Indications

Treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults.

Dosage regimen and administration

Lutathera is a radiopharmaceutical and should be handled with appropriate safety measures to minimize radiation exposure. 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. Lutathera should be infused directly from its original container. The vial must not be opened or the solution transferred to another container. (See Warning and precautions '4. General precaution', '10. Administrative precaution'.)

Before initiating treatment with Lutathera, somatostatin receptor imaging (scintigraphy or positron emission tomography (PET)) must confirm the overexpression of these receptors in the tumor tissue with the tumor uptake at least as high as normal liver uptake (tumour uptake score ≥ 2)

1. Adults

The recommended LUTATHERA dose is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. Administer pre-and concomitant medications

Lutathera must be administered by slow intravenous infusion over approximately 30 minutes. This medicinal product must not be injected as a bolus. The recommended infusion method for administration of Lutathera is the gravity method. (See Warning and precautions '10. Administrative precaution'.)

2. Pre and concomitant medications

1) Somatostatin Analogs
   - Before initiating Lutathera: Discontinue long-acting somatostatin analogs (e.g., long-acting octreotide) for at least 4 weeks prior to initiating Lutathera. Administer short-acting octreotide as needed; discontinue at least 24 hours prior to initiating Lutathera.
   - During Lutathera treatment: Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each Lutathera dose. Do not administer long-acting octreotide within 4 weeks of each subsequent Lutathera dose. Short-acting octreotide may be given for symptomatic management during Lutathera treatment, but must be withheld for at least 24 hours before each Lutathera dose.
   - Following Lutathera treatment: Continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing Lutathera until disease progression or for up to 18 months following treatment initiation.

2) Antiemetic

Administer antiemetics 30 minutes before the recommended amino acid solution

3) Amino acid solution

For renal protection, an intravenous amino acid solution containing lysine and arginine must be initiated 30 minutes before administering Lutathera. The amino acid solution should not be administered in the same arm as Lutathera. The amino acid infusion should continue during, and for at least 3 hours after the Lutathera infusion (at least 4 hours duration for total administration). The dose of the amino acid solution should not be decreased even if the dose of Lutathera is reduced

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

Table 1 Composition of the compounded amino acid solution

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

Commercially available amino acid solutions can be used if compliant with the specification listed in Table 2.

Table 2 Specification of commercially available amino acid solutions

Characteristic	**Specification**
L-Lysine HCl content	Between 18 g and 25 g*
L- Arginine HCl content	Between 18 g and 25 g**
Volume	1 to 2 L
Osmolality	<1.200 mOsmol/kg
**equivalent to 14.4 to 20 g lysine* ***equivalent to 14.9 to 20.7g arginine*	

An amino acid solution containing just lysine and arginine in the amounts specified in Table 2 is considered the medicinal product of choice, due to its lower total volume to be infused and lower osmolality.

3. Dose modification

Management of severe or intolerable adverse drug reactions may require temporary dose interruption, extending the dosing interval from 8 weeks up to 16 weeks, dose reduction, or discontinuation of treatment with Lutathera.

Before each administration and during treatment with Lutathera, below test should be performed to assess the patient's condition.

- Liver function test (ALT, AST, albumin, bilirubin)
- Kidney function test (creatinine, creatinine clearance)
- Haematology (Haemoglobin [Hb], white blood count, platelet count)

These tests should be performed at least once within 2 to 4 weeks prior to administration and shortly before the administration. It is also recommended to perform these tests every 4 weeks for at least 3 months after the last infusion of Lutathera and every 6 months thereafter, in order to be able to detect possible delayed adverse reactions.

Dosing may need to be modified based on the tests results.

Table 3 Recommended dose modifications for adverse drug reaction

ADRs	**Severity of ADRs**	**Dose modification**
Thrombocytopenia	Grade 2 (Platelets <75 to 50 x 10^9/L)[1] 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) for next dose. Permanently discontinue Lutathera for Grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 2, 3 or 4	Permanently discontinue Lutathera.
Anemia and neutropenia	Grade 3 (Hb <8.0 g/dL)[1]; transfusion indicated Grade 4 (life threatening consequences) 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) for next dose. Permanently discontinue Lutathera for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.

