Summary Report of Benefit-Risk Assessment

LUTATHERA SOLUTION FOR INFUSION 370 MBQ/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Lutetium (^{177}Lu) oxodotreotide
Product Registrant	Novartis (Singapore) Pte Ltd
Product Registration Number	SIN15947P
Application Route	Abridged evaluation
Date of Approval	01 June 2020

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A INTRODUCTION

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

The active substance, lutetium (^{177}Lu) oxodotreotide, binds to malignant cells which overexpress somatostatin subtype 2 receptors (SST2) receptors and delivers tumouricidal radiation (medium energy betas) to tumour cells.

Lutathera is available as a solution for infusion containing 370 MBq/ml 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 at the date and time of infusion. Other excipients in the solution for infusion are acetic acid, ascorbic acid, diethylene triamine pentaacetic acid, gentisic acid, sodium acetate, sodium chloride, sodium hydroxide and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, lutetium (^{177}Lu) oxodotreotide, is manufactured at Advanced Accelerator Applications (Italy) s.r.l. Italy and Advanced Accelerator Applications Ibérica S.L.U. Spain. The drug product, Lutathera Solution for Infusion 370 MBq/mL, is manufactured at Advanced Accelerator Applications (Italy) s.r.l. Italy and Advanced Accelerator Applications Ibérica S.L.U. Spain.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturers are compliant with Good Manufacturing Practice (GMP). Process validation was conducted on twelve consecutive production-scale batches.

The characterisation of the drug substance is in accordance with ICH guidelines. The synthesis of the Drug Substance and its formulation into the Drug Product, are part of an automated continuous process which does not allow for the isolation and testing of the pure Drug Substance. As such, information on the potential and actual impurities, drug substance specifications, container closure system and stability were provided as part of the drug product.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and Ph. Eur./USP monographs and impurity limits are considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods were appropriately validated in

accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 72 hours when stored at or below 25ºC. The container closure system is a colourless type 1 30mL glass vial with bromobutyl rubber septum and capped with an aluminium cap; the vial is enclosed within a lead shielded container and each vial contains 20.5 - 25.0 mL of product.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of lutetium oxodotreotide for the treatment of GEP-NETs was based on one pivotal study, NETTER-1 and one supporting study, ERASMUS.

The NETTER-1 study was a Phase III, multicentre, open-label, randomised study of lutetium oxodotreotide plus best supportive care [octreotide long-active release (LAR) 30mg] compared with high dose octreotide LAR (60 mg) in patients with inoperable, progressive, somatostatin receptor-positive, histologically proven midgut carcinoid tumours.

A total of 229 patients in the study were randomised in a 1:1 ratio to receive lutetium oxodotreotide plus intramuscular octreotide LAR 30mg every 4 weeks (best supportive care) or intramuscular octreotide LAR 60mg every 4 weeks. The total cumulative amount of lutetium oxodotreotide was 29.6 GBq (800 mCi), administered as four intravenous doses of 7.4 GBq (200 mCi). The doses were given at 8 ± 1-week intervals, and could be extended to 16 weeks for resolving acute toxicity. Parenteral amino acid infusion was given concomitantly with each administration of lutetium oxodotreotide for renal protection. Pre-medication with intravenous anti-emetic was given prior to amino acid infusion. Dose modifications for lutetium oxodotreotide were allowed for pre-defined toxicities. Patients received treatment until unacceptable toxicity or progression of disease. The use of octreotide LAR 60mg dose is an accepted treatment option in patients who had progressed on the standard octreotide LAR 30mg dose, hence the use of octreotide LAR 60mg as an active comparator was considered acceptable.

The primary efficacy endpoint was progression-free survival (PFS), defined as time from randomisation to documented, centrally assessed disease progression per RECIST 1.1 or death due to any cause. Key secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS) which were tested using a gate-keeping testing procedure to adjust for multiplicity. Other secondary efficacy endpoints were time to tumour progression (TTP) and duration of response (DoR). Tumour assessments were performed using CT or MRI scans every 12 weeks until the PFS primary analysis, then until 76 weeks after randomisation. For the determination of PFS and ORR, a central blinded Image Reading Centre (IRC) reviewed the available radiographic studies. The primary analysis was conducted after 74 PFS events.

The full analysis set population comprised 116 patients in the lutetium oxodotreotide arm and 113 patients in the octreotide LAR 60mg arm. The majority of patients (75.7%) in the lutetium oxodotreotide arm received 4 administrations with a mean total dose of 29.1 GBq.

The patient demographics and baseline disease characteristics were generally well-balanced between the treatment arms. The median age was 64 years, about half of the patients were male (50.7%), and the majority of patients were Caucasian/ White (82.1%). The presence of metastases was confirmed for almost all patients (99.1%). All patients had a histological

confirmation of midgut carcinoid tumour, a Ki67 index of less than 20%, and a confirmation of disease progression.

