

Date: 3 July 2025

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lutathera

International non-proprietary name: lutetium(¹⁷⁷Lu) oxodotreotide

Lutetium-177 is produced from ytterbium-176 and is non-carrier added.

Pharmaceutical form: solution for injection/infusion

Dosage strength(s): 370 MBq/mL

Route(s) of administration: intravenous

Marketing authorisation holder: Novartis Pharma Schweiz AG

Marketing authorisation no.: 69776

Decision and decision date: approved on 22.11.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC _{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C _{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC ₅₀	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCA	Non-carrier added
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
Tc	Calibration Time
TEAE	Treatment-emergent adverse event

TFA	Trifluoroacetic acid
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status

The applicant requested new active substance status for lutetium(¹⁷⁷Lu) oxodotreotide in the above-mentioned medicinal product.

Orphan drug status

The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 05 December 2012.

Diagnostic or therapeutic radiopharmaceutical

This application for a diagnostic radiopharmaceutical / therapeutic radiopharmaceutical has been reviewed by Swissmedic and the Expert Commission for Radiopharmaceuticals.

2.2 Indication and dosage

The modules 4 and 5, the non-radioactive part of module 3, and the production of the final product are identical to those of the already approved preparation Lutathera CA (MAH No. 66580). Therefore, indication and dosage are also identical to those of the already approved Lutathera CA. The Information for healthcare professionals is applied for as a joint information for both preparations.

2.2.1 Requested indication

The indication requested is the same as the already approved indication for Lutathera CA.

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:

The dosage recommendation requested is the same as the already approved dosage recommendation for Lutathera CA.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	08 February 2024
Formal control completed	09 February 2024
Preliminary decision	18 June 2024
Response to preliminary decision	06 August 2024
Final decision	22 November 2024
Decision	approval

3 Medical context

Not applicable, see section 2.2

4 Quality aspects

4.1 Drug substance

Drug Substance Precursor (non-radioactive)

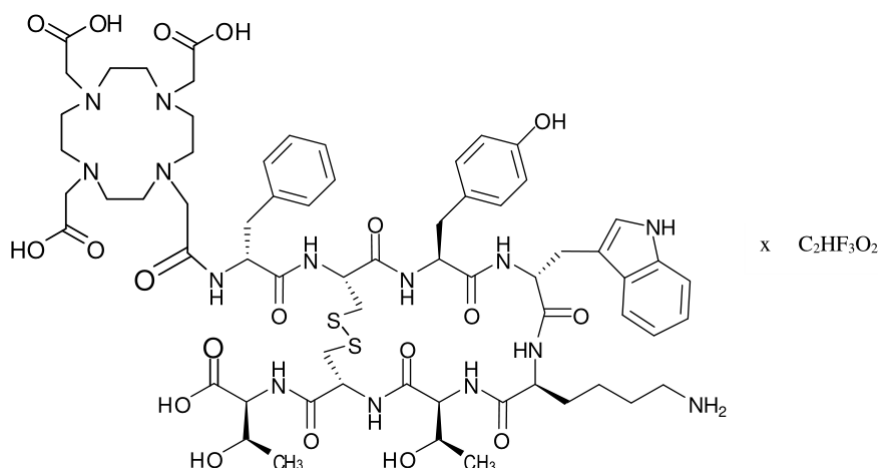
INN: Oxodotreotide

Chemical name: 2,2',2''-(10-(2-((R)-1-((4R,7S,10S,13R,16S,19R)-13-((1H-indol-3-yl)methyl)-10-(4-aminobutyl)-4-((1S,2R)-1-carboxy-2-hydroxypropylcarbonyl)-16-(4-hydroxybenzyl)-7-((R)-1-hydroxyethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-9-ylamino)-1-oxo-3-phenylpropan-2-ylamino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid

Molecular formula: $C_{65}H_{90}N_{14}O_{19}S_2 \times C_2HF_3O_2$

Molecular mass: 1435.62 g/mol (without counter ion)

Molecular structure:



Physicochemical properties: Oxodotreotide (TFA salt) is a white to off white powder and is freely soluble in water (10 mg peptide gross weight in 100 μ L water).