Renal toxicity	Defined as: • Creatinine clearance less than 40 mL/min[1]; calculate using Cockcroft Gault with actual body weight, or • 40% increase in baseline serum creatinine, or • 40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.	Withhold dose until complete resolution or return to baseline. Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete resolution or return to baseline. If reduced dose does not result in renal toxicity, administer Lutathera at 7.4 GBq (200 mCi) for next dose. Permanently discontinue Lutathera for renal toxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent renal toxicity	Permanently discontinue Lutathera.
Hepatotoxicity	Defined as: • Bilirubinemia >3 times the upper limit of normal (Grade 3 or 4)[2], or • Hypoalbuminemia2 less than 30 g/L with a decreased prothrombin ratio less than 70%.	Withhold dose until complete resolution or return to baseline. Resume Lutathera at 3.7GBq (100 mCi) in patients with complete resolution or return to baseline. If reduced Lutathera dose does not result in hepatotoxicity, administer Lutathera at 7.4 GBq (200 mCi) for next dose. Permanently discontinue Lutathera for hepatotoxicity; requiring a treatment delay of 16 weeks or longer.
	Recurrent hepatotoxicity.	Permanently discontinue Lutathera.
Other non-hematologic toxicity	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 mCi) for next dose. Permanently discontinue Lutathera for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.

[1] The same thresholds are also applicable to baseline values at the time of treatment initiation (see section Warnings and precautions).

[2] If same thresholds are seen at baseline treatment initiation to be considered after benefit risk assessment (see section Warnings and precautions)

Warning and precaution

1. Contraindications

1) Hypersensitivity to the active substance, to any of the excipients

2) Established or suspected pregnancy or when pregnancy has not been excluded.

2. Administration with caution

1) Patient with urinary incontinence : radioactive contamination can be spread by patient's urine. (See '10. Administrative precautions')
2) Patient with hematologic impairment, previous chemotherapy or previous external beam radiotherapy : hamatological test should be performed before administration to decide Lutathera treatment as these patients may be at greater risk of toxicity. (See Dosage regimen and administration and '4. General precaution')
3) Patient with renal impairment : Amino acid solution should be concomitant to reduce radiation exposure to kidney as Lutathera excrete through kidney. Patients with creatinine clearance <40 mL/min should not be treated with Lutathera. Renal function test should be performed before administration to decide Lutathera treatment, and renal function should be monitored more frequently for these patients. (See Dosage regimen and administration and '4. General precaution')
4) Patient with hepatic impairment : Patients with hepatic impairment may be at increased risk of hepatotoxicity due to radiation exposure. Liver function test should be performed before administration to decide Lutathera treatment. (See Dosage regimen and administration and '4. General precaution')

3. Adverse drug reactions

1) Summary of the safety profile

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

The most common adverse reactions in patients receiving Lutathera treatment were nausea and vomiting which occurred at the beginning of the infusion in 58.9% and 45.5% of patients,

respectively. The causality of nausea / vomiting is confounded by the emetic effect of the concomitant amino acids infusion administered for renal protection.

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

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

2) Tabulated summary of adverse drug reactions

Adverse drug reactions from clinical trials (Table 4) are listed by MedDRA system organ class. The frequencies are categorized as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 4 Frequency of adverse drug reactions reported from clinical trials

MedDRA System Organ Class (SOC)	**Very common**	**Common**	**Uncommon**
Infections and infestations			Conjunctivitis Respiratory tract infection Cystitis Pneumonia Herpes zoster Ophthalmic herpes zoster Influenza Staphylococcal infections Streptococcal bacteraemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (myelodysplastic syndrome)	Acute myeloid leukaemia Acute leukaemia Chronic myelomonocytic leukaemia
Blood and lymphatic system disorders	Thrombocytopenia[2] Lymphopenia[3] Anaemia[4] Pancytopenia	Leukopenia[5] Neutropenia[6]	Refractory cytopenia with unilineage dysplasia Nephrogenic anaemia Bone marrow failure Thrombocytopenic purpura
Immune system disorders			Hypersensitivity
Endocrine disorders		Secondary hypothyroidism	Hypothyroidism Diabetes mellitus Carcinoid crisis Hyperparathyroidism

Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia Dehydration Hypomagnesaemia Hyponatraemia	Hypoglycaemia Hypernatraemia Hypophosphatemia 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 Chocking sensation
Gastrointestinal disorders	Nausea Vomiting	Abdominal distension Diarrhoea Abdominal pain Constipation Abdominal pain upper Dyspepsia Gastritis	Dry mouth Flatulence Ascities Gastrointestinal pain Stomatitis Haematochezia Abdominal discomfort Intestinal obstruction Colitis Pancreatitis acute Rectal haemorrhage Melaena Abdominal pain lower Haematemesis Haemorrhagic ascites Ileus
Hepatobiliary disorders		Hyperbilirubinaemia[9]	Pancreatic enzymes decreased Hepatocellular injury Cholestasis

			Hepatic congestion Hepatic failure
Skin and subcutaneous tissue disorders		Alopecia	Rash Dry skin Swelling face Hyperhidrosis Pruritus generalized
Musculoskeletal and connective tissue disorders		Musculoskeletal pain[8] Muscle spasms	
Renal and urinary disorders		Acute kidney injury Haematuria Renal failure Proteinuria	Leukocyturia Urinary incontinence Glomerular filtration rate decreased Renal disorder Acute pre-renal failure Renal impairment
General disorders and administration site conditions	Fatigue[1]	Injection site reaction[11] Oedema peripheral Administration site pain Chills Influenza like illness	Injection site mass Chest discomfort Chest pain Pyrexia Malaise Pain Death Feeling abnormal
Investigations		Blood creatinine increased GGT* increased ALT** increased AST*** increased Blood ALP**** increased	Blood potassium decreased Blood urea increased Glycosylated haemoglobin increased Haematocrit decreased Protein urine Weight decreased Blood creatine phosphokinase increased Blood lactate dehydrogenase increased Blood catecholamines C-reactive protein increased
Injury, poisoning and procedural complications			Clavicle fracture
Surgical and medical procedures		Transfusion	Abdominal cavity drainage Dialysis Gastrointestinal tube insertion Stent placement Abscess drainage Bone marrow harvest Polypectomy
Social circumstances			Physical disability

[1] *Includes Asthenia and fatigue*
[2] *Includes Thrombocytopenia and platelet count decreased*
[3] *Includes Lymphopenia and lymphocyte count decreased*
[4] *Includes Anaemia and haemoglobin decreased*
[5] *Includes Leukopenia and white blood cell count decreased*
[6] *Includes Neutropenia and neutrophil count decreased*
[7] *Includes Hypertension and hypertensive crisis*
[8] *Includes Arthralgia, pain in extremity, back pain, bone pain, flank pain, musculoskeletal chest pain and neck pain*
[9] *Includes Blood bilirubin increased and hyperbilirubinaemia*
[10] *Includes Headache and migraine*
[11] *Includes injection site reaction, injection site hypersensibility, injection site induration, injection site swelling*
** Gamma-glutamyltransferase*
***Alanine amino transferase*
**** Aspartate amino transferase*
***** Alkaline phosphatase*

4. General precaution

1) Risk of radiation exposure

Lutathera contributes to a patient's overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. The radiation exposure must be justifiable by the likely benefit.

Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Patients should be instructed to drink substantial quantities of water (1 glass every hour) on the day of infusion and the day after to facilitate elimination. The patient should also be encouraged to defecate every day and to use laxative if needed.

Patients treated with Lutathera should be kept away from others during the administration and up to reaching the radiation emission limits stipulated by applicable laws, usually within the 4 to 5 hours following Lutathera administration.

Radiation exposure should be minimized to patients, medical personnel, and household contacts after treatment with Lutathera for at least 7 days and also consistent with institutional good radiation safety practices and patient management procedures. (See '10. Administrative precaution')

2) Hematological toxicity

Myelosuppression was reported in the majority of patients treated with Lutathera. Patients with impaired hematological function, as well as patients who received prior chemotherapy or external beam radiotherapy may be at higher risk of hematologic toxicity during Lutathera treatment.

In NETTER-1, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide compared to patients receiving high-dose long-acting octreotide (all grades/grade 3 or 4): anemia (81%/0) versus (54%/1%); thrombocytopenia (53%/1%) versus (17%/0); and neutropenia (26%/3%) versus (11%/0).
In NETTER-1, platelet nadir occurred at a median of 5.1 weeks 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.
Monitor blood cell counts. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction. (See Dosage regimen and administration)
Treatment initiation in patients with severely impaired hematological function at baseline prior to Lutathera therapy is not recommended (e.g., Hb <4.9 mmol/L or 8 g/dL, platelets <75 x 10^9/L or 75 x 10^3/mm^3, or leukocytes <2 x 10^9/L or 2000/mm^3).