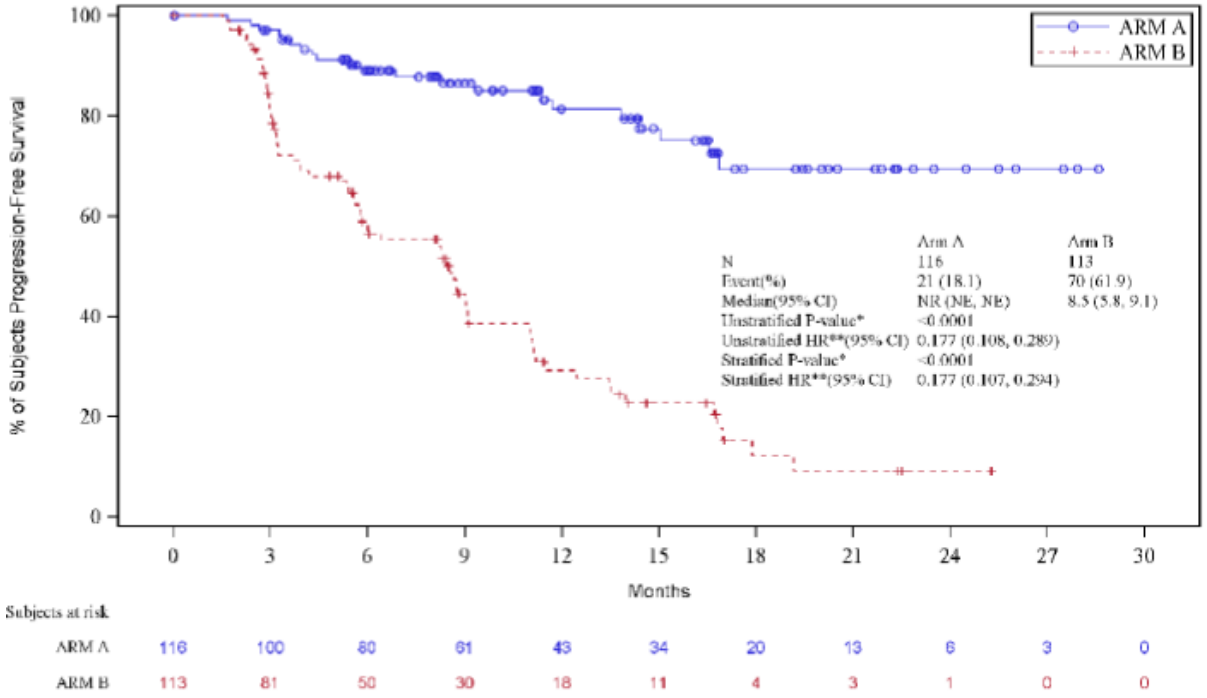
Summary of key efficacy results

	Lutetium octreotide	Octreotide LAR 60mg
Primary endpoint		
PFS per IRC		
PFS events, n (%)	21 (18.1%)	70 (61.9%)
Median PFS (months) (95% CI)	not reached	8.5 (5.8, 9.1)
Unstratified HR (95% CI)	0.177 (0.108, 0.289)	
Unstratified log-rank p-value	<0.0001[a]	
Key secondary endpoints		
ORR per IRC		
ORR, % (95% CI)	14.7 (7.8, 21.6)	4.0 (0.2, 7.8)
Fisher's exact test p-value	0.0141[a]	
OS (Pre-specified interim analysis)		
OS events, n (%)	17 (14.7)	31 (27.4)
Median OS (months) (95% CI)	not reached	27.4 (20.1, not estimated)
Unstratified HR (95% CI)	0.459 (0.254, 0.830)	
Unstratified log-rank p-value	0.0083[b]	

[a] Statistically significant.
[b] The pre-specified threshold for statistical significance (0.0085%) was not reached.

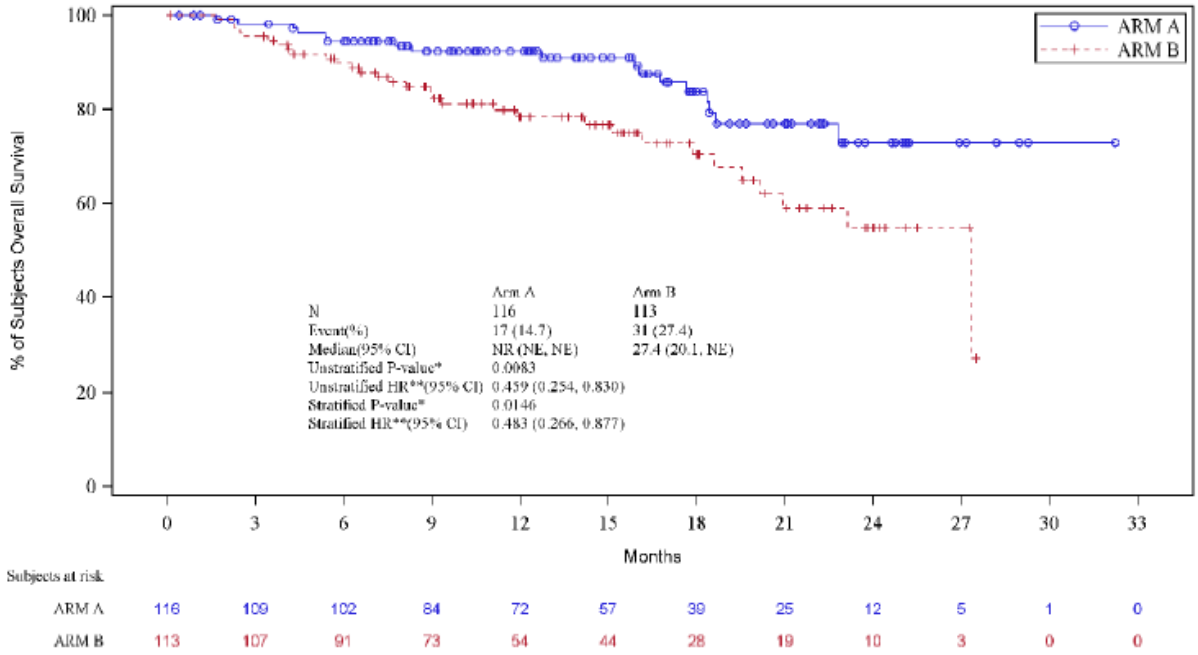
Treatment with lutetium oxodotreotide resulted in a statistically significant improvement in PFS over the octreotide LAR 60mg arm (HR 0.177; 95% CI 0.108, 0.289; p<0.0001). The median duration of PFS was not reached in the lutetium oxodotreotide arm compared to 8.5 months in the octreotide LAR 60mg arm. The PFS results were consistent in various sensitivity analyses using alternative handling of missing data and censoring rules, as well as local assessment, demonstrating robustness of the data.