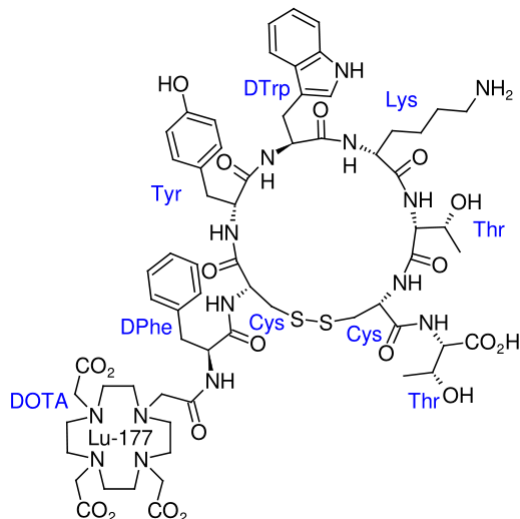
Synthesis: The drug substance precursor is obtained by adopting solid phase peptide synthesis. After coupling both the amino acid derivatives and the DOTA (1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid) ligand to the resin, the linear crude peptide is cleaved from the solid support, isolated and purified by preparative HPLC. Subsequent oxidation leads to the disulfide bridge formation, and thus, the cyclisation of the peptide. Oxodotreotide is then purified again by preparative HPLC and isolated by lyophilisation.

Specification: In order to ensure a consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described, and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability: Appropriate stability data have been presented. Based on the results, satisfactory re-test periods have been established when stored at $-20^{\circ}C \pm 5^{\circ}C$ (bulk in PETG bottles with HDPE screw cap; aliquots in type I borosilicate glass vials).

Drug Substance (radioactive)

INN: lutetium (¹⁷⁷Lu) oxodotreotide
 Chemical name: Lutetium(¹⁷⁷Lu)-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic(2-7)disulfide
 Molecular formula: C₆₅H₈₇N₁₄O₁₉S₂¹⁷⁷Lu
 Molecular mass: 1609.6 g/mol
 Molecular structure:



The drug substance ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate is a complex resulting from the sequestration of radioisotope lutetium-177 (¹⁷⁷Lu) with DOTA⁰-Tyr³-Octreotate.

Lu-177 is a non-carrier added (NCA) product produced by the neutron bombardment of ytterbium oxide target material enriched in the isotope Yb-176. The Yb-176 is transmuted to Yb-177, which decays to Lu-177.

The radioactive drug substance ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate is produced as an aqueous concentrated solution. Due to its radioactive nature (decay), the drug substance is not isolated. The synthesis of the drug substance (¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate) and its formulation into the drug product (¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate 370 MBq/mL solution for infusion) are part of an automated continuous process that does not allow isolation and testing of the pure drug substance.

4.2 Drug product

Description and composition:

The drug product (¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate 370 MBq/mL solution for infusion) is a sterile ready-to-use solution for infusion containing ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate as drug substance with a volumetric activity of 370 MBq/mL at reference date and time (calibration time (tc)).

The drug product is a single dose vial, containing a suitable amount of solution that allows delivery of 7.4 GBq of radioactivity at injection time. The filling volume needed for an activity of 7.4 GBq at injection time is calculated and can range from 20.5 – 25.0 mL.

Pharmaceutical development:

The chosen excipients act as pH adjusters, radiation stability enhancers, sequestering agent, and isotonicising agents. The applicant developed an automatic continuous process at production scale in order to obtain the drug product.

Manufacture:

The manufacturing process of Lutathera 370 MBq/mL solution for infusion starts when the synthesis of the drug substance ($^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$) is finalised in a synthesis cell. The formulation buffer solution is added, and the homogenised solution is filtered through a sterilising filter and dispensed into the vials, followed by measurement of the weight and the radioactivity of each vial, and placing the vials into the corresponding shielded container.

Adequate process parameters and in-process controls are defined in order to ensure a consistent quality of the drug product.

Specification:

For the control of the finished product, adequate tests and acceptance criteria for release and end of shelf-life have been established. The specifications include relevant physicochemical characteristics, identification of the drug substance, assay and (chemical and radiochemical) purity tests, specific activity, and radionuclidic purity, as well as sterility and bacterial endotoxin tests. The applied test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container closure system:

Container closure system consists of a sterile 30 mL capacity glass vial made of Type I clear colourless glass in compliance with Ph. Eur. whose use is well-established for parenteral solutions. Vials are closed with bromobutyl rubber septum (in compliance with Ph. Eur.) and capped with an aluminium cap that has a centred, circular opening.