3) Secondary myelodysplastic syndrome and leukemia

Late-onset myelodysplastic syndrome (MDS) and acute leukemia have been reported after treatment with Lutathera. In a phase III study (NETTER-1), with a median follow-up time of 24 months, MDS was reported in 3 patients (2.7%) receiving Lutathera-plus long-acting octreotide compared to no patients receiving high-dose long-acting octreotide.
In a phase I/II study (ERASMUS), 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development onset of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

4) Renal toxicity

Renal dysfunction can develop during and after treatment with Lutathera. In ERASMUS, 8 patients (1%) developed renal failure 3 to 36 months following treatment with Lutathera.
Because lutetium (177Lu) oxodotreotide is almost exclusively eliminated through the renal system, it is mandatory to concomitantly administer an amino acid solution containing the amino acids L-lysine and L-arginine. The amino acids solution will help to decrease reabsorption of lutetium (177Lu) oxodotreotide through the proximal tubules, resulting in a significant reduction in the kidney radiation dose. When the recommended concomitant amino acids infusion is delivered (initiated 30 minutes before administering Lutathera.

continued during, and for at least 3 hours after the Lutathera infusion), a mean reduction in kidney radiation exposure of about 47% has been reported. It is not recommended to decrease the amount of amino acid solution in case of Lutathera dose adaptation.
Patients should be encouraged to empty their bladder as frequently as possible during the administration of amino acids and the hours after administration.
Renal function as determined by serum creatinine and calculated creatinine clearance must be assessed at baseline, during and at least for the first year after treatment. (See 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.

5) Hepatobiliary toxicity

Many patients referred for Lutathera therapy have hepatic metastasis. In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis.
Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure.
Liver function test (ALT, AST, bilirubin and serum albumin) should be monitored before treatment with Lutathera. Lutathera may need to be with held, dose reduced, or permanently discontinued. (See Dosage regimen and administration)

6) Endocrine and metabolism

In ERASMUS, neuroendocrine hormonal crises, with symptoms including flushing, diarrhea, bronchospasm and hypotension, were reported in 1% of patients and typically occurred during or within 24 hours following the administration of the first Lutathera dose. Two (<1%) patients were reported to have hypercalcemia.
Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release. Observation of patients by overnight hospitalisation should be considered in some cases (e.g. patients with poor pharmacologic control of symptoms).
In case of hormonal crises, recommended treatments are: intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting.

7) Tumour lysis syndrome

Tumour lysis syndrome has been reported following therapy with medicines containing lutetium (^{177}Lu). Patients with a history of renal insufficiency and high tumour burden may be at greater risk and should be treated with increased caution. Renal function as well as electrolyte balance should be assessed at baseline and during treatment.

5. Interactions

1) 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 avoided for at least 4 weeks prior to the administration of Lutathera.

If necessary, patients may be treated with short acting somatostatin analogs until 24 hours preceding Lutathera administration.

2) Corticosteroid

There is some evidence that corticosteroids can induce down-regulation of subtype 2 somatostatin receptors (SST2). Repeated administration of high-doses of glucocorticosteroids should be avoided during treatment with Lutathera. Patients with history of chronic use of glucocorticosteroids should be carefully evaluated for sufficient somatostatin receptor expression.

It is not known if there is of interaction between glucocorticosteroids used intermittently for the prevention of nausea and vomiting during Lutathera administration. Therefore, glucocorticosteroids should be avoided as preventive anti-emetic treatment. In the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, it can be given at least 1 hour later after the end of Lutathera infusion.

3) Metabolic and transporter based interaction

In vitro metabolism studies and plasma protein binding studies performed on lutetium (175Lu) oxodotreotide showed an absence of significant inhibitory or induction effects on human CYP450 enzymes, no potential interactions with P-glycoprotein (efflux transporter), as well as OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, and BCRP transporters, and that

Lutathera is not a highly-protein bound compound. Therefore, Lutathera has a low probability of causing clinically relevant drug-drug interactions.

6. Pregnancy, lactation, females, and males of reproductive potential

1) Pregnancy

Lutathera is contraindicated in patients with established or suspected pregnancy or when pregnancy has not been excluded. Based on its mechanism of action, Lutathera can cause fetal harm when administered to a pregnant woman.

