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 randomization, 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.

Table 12-3 OS results in NETTER-1 phase III study in patients with progressive midgut carcinoid tumors (FAS)

	LUTATHERA and octreotide LAR	High-dose octreotide LAR
Interim OS analysis (24 July 2015) – N=229*		
Deaths (%)	17 (14.7%)	31 (27.4%)
Median in months (95% CI)	NR (NE; NE)	27.4 (20.1; NE)
Hazard ratio [a] (99.9915% CI)	0.46 (0.14; 1.51)	
p-value[b]	0.0083	
Final OS analysis (18 January 2021) – N=231**		
Deaths (%)	73 (62.4%)	69 (60.5%)
Median in months (95% CI)	48.0 (37.4; 55.2)	36.3 (25.9; 51.7)
Hazard ratio [a, c] (95% CI)	0.84 (0.60; 1.17)	
p-value[d]	0.3039	
OS rate over time – N=231**		
% at 12 months (95% CI)	91.0 (84.0; 95.1)	79.7 (70.8; 86.1)
% at 24 months (95% CI)	76.0 (66.7; 83.0)	62.7 (52.6; 71.2)
% at 36 months (95% CI)	61.4 (51.4; 69.9)	50.1 (40.0; 59.4)
% at 48 months (95% CI)	49.5 (39.5; 58.6)	41.8 (31.8; 51.4)
% at 60 months (95% CI)	37.1 (27.8; 46.4)	35.4 (25.7; 45.2)

a: Hazard ratio based on unstratified Cox model

b: Pre-specified significance criteria threshold at 0.000085; p-value is not significant

c: Hazards were not proportional

d: Unstratified Log-rank Test two-sided p-value; p-value is not significant

**: Analysis performed on 116 patients in the Lutathera arm and 113 patients in the high-dose octreotide LAR arm (N=229)*

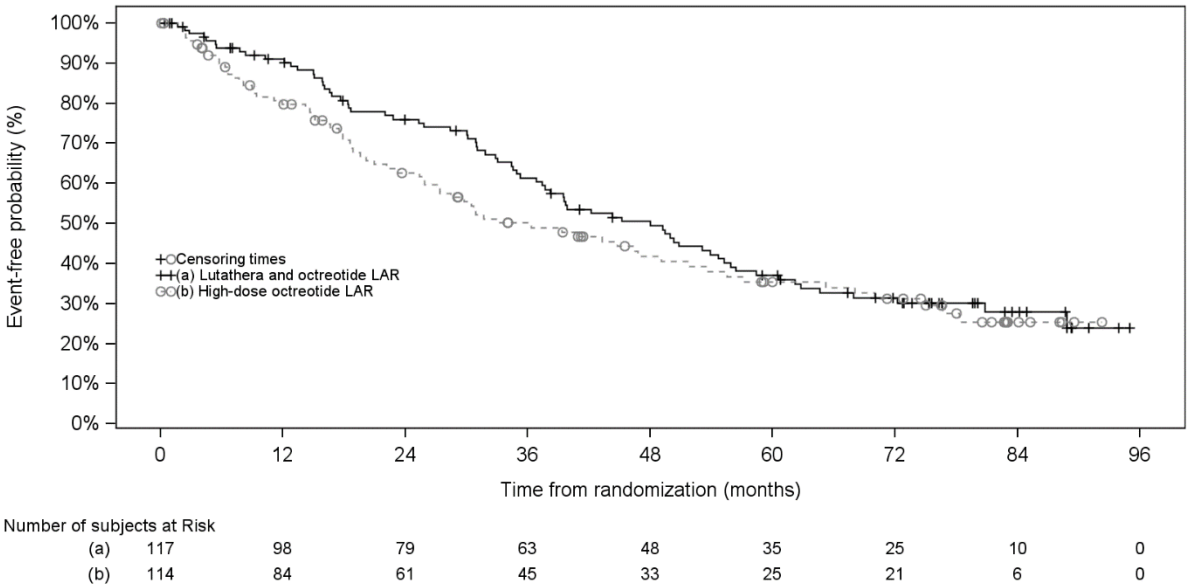
***: Analysis performed on 117 patients in the Lutathera arm and 114 patients in the high-dose octreotide LAR arm (N=231)*

NR=Not reached

NE=Not estimable

The OS Kaplan-Meier graph for the FAS at the cut–off date 18 January 2021 is depicted in Figure 12-3.