The vial is enclosed within a plastic sealed, lead shielded container (secondary packaging) used during transport and storage of the product.

Stability:

Appropriate stability data have been generated according to the relevant international guidelines. The shelf-life of the drug product is defined as 72 hours after calibration time, which corresponds to the End of Production, when stored below 25°C.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Not applicable, see section 2.2

6 Clinical aspects

Not applicable, see section 2.2.

7 Risk management plan summary

Not applicable, see section 2.2.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Lutathera was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

Lutathera 370 MBq/ml solution for infusion

Lutathera CA 370 MBq/ml solution for infusion

Composition

Active substances

Lutathera: Lutetium (^{177}Lu) oxodotreotide 370 MBq/ml solution for infusion at the date and time of calibration. Lutetium-177 is produced from ytterbium-176 and is non-carrier added.

Lutathera CA: Lutetium (^{177}Lu) oxodotreotide 370 MBq/ml solution for infusion at the date and time of calibration. Lutetium-177 is produced from lutetium-176 and is carrier-added. The medicinal product contains the impurity lutetium-177m.

Excipients

Acetic acid, sodium acetate 0.66 mg/ml, gentisic acid, ascorbic acid, pentetic acid, sodium chloride 6.85 mg/ml, sodium hydroxide 0.64 mg/ml, water for injections.

Each ml of solution contains up to 0.14 mmol (3.24 mg) of sodium.

Pharmaceutical form and quantity of active substance per unit

Lutathera/Lutathera CA is for intravenous administration only.

Lutathera/Lutathera CA is a sterile, clear, colourless or slightly yellow solution for infusion with a pH of 4.5-6.0.

Specifications at expiration:

Radiochemical purity: lutetium (^{177}Lu) oxodotreotide $\geq 95\%$

Radionuclidic purity: lutetium (^{177}Lu) oxodotreotide $> 99.9\%$

Lutathera CA: Radionuclidic purity: lutetium-177m ($^{177\text{m}}\text{Lu}$) $< 0.1\%$

1 ml of solution contains 370 MBq of lutetium (^{177}Lu) oxodotreotide at the date and time of calibration.

Total activity per vial is 7,400 MBq ($\pm 10\%$) at the date and time of infusion.

Given the fixed volumetric activity of 370 MBq/ml at the date and time of calibration, the adjustment of total activity at the date and time of infusion is performed by filling the vial with an adjusted volume of between 20.5 ml and 25 ml per vial in order to provide the required amount of radioactivity at the date and time of infusion.

Indications/Potential uses

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

Dosage/Administration

This medicinal product is intended exclusively for hospital use and may only be administered by medical specialists with a federal post-graduate qualification in nuclear medicine.

Due to the amount of radioactivity administered, the patient must remain in an isolation room after treatment. Radiation protection precautions must be taken (see “Warnings and precautions” and “Notes on handling/radioprotection” under “Other information”).

Before starting treatment with Lutathera/Lutathera CA, somatostatin receptor imaging (scintigraphy or positron emission tomography [PET]) must confirm the overexpression of these receptors in the tumour tissue, with uptake in tumour foci at least as high as normal hepatic uptake.

Usual dosage

Adults

As a general rule, the recommended treatment protocol in adults consists of 4 infusions of 7,400 MBq each. There must be an interval of 8 weeks (\pm 1 week) between each infusion (see also “Dose modification”).

Amino acid solution

To protect renal function, an amino acid solution containing L-lysine and L-arginine must be administered intravenously for 4 hours (see **Table 1** and **Table 2**). The infusion of the amino acid solution should be initiated 30 minutes prior to administration of Lutathera/Lutathera CA.

Infusion of the amino acid solution and Lutathera/Lutathera CA through a separate venous access in each of the patient’s arms is the preferred method. However, if two intravenous lines are not possible due to poor venous access or institutional/hospital preferences, the amino acid solution and Lutathera/Lutathera CA may be infused through the same line via a three-way valve while monitoring the flow rate and venous line patency. The dose of the amino acid solution should not be decreased even if a reduced dose of Lutathera/Lutathera CA is administered.