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

2) Lactation

There are no data on the presence of lutetium (177Lu) oxodotreotide in human milk after administration, or its effects on the breastfed infant or milk production. No lactation studies in animals were conducted.

Because of the potential risk for serious adverse reactions in breastfed infants, women receiving Lutathera should be advised to not breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose. If Lutathera treatment is started during breastfeeding, breastfeeding should be discontinued.

3) Females and males of reproductive 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. LUTATHERA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the final 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.

No animal studies were conducted to determine the effects of lutetium (177Lu) oxodotreotide on fertility. The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a

radiation absorbed dose to the testes and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

7. Padiatric and elderly patient

1) Pediatric patients

The safety and efficacy of Lutathera have not been established in pediatric patients (< 18 years old).

2) Elderly patients

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

8. Renal and hepatic impairment

1) Renal impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment, however, renal function should be monitored more frequently as these patients may be at greater risk of toxicity. The pharmacokinetic profile and safety of Lutathera in patients with severe renal impairment (creatinine clearance <30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied.

2) Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The pharmacokinetic profile and safety of Lutathera in patients with severe hepatic impairment (total bilirubin >3 times upper limit of normal and any AST) has not been studied.

9. Overdosage

Overdose is not expected 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 case 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 absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding during the first 48 hours after infusion. It is helpful to estimate the effective dose that was applied. Hematologic monitoring, including white blood cells, platelets, and hemoglobin, and blood chemistry monitoring, including serum creatinine and blood glucose should be performed every week for 10 weeks.

10. Administrative precaution

1) Method of administration

Preparation and administration

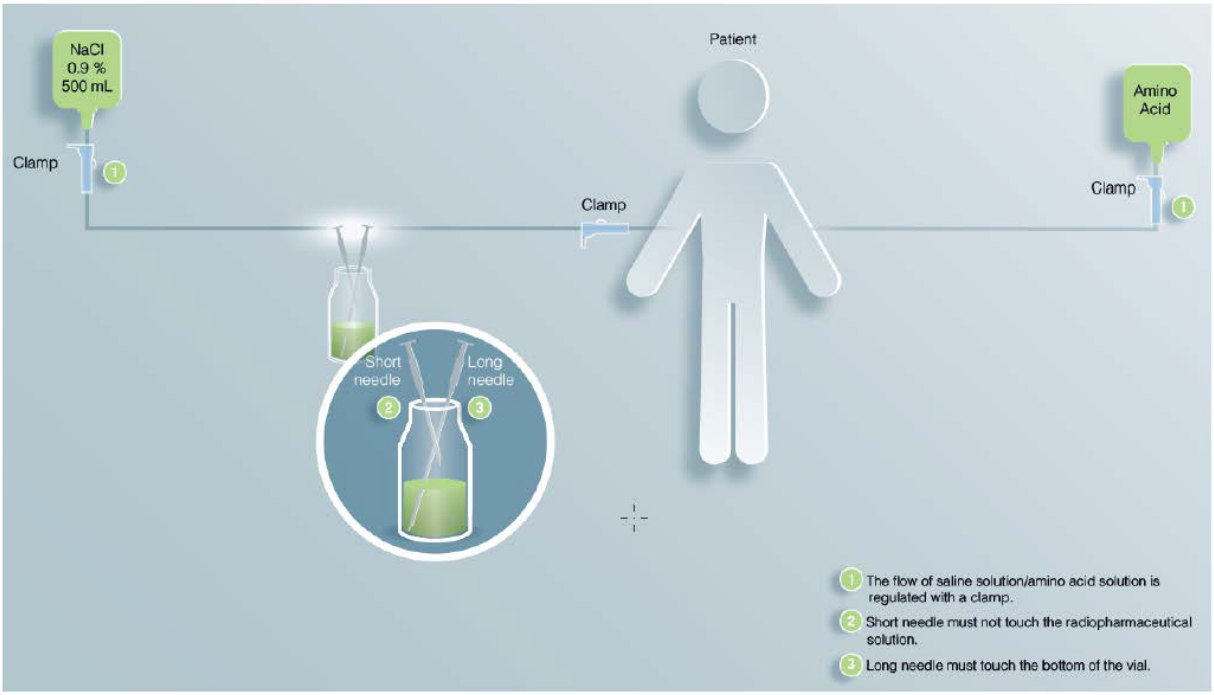
- Aseptic technique and radiation shielding should be used when administering the Lutathera solution. Use tongs when handling the vial to minimize radiation exposure.
- Lutathera should not be injected directly into any other intravenous solution.
- The amount of radioactivity of Lutathera in the radiopharmaceutical vial should be confirmed with an appropriate dose calibrator prior to and after Lutathera administration.
- The product should be visually inspected under a shielded screen for particulate matter and discoloration prior to administration. The vial should be discarded if particulates or discoloration are present.