Figure 12-3 OS Kaplan-Meier curves for patients with progressive midgut carcinoid tumors - 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 12-4). At 60 months after randomization, 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 12-4 OS by restricted mean survival time (RMST) observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumors (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 Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (generic instrument) and its neuroendocrine tumor 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 Lutathera treatment arm as compared to patients in the high-dose octreotide LAR arm.

ERASMUS Study

The efficacy of Lutathera in patients with foregut (including bronchial), midgut, and hindgut neuroendocrine tumors (NETs) was assessed in 360 patients in the ERASMUS study. In ERASMUS, Lutathera was initially provided under a general peptide receptor radionuclide therapy protocol at a single site in the Netherlands. A subsequent Lutathera-specific protocol written eight years after study initiation did not describe a specific sample size or hypothesis testing plan but allowed for retrospective data collection. A total of 1,214 patients received Lutathera in ERASMUS, of whom 578 patients had baseline tumor assessment. Of the 578 patients with baseline tumor assessment, 360 (62%) patients had gastroenteropancreatic (GEP) and bronchial NETs and long-term follow-up. Out of the 360 patients (full analysis set, FAS), 183 had midgut tumors, 133 had pancreatic tumors, 19 patients had bronchial tumors, 13 had hindgut tumors and 12 had foregut tumors (other than bronchial and pancreatic). The median age in the FAS was 60 years (30 to 85 years), 51% were male, 71% had a baseline Karnofsky performance status ≥90, 51% had progressed within 12 months of treatment, and 7% had received prior chemotherapy. Fifty-two percent (52%) of patients received a concomitant long-acting release somatostatin analog.

Lutathera 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. The median dose of Lutathera was 29.6 GBq (800 mCi). The major efficacy outcome was investigator-assessed ORR as an aggregate of the best overall response (BOR) in the 5 subtypes of NETs.

Patients in the FAS had their tumors assessed using either the RECIST v1.1 criteria (145 patients, 40%) or the SWOG assessment which was retrospectively algorithmically converted to RECIST v1.1 (215 patients, 60%).

The overall investigator assessed ORR was 45% (95% CI: 40; 50) and the median duration of response (DoR) was 22.9 months (95% CI: 17; 25) (Table 12-5). The observed ORR was highest for pancreatic NET patients (61%, 95% CI: 52; 69) and lowest for midgut NET patients (33%, 95% CI: 27; 41). In the subset of 145 patients who were evaluated by the investigators using RECIST v1.1 criteria, the ORR was 41% (95% CI: 33; 50), and median DoR was 35 months (95% CI: 17; 38), and in the subset of 215 patients who were evaluated by the investigators using the converted SWOG criteria, the ORR was 47% (95% CI: 41; 54), and median DoR was 18.5 months (95% CI: 15; 24).

Table 12-5 Best response, ORR and DoR observed in the ERASMUS phase I/II study with GEP and bronchial NETs – (FAS, N=360) †

	N	CR		PR		SD		ORR				DoR (months)		
Tumor type		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95%CI**		**Median**	**95%CI**	
All NETs‡	360	11	3%	151	42%	183	51%	162	45%	40%	50%	23	17	25
Bronchial	19	0	0%	7	37%	11	58%	7	37%	16%	62%	27*	2	ND
Pancreatic	133	7	5%	74	56%	47	35%	81	61%	52%	69%	23	17	33
Foregut**	12	1	8%	6	50%	4	33%	7	58%	28%	85%	NR*	15	ND
Midgut	183	3	2%	58	32%	115	63%	61	33%	27%	41%	18	15	24
Hindgut	13	0	0%	6	46%	6	46%	6	46%	19%	75%	18*	6	ND