Kaplan-Meier curves of PFS per IRC



Improvement in ORR was also statistically significant in favour of the lutetium oxodotreotide arm over octreotide LAR 60mg arm (14.7% versus 4.0%; p=0.0141). There were 14 partial responses and 1 complete response. At the pre-specified interim analysis for OS (i.e. time of primary analysis of PFS, or 24 July 2015 data cut-off date), although the pre-specified alpha threshold (0.0085%) was not reached, a trend for longer survival for the lutetium oxodotreotide arm was observed, with a HR of 0.459 (95% CI 0.254, 0.830; p=0.0083). At an updated analysis (30 Jun 2016 data cut-off date), the HR was 0.536 (95% CI 0.333 to 0.864), p=0.0094. The median OS was not reached in the lutetium oxodotreotide arm and was 27.4 months in the octreotide LAR 60mg arm. Although a trend for positive OS results had been observed, results from the final analysis would be required to confirm the observed improvement in OS. Longer follow-up will be required to confirm the OS benefit. The median TTP and the median DoR had not been reached for the lutetium oxodotreotide arm.

Kaplan-Meier curves of OS (Pre-specified interim analysis, 24 July 2015)



Additional supportive data were available from the ERASMUS study. The ERASMUS study was a Phase I/II, investigator- sponsored, open-label, non-randomised study to evaluate the efficacy of lutetium oxodotreotide in patients with somatostatin receptor-positive tumours. Patients in the study received similar doses of lutetium oxodotreotide as in the NETTER-1 study. Similar concomitant amino acid infusion and pre-medication with anti-emetics were also given.

The primary efficacy endpoint was tumour response rate, defined as the sum of complete responses and partial responses, per RECIST 1.1. Key secondary efficacy endpoints were PFS, TTP and OS.

Of 1214 patients with somatostatin receptor-positive tumours enrolled in the study, a total of 360 patients with GEP-NET were included in the primary efficacy analyses. The median age was 60 years and about half of the patients were male (50.8%). About half of the patients had progressive disease at baseline (51.1%). Majority of the GEP-NETs were of midgut origin (50.8%), followed by pancreatic (36.9%), bronchial (5.3%), hindgut (3.6%) and foregut origins (3.3%).

The ORR was 45.0% (ranged from 33.3% to 60.9% for various GEP-NET tumour types). The median PFS was 28.5 months (ranged from 18.4 months to 43.9 months), the median OS was 61.2 months (ranged from 50.6 to 66.4 months) and the median TTP was 34.5 months. Across various GEP-NET tumour types, the largest effects were seen for pancreatic NETs and foregut NETs. In patients with progressive GEP-NETs, the ORR was 45.0%, the median PFS was 26.9 months, the median OS was 57.2 months and the median DoR was 16.3 months.

Overall, the NETTER-1 study met its primary endpoint. In the ERASMUS study, the efficacy results were consistent across different GEP-NET tumour types, as well as with the results for midgut NETs in the NETTER-1 study. Given that the mechanism of action of lutetium oxodotreotide is based on binding to SSTR on tumour cells, it is expected to be efficacious in somatostatin receptor-positive GEP-NETs irrespective of their location. These results adequately supported the efficacy of lutetium oxodotreotide for the treatment of GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumours.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of lutetium oxodotreotide for the treatment of GEP-NETs was based on safety data derived from 223 patients who received at least one dose of study treatment in the NETTER-1 study, and 811 patients (all tumour types) who received at least one dose of lutetium oxodotreotide in the ERASMUS study.

In the NETTER-1 study, 26.1% of the patients received a total cumulative dose of lutetium oxodotreotide of at least 800 mCi and 79.3% received at least 600 mCi. Patients in the octreotide LAR 60mg arm received a weekly mean dose of 14.8mg and a median of 8 administrations.

Overview of safety profile

Adverse event (AE)	Lutetium oxodotreotide (N=112)	Octreotide LAR 60mg (N=111)
Treatment-emergent AE (TEAE)	110 (98.2%)	103 (92.8%)
Treatment-related AE	102 (91.1%)	45 (40.5%)
Grade ≥ 3 TEAE	64 (57.2%)	41 (36.9%)
Treatment-related Grade ≥ 3 AE	34 (30.4%)	5 (4.5%)
Serious treatment-emergent AE (SAE)	35 (31.3%)	27 (24.3%)
Treatment-related SAE	13 (11.6%)	3 (2.7%)
Discontinuations due to TEAE	14 (12.5%)	12 (10.8%)
Deaths due to TEAE	7 (6.3%)	9 (8.1%)

The most commonly reported treatment-related AEs with higher incidences in the lutetium oxodotreotide arm compared to the octreotide LAR 60mg arm were nausea (58.9% versus 3.6%), vomiting (45.5% versus 3.6%), fatigue (24.1% versus 0%), decreased appetite (13.4% versus 0%), thrombocytopenia (13.4% versus 2.7%), lymphopenia (13.4% versus 8.0%) and anemia (12.5% versus 0%). The majority (81.3%) of the nausea and vomiting occurred in the lutetium oxodotreotide arm were considered related to the amino acid co-infusion.

The most commonly reported treatment-related Grade ≥ 3 AEs in the lutetium oxodotreotide arm compared to the octreotide LAR 60mg arm were lymphopenia (8.0% versus 0%), nausea (3.6% versus 0%), vomiting (3.6% versus 0%), lymphocyte count decreased (3.6% versus 0%) and thrombocytopenia (2.7% versus 0%).