Considering the high quantity of amino acid solution and the considerable volumes that commercially available solutions require to meet the above specifications, the compounded solution is considered the product of choice due to its lower volume to be infused and lower osmolality. The amino acid solution can be prepared as a compounded product in compliance with the hospital’s sterile medicinal product preparation good practices and according to the composition specified in **Table 1**.

Table 1 Composition of the compounded amino acid solution

Composition	Quantity
L-Lysine HCl	25 g (equivalent to 20 g lysine)
L-Arginine HCl	25 g (equivalent to 20.7 g arginine)
Sodium chloride 9 mg/ml (0.9%) solution for injection or water for injections	1 l

The pH of the compounded amino acid solution prepared according to the composition specified in **Table 1** must be adjusted to 7.4 ± 0.2 using sodium hydroxide (NaOH).

Alternatively, some commercially available amino acid solutions can be used if compliant with the specifications indicated in **Table 2**.

Table 2 Specification for commercially available amino acid solutions

Characteristic	Specification
L-Lysine HCl	Between 18 and 25 g (equivalent to 14.4 to 20 g L-lysine)
L-Arginine HCl	Between 18 and 25 g (equivalent to 14.9 to 20.7 g L-arginine)
Volume	1 to 2 l
Osmolality	<1,200 mOsmol/kg

Treatment monitoring

Laboratory tests are required before each administration and during treatment to re-assess the patient's condition and adapt the therapeutic protocol if necessary (dosage, interval between infusions, number of infusions).

The minimum laboratory tests to be performed before each infusion are:

- Haematology (haemoglobin [Hb], white blood cell count with differential counts, platelet count)
- Renal function (serum creatinine and creatinine clearance by Cockcroft-Gault formula)
- Liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum albumin, international normalised ratio (INR) and bilirubin)

These tests must be performed at least once in the 2 to 4 weeks prior to administration and once just before administration. It is also recommended to perform these tests every 4 weeks for at least 3 months after the last infusion of Lutathera/Lutathera CA and every 6 months thereafter in order to detect possible delayed adverse effects (see "Adverse effects"). The dosage may need to be adjusted based on laboratory results.

Dose modification

Management of severe or intolerable adverse effects may require temporary dose interruption (extension of the dosing interval from 8 weeks to up to 16 weeks), dose reduction or permanent discontinuation of treatment with Lutathera/Lutathera CA (see **Table 3** and **Figure 1**).

Table 3 Recommended dose modifications for adverse effects (AEs)

AE	Severity of AE	Dose modification
Thrombocytopenia	First occurrence of: Grade 2 (platelets <75 to $50 \times 10^9/l$) Grade 3 (platelets <50 to $25 \times 10^9/l$) Grade 4 (platelets $<25 \times 10^9/l$)	Withhold dose until complete or partial resolution (grade 0 to 1). Resume Lutathera/Lutathera CA at 3,700 MBq (100 mCi) after complete or partial resolution. If reduced dose does not result in grade 2, 3 or 4 thrombocytopenia, administer Lutathera/Lutathera CA at 7,400 MBq (200 mCi) during next administration. Permanently discontinue Lutathera/Lutathera CA in the case of grade 2 or higher thrombocytopenia requiring a dosing interval of more than 16 weeks.
	Recurrent grade 2, 3 or 4	Permanently discontinue Lutathera/Lutathera CA.
Anaemia and neutropenia	First occurrence of anaemia: Grade 3 (Hb <8.0 g/dl); transfusion indicated Grade 4 (life-threatening consequences) First occurrence of neutropenia: Grade 3 (absolute neutrophil count [ANC] <1.0 to $0.5 \times 10^9/l$) Grade 4 (ANC $<0.5 \times 10^9/l$)	Withhold dose until complete or partial resolution (grade 0, 1 or 2). Resume Lutathera/Lutathera CA at 3,700 MBq (100 mCi) after complete or partial resolution. If reduced dose does not result in grade 3 or 4 anaemia or neutropenia, administer Lutathera/Lutathera CA at 7,400 MBq (200 mCi) during next administration. Permanently discontinue Lutathera/Lutathera CA in the case of grade 3 or higher anaemia or neutropenia requiring a dosing interval of more than 16 weeks.