CR = Complete response; PR = Partial response; SD = Stable disease; ORR = Objective response rate (CR + PR); DoR = Duration of response; ND = Not detected; NR = Not reached

†Results are based on patients that had NET tumors, long-term follow-up, baseline tumor assessment and either had assessments using the RECIST v1.1 criteria or the SWOG converted criteria

‡Includes foregut, midgut and hindgut
**The sample sizes for bronchial, foregut, and hindgut DoR entries are small and therefore the results are less reliable*
***Foregut NETs other than bronchial and pancreatic*

The overall median PFS and OS for the FAS population with GEP and bronchial NETs as well as per tumor type are presented in Table 12-6.

Table 12-6 PFS and OS observed in the ERASMUS phase I/II study in patients with GEP and bronchial NETs – (FAS, N=360) †

		PFS Time (months)			OS Time (months)		
	N	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

** 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).

13 Non-clinical safety data

Safety pharmacology and animal toxicology

Toxicological studies conducted with the radiolabeled compound in rats demonstrated that a single intravenous injection of up to 4.55 GBq/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 micrograms/kg (rats) and 3,200 micrograms/kg (dogs), the cold compound was well tolerated in both species and no deaths were observed.

In repeat dose toxicology studies in rats in which the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) was administered four times at two-week interval, the primary target organ was the pancreas, a high SSTR2 expressing organ. Pancreatic acinar apoptosis occurred at lutetium (^{175}Lu) oxodotreotide doses ≥5,000 micrograms/kg. The dose of 1,250 micrograms/kg was considered to be the no observed effect level (NOEL) in this rat study. Pancreatic acinar cell atrophy also occurred in repeat dose toxicology studies in dogs at doses ≥500 micrograms/kg. Acinar apoptosis was the only histological change observed in the high dose group. Therefore, also considering the reversibility of acinar apoptosis after recovery, 3,200 micrograms/kg was considered to be the no observed adverse effect level (NOAEL) in the repeated toxicology study in dogs, which is equivalent to 400 times the human dose (based on body surface area scaling).

The cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) did not show any effect on cardiac conduction times or body temperature and did not cause arrhythmia at the doses tested (from 80 to 800 micrograms/kg) in dogs.

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.

Carcinogenicity and mutagenicity

Mutagenicity studies and long-term carcinogenicity studies have not been carried out with lutetium (^{177}Lu) oxodotreotide; however, radiation is a carcinogen and mutagen.

Reproductive toxicity

For information on reproductive toxicity, see section Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section Dosage regimen and administration.

Shelf life

72 hours from the date and time of calibration.

Special precautions for storage

Store at or below 25ºC. Do not freeze Lutathera.

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

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

Lutathera must be kept out of the reach and sight of children.

Nature and contents of container

Clear, colorless type I glass vial, closed with a bromobutyl rubber stopper and aluminum cap.

Each vial contains a volume that ranges from 20.5 to 25.0 mL of solution, corresponding to a radioactivity of 7.4 GBq (200 mCi) ± 10% at the date and time of infusion.

The vial is enclosed within a lead shielded container and placed in a plastic sealed container.

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with national regulations.

Radioprotection rules

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 (see section Warnings and precautions).

Patients should be encouraged to remain hydrated and to urinate frequently before, on the day of and the day after administration of Lutathera to facilitate elimination (e.g.: at least 1 glass of water every hour). They should also be encouraged to defecate every day and to use laxative if needed. Urine and feces 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 next paragraph) to minimize radiation exposure to others.

The following general recommendations can be considered along with national, local and institutional procedures and regulations following each administration of Lutathera:

- Close contact (less than 1 meter) with other people should be limited for 7 days.
- 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.
- 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 Lutathera 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 Lutathera 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 upon its severity, this event should be declared as an adverse drug reaction.

Patients with urinary incontinence

During the first 2 days following administration of Lutathera, 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.

Manufacturer:

See folding box.

® = registered trademark

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