The AEs of special interest reported with lutetium oxodotreotide included haematotoxicity, secondary haematological malignancies, nephrotoxicity and hepatotoxicity. The AEs of special interest reported with at least 5% difference between the lutetium oxodotreotide arm and the octreotide LAR 60mg arm included Grade 3-4 leukopenia (44.6% versus 3.6%), Grade 2-4 thrombocytopenia (8.9% versus 1.8%), radiation-induced nephropathy (33.9% versus 18.9%), renal disorder (17.9% versus 8.1%) and acute radiation toxicity (10.7% versus 3.6%).

Of the AEs reported, the most notable safety concerns with lutetium oxodotreotide were nephrotoxicity and haematotoxicity resulting from radiation exposure. The risk of nephrotoxicity could be reduced by co-infusion of amino acid solution, which decreases renal radiation exposure by about 47%. The clinical management of nephrotoxicity and haematotoxicity are adequately described in the package insert.

In the ERASMUS study, 65.1% of the patients in the safety analysis set received a total cumulative dose of lutetium oxodotreotide of at least 800 mCi and 81.4% received at least 600 mCi. In the study, safety information was not routinely collected. Post-hoc safety review found the following AEs of special interest: myelodysplastic syndrome (2.0%), hypotension (1.2%), cardiac failure (1.5%), myocardial infarction (1.1%), renal failure (1.0%), renal impairment (1.2%) and acute leukemia (0.5%).

Overall, the safety profile of lutetium oxodotreotide in GEP-NETs was considered acceptable for the intended population given the disease setting. The package insert has included recommendations for dose modifications for toxicities, as well as adequate warnings and information on clinical management of the AEs.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The clinical management of GEP-NETs involves a multi-modal approach including surgery, locoregional therapies, radiotherapy and systemic medical treatment. Systemic treatment options include somatostatin analogues, chemotherapy, and targeted therapy such as everolimus and sunitinib. For patients with advanced and progressive disease, there are limited treatment options with significant efficacy, hence new therapeutic options are required to improve treatment outcomes, particularly in terms of overall survival.

The improvement in PFS for lutetium oxodotreotide (HR 0.177; 95% CI 0.108, 0.289; p<0.0001), together the improvement in ORR (14.7% versus 4%; p=0.0141) and the trend for improved survival compared to high dose octreotide LAR (HR of 0.459; 95% CI 0.254, 0.830; p=0.0083), were considered clinically meaningful. While the final analysis was lacking and longer follow-up will be required to confirm the OS benefit, the overall evidence taken together with PFS was adequate to support the use in patient with unresectable, somatostatin receptor-positive, histologically proven midgut carcinoid tumours who progressed on standard dose of octreotide LAR.

The results from the ERASMUS study provided additional data in patients with various GEP-NET tumour types. The ORR, PFS and OS results were consistent across different GEP-NET tumour types, and also consistent with the results for midgut NETs in the NETTER-1 study.

The safety profile of lutetium oxodotreotide was considered to be manageable and acceptable relative to the benefits. The AEs of special interest reported with lutetium oxodotreotide included haematotoxicity, secondary haematological malignancies, nephrotoxicity and

hepatotoxicity. These risks have been adequately addressed in the local package insert via the provision of relevant warnings and precautions, as well as dose modification recommendations in the event of toxicities.

Overall, the benefit-risk profile of lutetium oxodotreotide in the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor-positive GEP-NETs was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of lutetium oxodotreotide for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor-positive GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumours in adults was deemed favourable and approval of the product registration was granted on 01 June 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

NOVARTIS

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.

Active substance

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

The total amount of radioactivity per single dose vial is 7.4 GBq 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 is adjusted between 20.5 mL and 25.0 mL in order to provide the required amount of radioactivity at the date and time of infusion.

Lutetium (177Lu) has a half-life of 6.647 days. Lutetium (177Lu) decays by beta-emission to stable Hafnium (177Hf) with the most abundant beta-(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, sodium acetate, gentisic acid, ascorbic acid, pentetic acid, sodium chloride, sodium hydroxide, water for injection.

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 (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).

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.

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 (see Table 4-3 Recommended dose modifications for adverse drug reactions).

Pre and concomitant medications

Antiemetics

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

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. 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 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	1 L

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

Commercially available amino acid solutions (e.g., LysaKare®) can be used if compliant with the specification listed in Table 4-2. An amino acid solution containing just lysine and arginine in the amounts specified in Table 4-1 (e.g. LysaKare®) is considered the medicinal product of choice, due to its lower total volume to be infused and lower osmolality.

Table 4-2 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	<1200 mOsmol/kg

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

Monitoring recommendations

Before each administration and during treatment with Lutathera, hematology (platelet count, white blood cell count and hemoglobin (Hb)), kidney function test (serum creatinine) and liver function test (alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin and bilirubin) should be performed to assess the patient's condition.

These laboratory tests should be performed shortly before each administration and 4 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 then every 6 months thereafter, in order to be able to detect possible delayed adverse drug reactions (ADRs). Dosing may need to be modified based on the tests results as described in Table 4-3 Recommended dose modifications for adverse drug reactions) (see section Warnings and precautions).

Dose modifications

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. Recommended dose modifications of Lutathera for adverse drug reactions are provided in Table 4-3.

Table 4-3 Recommended dose modifications for adverse drug reactions

ADRs	Severity of ADRs	Dose modification
Thrombocytopenia	Grade 2 (Platelets <75 to 50 x 10^9/L)[1]	Withhold dose until complete or partial resolution (Grade 0 to 1).
	Grade 3 (Platelets <50 to 25 x 10^9/L)	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.
	Grade 4 (Platelets <25 x 10^9/L)	

ADRs	Severity of ADRs	Dose modification
		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 • Hypoalbuminemia[2] 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.