Administration instructions

The gravity method is the recommended method for administration of Lutathera. Treating physicians may use other methods deemed appropriate and safe, including the use of infusion pumps, particularly when dose reduction is required. Radiation safety precautions must be considered regardless of the administration method used.

Gravity infusion method

Figure 1 Gravity infusion method - tubing connection scheme



- 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 Lutathera 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 sodium chloride solution to flow into the Lutathera vial prior to the initiation of the Lutathera infusion and do not inject Lutathera directly into the sodium chloride.
- 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 prefilled with 0.9% sterile sodium chloride and that is used exclusively for the Lutathera infusion into the patient.
- Use a clamp or pump to regulate the flow of the sodium chloride solution via the short needle into the Lutathera vial at a rate of 50 mL/hour to 100 mL/hour for 5 to 10 minutes and then 200 mL/hour to 300 mL/hour for an additional 25 to 30 minutes (the sodium chloride solution entering the vial through the short needle will carry the LUTATHERA

from the vial to the patient via the catheter connected to the long needle over a total duration of 30 to 40 minutes).

- The infusion rate should be adjusted depending on the patient's venous status. Constant intra vial pressure should be maintained during the entire infusion.
- Do not administer Lutathera as an intravenous bolus.
- During the infusion, ensure that the level of solution in the Lutathera vial remains constant.
- 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.
- Dispose of any unused Lutathera or waste material in accordance with local and federal laws.

Radiation dosimetry

Dosimetry and pharmacokinetics of lutetium (^{177}Lu) oxodotreotide have been studied in a subset of 20 patients enrolled in the Phase III NETTER-1 substudy, in order to define the pharmacokinetic profile of lutetium (^{177}Lu) 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 5. The maximum penetration in tissue is 2.2 mm and the mean penetration is 0.67 mm.

Table 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)*				

2) Radioprotection rules

Lutathera should always be infused through an intravenous catheter placed exclusively for its infusion. The adequate position of the catheter should be checked before and during infusion. The nuclear medicine physician should determine when the patient can leave the controlled area of the hospital, i.e. when the radiation exposure to third parties does not exceed regulatory thresholds.

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

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

material/electrode after measurement, and eventually monitoring the radioactivity of equipment after use.

Before the patient is released, the nuclear medicine physician should explain the necessary radioprotection rules of interacting with family members and third parties, and the general precautions the patient must follow during daily activities after treatment to minimize radiation exposure to others.

Close contact with other people should be restricted during 7 days following an administration of Lutathera, and for children and pregnant women it should be limited to less than 15 minutes for each day while keeping a distance of at least 1 meter. Patients should sleep in a separate bedroom for 7 days, which should be extended to 15 days in case of pregnant partners or children.

3) 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 eventually the absorbed dose should be determined. The extravasation area should be delimited with an indelible pen and a picture should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated.

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

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

In order to accelerate 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, sodium chloride 9 mg/mL (0.9%) solution for injection flush injection, or applying warm compresses or a heating pad to the infusion site to accelerate vasodilation should be considered.

Symptoms, especially inflammation and/or pain, should be treated. Depending on the situation, the nuclear medicine physician should inform the patient about the risks linked to extravasation injury, and give advice about potential treatment and necessary follow-up

requirements. The extravasation area must be monitored until the patient is discharged from the hospital. Depending upon its seriousness, this event should be declared as an adverse reaction.

4) 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.

11. Special precautions for storage

Store between 2 to 27°C. Store in the original package to protect from ionizing radiation (lead shielding). Storage of radiopharmaceuticals should be in accordance with country regulations on radioactive materials. Lutathera must be kept out of the reach and sight of children. 72 hours from the date and time of calibration.