ADRs	Severity of ADRs	Dose modification
	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)

Special populations

Renal impairment

Lutathera is substantially excreted by the kidneys, thus impaired renal function could lead to increased radiation exposure. Patients with creatinine clearance <40 mL/min should not be treated with Lutathera. 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, and treatment with Lutathera in those patients is contraindicated. No dose adjustment is recommended for renally impaired patients with creatinine clearance ≥40 mL/min; however, renal function should be monitored more frequently as these patients may be at greater risk of toxicity.

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.

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

Patients with hepatic impairment with either total bilirubinemia >3 times the upper limit of normal or albuminemia <30 g/L and prothrombin ratio decreased <70%, should only be treated with Lutathera after careful benefit-risk assessment.

Pediatric patients (below 18 years)

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

Elderly (65 years or above)

No dosage adjustment is required in patients 65 years or above as clinical experience has not identified differences in responses between the elderly and adult patients.

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 (see section Pharmaceutical information). Treating physicians may use other methods deemed appropriate and safe, including the use of infusion pumps, particularly when dose reduction is required (see Table 4-3 Recommended dose modifications for adverse drug reactions). Radiation safety precautions must be considered regardless of the administration method used (see section Warnings and precautions and section Pharmaceutical information).

Instructions for the gravity method:

- 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. 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±10minutes, 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.
- 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 (177Lu) 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 (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 4-4 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 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. 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 (see section Pharmaceutical information). Radiation exposure should be minimized to patients, medical personnel, and household contacts 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).

Hematological toxicity

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 transient. 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.

Hematological evaluation of patients must be performed at baseline and prior to every dose of Lutathera. Treatment with Lutathera should be withheld, the dose reduced, or permanently discontinued based on the severity of the hematological toxicity as described in Table 4-3 Recommended dose modifications for adverse drug reactions.

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).

Secondary myelodysplastic syndrome and leukemia

Late-onset myelodysplastic syndrome (MDS) and acute leukemia 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 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), 16 patients (2%) 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.

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 at least 3 hours after each Lutathera dose (see section Dosage regimen and administration). The amino acid solution helps to decrease reabsorption of lutetium (177Lu) oxodotreotide through the proximal tubules resulting in decrease in the radiation dose to the kidneys. Patients should be advised to urinate frequently during and after administration of Lutathera.

Monitor serum creatinine and creatinine clearance. 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 greater risk of toxicity. Treatment with Lutathera in patients with creatinine clearance <40 mL/min at baseline is not recommended. Lutathera has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease, and treatment with Lutathera in those patients is contraindicated. More frequent monitoring of renal function is recommended in renally impaired patients with creatinine clearance >40 mL/min. 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 section Warnings and precautions).

Hepatobiliary toxicity

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.

Patients with baseline liver impairment with either total bilirubinemia >3 times the upper limit of normal or albuminemia <30 g/L and prothrombin ratio decreased <70%, should only be treated with Lutathera after careful benefit-risk assessment.

Transaminases, bilirubin and serum albumin should be monitored during treatment with Lutathera. Lutathera may need to be withheld, dose reduced, or permanently discontinued as described in Table 4-3 Recommended dose modifications for adverse drug reactions.

Endocrine and metabolism

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).

Embryo-fetal toxicity

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

Females and males of reproductive potential should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Lutathera, and for 6 months after the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for 4 months after the last dose of Lutathera (see section Pregnancy, lactation, females and males of reproductive potential).

Risk of infertility

Lutathera may cause infertility in males and females. The recommended cumulative dose of 29.6 GBq of Lutathera, results in a radiation absorbed dose to the testis and ovaries, within the range where temporary or permanent infertility can be expected following external beam radiotherapy (see section Pregnancy, lactation, females and males of reproductive potential).

Warnings and precautions regarding the renal protective amino acid solution

Hyperkalemia associated with amino acid solution

A transient increase in serum potassium levels may occur in patients receiving arginine and lysine, usually returning to normal levels within 24 hours from the start of the amino acid infusion.

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

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

Vital signs should be monitored during the infusion regardless of baseline serum potassium levels. Patients should be instructed to drink substantial quantities of water (at least 1 glass every hour) on the day of infusion to remain hydrated and facilitate excretion of excess serum potassium.

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

Heart failure

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

Metabolic acidosis

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

7 Adverse drug reactions

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 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 acids infusion administered for renal protection.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (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. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. 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 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

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
			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

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

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
		Blood ALP**** increased	Protein urine Weight decreased Blood creatine phosphokinase increased Blood lactate dehydrogenase increased Blood catecholamines C-reactive protein increased
Injury, poisoning and procedural complications			Clavicle fracture
Surgical and medical procedures		Transfusion	Abdominal cavity drainage Dialysis Gastrointestinal tube insertion Stent placement Abscess drainage Bone marrow harvest Polypectomy
Social circumstances			Physical disability

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

Description of selected adverse drug reactions

Myelosuppression

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.

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 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 (see section Dosage regimen and administration).

Corticosteroids

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 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.

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.

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 (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.

9.2 Lactation

Risk summary

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. If Lutathera treatment is started during breastfeeding, breastfeeding should be discontinued permanently.

9.3 Females and males of reproductive potential

Pregnancy testing

The pregnancy status for females of reproductive potential should be verified prior to initiating treatment with Lutathera (see section Warnings and precautions).

Contraception

Females:

Lutathera can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception during treatment and for 6 months after the last dose of Lutathera (see section Warnings and precautions).

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 (see section Warnings and precautions).

Infertility

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 testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy (see section Warnings and precautions).

10 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.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Other therapeutic radiopharmaceuticals, ATC code: V10XX04.

Mechanism of action (MOA)

Lutetium (177Lu) oxodotreotide has a high affinity for subtype 2 somatostatin receptors (SST2). It binds to malignant cells which overexpress SST2 receptors.

Lutetium (177Lu) is a beta-emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted 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 therapeutic dose was assessed in an open label study in 20 patients with somatostatin receptor-positive midgut carcinoid tumors. No clinically relevant changes in the mean QTc interval (i.e., >20 ms) were detected. Single doses of Lutathera resulted in mean QTcF change from baseline of 2.8 msecs during first 2 hours, 4.2 at 4 hours, 10 at 8 hours and 11.1 m secs 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.

Pharmacokinetics (PK)

The pharmacokinetics of lutetium (177Lu) oxodotreotide have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors. The mean blood exposure (AUC) of lutetium (177Lu) oxodotreotide at the recommended dose is 41 ng.h/mL [coefficient of variation (CV) 36%]. The mean maximum blood concentration (Cmax) 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 for lutetium (177Lu) oxodotreotide is 460 L (CV 54%).

Within 4 hours after administration, lutetium (177Lu) 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%.

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

Biotransformation/metabolism

Lutetium (177Lu) 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 substudy, lutetium (177Lu) 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 (177Lu) oxodotreotide. The mean (± standard deviation) blood elimination half-life is 3.5 (±1.4) hours and the mean terminal blood half-life is 71 (± 28) hours.

Excretion

Lutetium (177Lu) 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 (177Lu) oxodotreotide in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium (177Lu) oxodotreotide, greater than 99% will be eliminated within 14 days after administration of Lutathera (see section Warnings and precautions).

Geriatric patients (65 years or above)

The pharmacokinetics profile in elderly patients (≥65 years) has not been established. No data are available.

12 Clinical studies

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) every 8 weeks) co-administered with an amino acid solution plus best supportive care (BSC; octreotide long acting release [LAR] 30 mg every 4 weeks 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 1.1), based on independent radiology assessment. Secondary efficacy endpoints included objective response rate (ORR), overall survival (OS), and quality of life (QoL).

Two hundred twenty-nine (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 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 x ULN, and 65% had alkaline phosphatase ≤ULN.

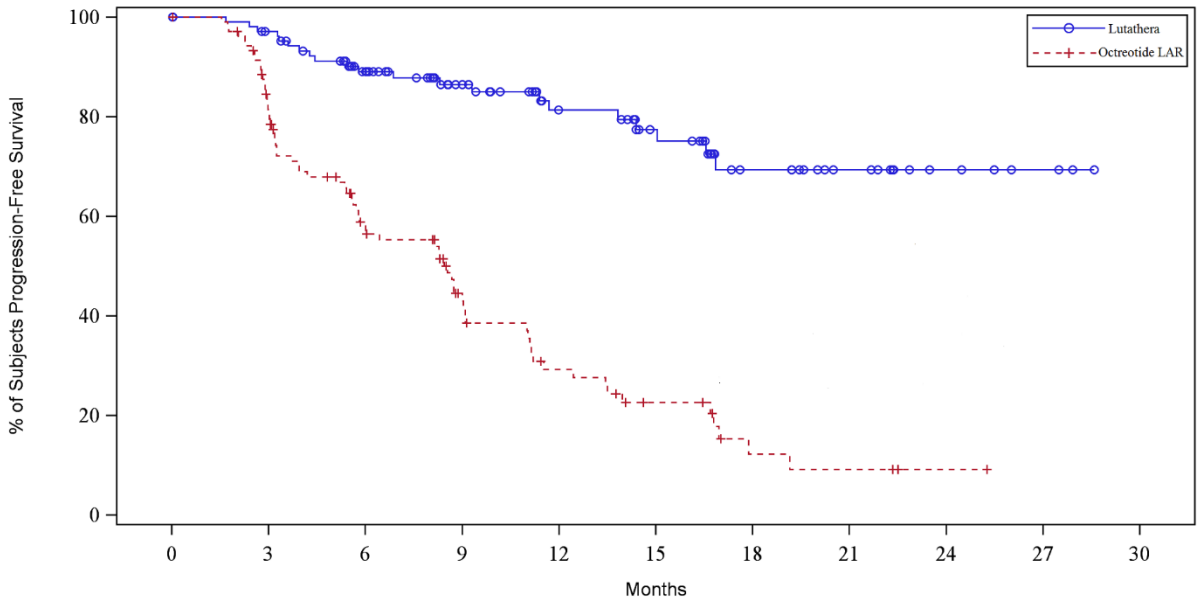
At the time of the final per-protocol PFS statistical analysis (cut-off date 24 July 2015), the number of centrally confirmed disease progressions or deaths was 21 events in the Lutathera arm and 70 events in the octreotide LAR arm (Table 12-1). PFS differed significantly ($p<0.0001$) between the treatment groups. The median PFS for Lutathera was not reached at the time of analysis whereas the one of octreotide LAR was 8.5 months. The hazard ratio for Lutathera was 0.18 (95% CI: 0.11, 0.29), indicating 82% reduction in the risk for a patient to progress or die under Lutathera compared to octreotide LAR.

Table 12-1 Efficacy results in NETTER-1 phase III study in patients with midgut carcinoid tumor, cut-off date 24 July 2015 (full analyses set (FAS), N=229)

	LUTATHERA and Long-Acting Octreotide (30 mg) N=116	Long-Acting Octreotide (60 mg) 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 of patients with progressive midgut carcinoid tumor - cut-off date 24 July 2015 (NETTER-1 phase III study; FAS, N=229)**



The investigator-assessed 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 octreotide LAR arm. With respect to OS, at the time of interim analysis (24 July 2015), there were 17 deaths in the Lutathera arm and 31 in octreotide LAR 60 mg arm and the hazard ratio was 0.459 in favor of Lutathera, but did not reach the level of significance for interim analysis (HR 99.9915% CI: 0.140, 1.506). OS median was 27.4 months in octreotide LAR arm and was not reached in Lutathera arm.

An update conducted about one year later (30 June 2016) showed similar trend with 28 deaths in the Lutathera arm and 43 in octreotide LAR 60 mg arm, an HR of 0.536, and a median OS of 27.4 months in octreotide LAR arm and still not reached in Lutathera arm. The final OS analysis is foreseen after 158 cumulative deaths.

Health Related Quality of Life (HRQOL) was assessed using the European 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 on Lutathera treatment as compared to patients on Octreotide LAR arm.

ERASMUS Study

The efficacy of Lutathera in patients with foregut, midgut, and hindgut GEP-NETs was assessed in the ERASMUS study. 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 which 360 patients had long-term follow-

up, baseline tumor assessment and GEP-NET tumors. 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 major efficacy outcome was investigator-assessed ORR. The median age in the efficacy subset was 61 years (25 to 88 years), 52% were male, 61% had a baseline Karnofsky performance status ≥90 (60 to 100), 60% had progressed within 12 months of treatment, and 15% had received prior chemotherapy. Fifty five percent (55%) of patients received a concomitant long acting release somatostatin analog. The median dose of Lutathera was 29.6 GBq (800 mCi).

The investigator ORR is an aggregate of the best overall response (BOR) in 5 subtypes of GEP-NETs. Out of the 360 patients, 19 patients had bronchial tumors, 133 had pancreatic tumors, 12 had foregut tumors, 183 had midgut tumors, and 13 had hindgut tumors. Patients had their tumors assessed using either the RECIST 1.1 criteria (145 patients, 40%) or the SWOG assessment which was retrospectively algorithmically converted to RECIST 1.1 (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). 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 criteria, the ORR was41% (95% CI: 33, 50), and median DoR was35 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 was47% (95% CI: 41, 54), and median DoR was18.5 months (95% CI: 15, 24).

Table 12-2 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**	
GEP-NET‡	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 (CR + PR); DoR = Duration of response; ND = Not detected; NR = Not reached

†Results are based on patients that either had assessments using the RECIST 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 (360 patients) as well as per tumor type are presented in Table 12-3.

Table 12-3 PFS and OS observed in the ERASMUS phase I/II study in patients with GEP and bronchial NET – (FAS, N=360)

	PFS Time (months)	OS Time (months)

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

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

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

13 Non-clinical safety data

Safety pharmacology and repeat dose toxicity

Toxicological studies conducted with the radiolabeled compound in rats have 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 (175Lu) 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 compound was well tolerated in both species and no deaths were observed.

In repeat dose toxicology studies in rats in which the cold compound was administered for four times at two-week interval the primary target organ was the pancreas, a high SSTR2 expressing organ. Pancreatic acinar apoptosis occurred at lutetium (175Lu) 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.

Lutetium (175Lu) 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 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 (177Lu) oxodotreotide; however, radiation is a carcinogen and mutagen.

Reproductive toxicity

Please see section Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities

Lutathera 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 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.

Instructions for use and handling

Method of administration

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

Lutathera must be administered by slow intravenous infusion over approximately 30 minutes, concomitantly with amino acid solution administered by contralateral intravenous infusion. Lutathera must not be injected as a bolus. For renal protection, an intravenous amino acid solution containing lysine and arginine must be initiated 30 minutes before administering Lutathera and should continue during, and for at least 3 hours after the Lutathera infusion. The dose of the amino acid solution should not be decreased even if the dose of Lutathera is reduced (see section Dosage regimen and administration).

Premedication with antiemetics should be injected with sufficient lead time prior to the start of amino acid solution infusion.

The recommended infusion method for administration of Lutathera is the gravity method. During the administration the recommended precaution measures should be undertaken.

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

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

Requirements

Storage of the vial:

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

Room and equipment preparation

Administration room:

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

Medicinal products to be administered:

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

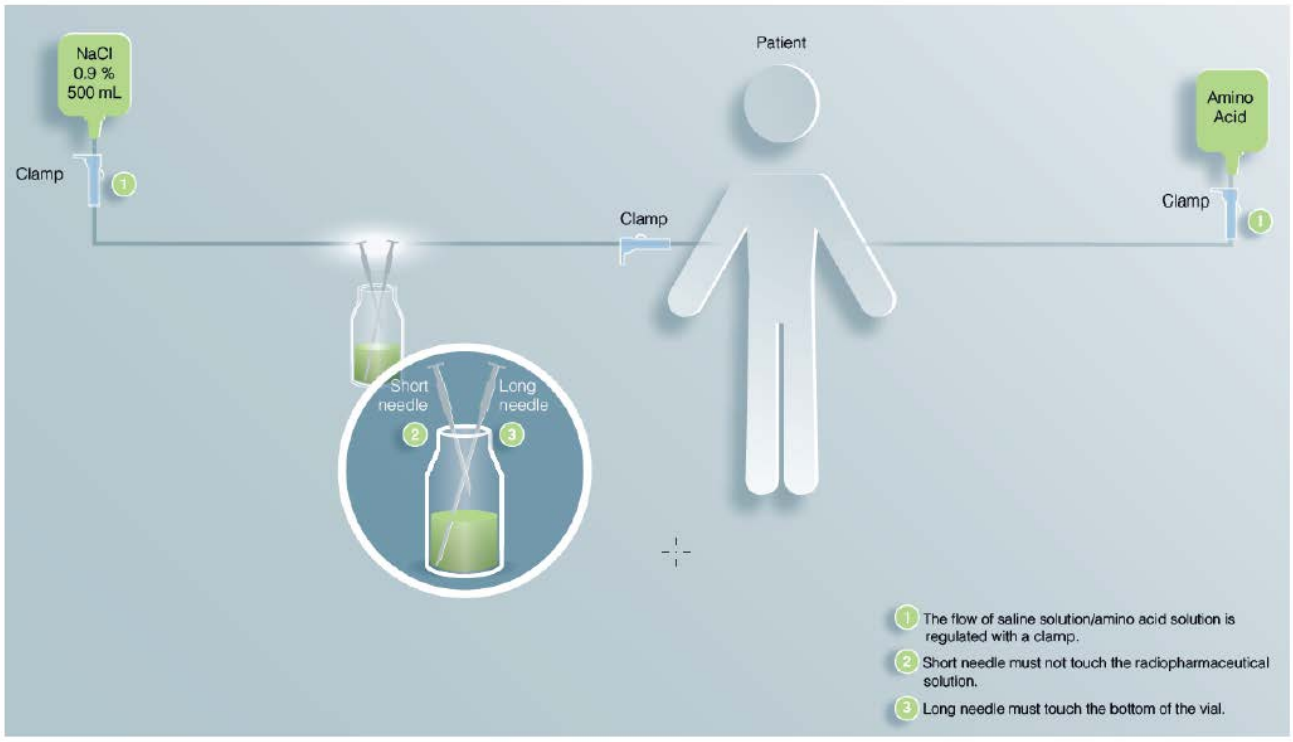
Care supplies and equipment:

- Two (2) infusion poles
- One (1) Long needle (9.0 cm to 10.0 cm, 18 gauge)
- One (1) Short needle (2.5 cm, 20 gauge)
- Two (2) gravity intravenous infusion sets with a clamp to regulate or stop the flow (one for Lutathera, one for amino acid solution administration)
- Two (2) peripheral intravenous plastic catheters
- One (1) sterile tubing line with a clamp to regulate or stop the flow
- A pair of tongs (for Lutathera vial handling)
- Calibrated radioactivity measurement system and Geiger counter to monitor the radioactivity of Lutathera

Lutathera vial tubing connections procedure (see Figure 14-1):

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

Figure 14-1 Gravity infusion method – tubing connection scheme



Administration procedure (gravity method)

During the infusion, the flow of sodium chloride 9 mg/mL (0.9%) solution for injection increases the pressure in the Lutathera vial, facilitating the flow of Lutathera into the catheter inserted in the patient's peripheral vein.

Careful monitoring of the vital signs during the infusion is recommended.

1. Two intravenous plastic catheters should be inserted into patient's peripheral veins, one on each arm.
2. The catheters should be connected to the infusion sets (one for Lutathera, one for amino acid solution).
3. Antiemetic premedication should be administered with sufficient lead time prior the start of amino acid solution infusion.
4. Administration of the amino acid solution should be initiated 30 minutes before Lutathera infusion, with an infusion rate of 250 to 500 mL/h (depending on volume). Amino acid solution should be administered over 4 hour time span. In case of severe nausea or vomiting during amino acid solution infusion, an antiemetic of a different pharmacological class can be administered.
5. Radioactivity in the Lutathera vial should be measured immediately before infusion using a calibrated radioactivity measurement system.

6. Lutathera infusion should start 30 minutes after the beginning of the amino acid solution infusion, with the infusion rate of up to approximately 400 mL/h (this infusion rate is the reference rate; 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. Lutathera should be administered over 30±10 minute time span. Constant intra-vial pressure should be maintained during the entire infusion.
7. Lutathera administration should be initiated by opening first the tubing line connected to the patient's peripheral vein, and then, by opening the infusion set connected to the bag of sodium chloride 9 mg/mL (0.9%) solution for injection. The pole height should be adjusted in order to compensate any increase or reduction of pressure inside the vial. Moving the patient's arm position should be avoided if possible (extreme flexion or extension which could lead to vein compression).
8. The flow of Lutathera from the vial to the patient should be monitored during the entire infusion. Soon after the start of the infusion, the radioactivity emission over the patient's thorax should be measured using Geiger counter to verify the presence of Lutathera in the bloodstream. Subsequent checks of the radioactivity emission should be performed approximately every 5 minutes at the level of the patient's thorax and vial. During the infusion, the radioactivity emission from the patient's thorax should steadily increase while the one from the Lutathera vial should decrease.
9. To ensure complete administration, the Lutathera vial should be kept under even pressure. The level of solution in the vial should remain constant during the entire infusion. Visual controls of the solution levels should be repeated during the administration by direct visual control (when PMMA container is used) or using a pair of tongs to handle the vial when the lead shipping container is used.
10. The infusion should be stopped once the radioactivity emission from the vial becomes stable for several minutes (or during two consecutive measurements). This is the only parameter to determine the procedure completion. The volume of sodium chloride 9 mg/mL (0.9%) solution for injection necessary to complete the infusion may vary.
11. Total activity administered is equal to the activity in the vial before infusion minus the activity remaining in the vial after the infusion. The measurements should be performed using a calibrated system.

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

Table 14-1 Administration procedure 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 the volume	4 hours
Lutathera with sodium chloride 9 mg/mL (0.9%) solution for injection	30	Up to 400	30 ±10 minutes

Directions for quality control

a. Packaging must be inspected for damage, and a survey meter should be used to determine if any radioactive contamination is present. Do not use product if the integrity of the vial is compromised.
b. Visually inspect the product for particulate matter and discoloration under a shielded screen. Do not use if particulates or discoloration are present.
c. Assay the dose in the vial in a suitable dose calibrator.
d. Use aseptic technique and radiation shielding to withdraw Lutathera solution.
e. Do not mix Lutathera with other intravenous solutions.
f. Measure the amount of radioactivity in the radiopharmaceutical vial with an appropriate and calibrated device prior to administration in order to confirm that the actual amount of radioactivity to be administered is equal to the planned amount at the infusion time. To perform calculation, also check vial volume on the documentation received with the product. Review estimated radiation absorbed dose per injection activity for organs and tissues of adult patients following an intravenous dose of Lutathera in Table 4-4 [see section Dosage regimen and administration].

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 (as given in next paragraph) 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.

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.

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.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer:

See folding box.

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® = registered trademark

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