Prescribing information for human medicines

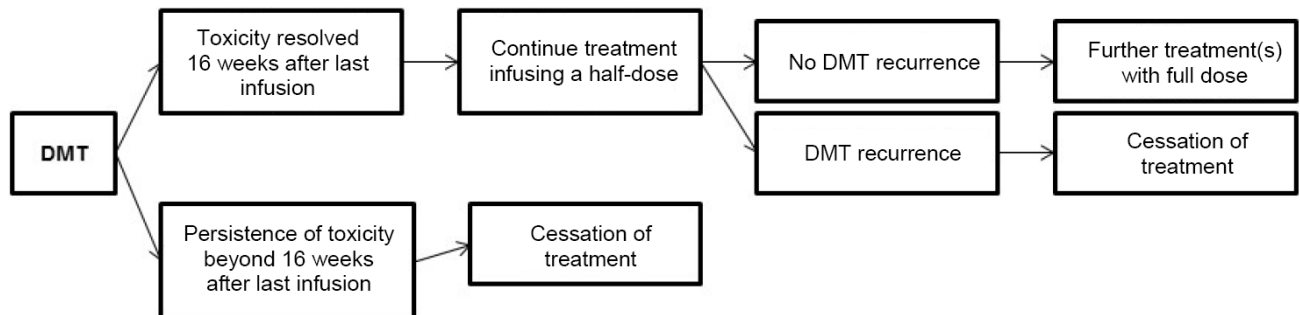
AE	Severity of AE	Dose modification
	Recurrent grade 3 or 4	Permanently discontinue Lutathera/Lutathera CA.
Renal toxicity	First occurrence of: <ul style="list-style-type: none"> ▪ Creatinine clearance less than 40 ml/min; calculated using Cockcroft-Gault formula and current body weight or ▪ 40% increase from baseline serum creatinine concentration or ▪ 40% decrease from baseline creatinine clearance; calculated using Cockcroft-Gault formula and current body weight. 	Withhold dose until resolution or return to baseline. Resume Lutathera/Lutathera CA at 3,700 MBq (100 mCi) after resolution or return to baseline. If reduced dose does not result in renal toxicity, administer Lutathera/Lutathera CA at 7,400 MBq (200 mCi) during next administration. Permanently discontinue Lutathera/Lutathera CA in the case of renal toxicity requiring a dosing interval of more than 16 weeks.
	Recurrent renal toxicity	Permanently discontinue Lutathera/Lutathera CA.
Hepatotoxicity	Defined as: <ul style="list-style-type: none"> ▪ Bilirubinaemia greater than 3 times the upper limit of normal (grade 3 or 4) or ▪ Albuminaemia <30 g/l with INR >1.5 	Withhold dose until resolution or return to baseline. Resume Lutathera/Lutathera CA at 3,700 MBq (100 mCi) after complete resolution or return to baseline. If reduced dose does not result in hepatotoxicity, administer Lutathera/Lutathera CA at 7,400 MBq (200 mCi) during next administration. Permanently discontinue Lutathera/Lutathera CA in the case of hepatotoxicity requiring a dosing interval of more than 16 weeks.
	Recurrent hepatotoxicity	Permanently discontinue Lutathera/Lutathera CA.
	First occurrence of grade 3 or 4	Withhold dose until complete or partial resolution (to grade 0 to 2).

AE	Severity of AE	Dose modification
Any other CTCAE* grade 3 or grade 4 adverse drug reaction		Resume Lutathera/Lutathera CA at 3,700 MBq (100 mCi) after complete or partial resolution. If no grade 3 or 4 toxicity occurs on reduced dose, Lutathera/Lutathera CA can be dosed at 7,400 MBq (200 mCi) at next administration. Permanently discontinue Lutathera/Lutathera CA in the case of a grade 3 or higher adverse drug reaction requiring a dosing interval of more than 16 weeks.
	Recurrent grade 3 or 4 toxicity	Permanently discontinue Lutathera/Lutathera CA.

No dose modification required for grade 3 or 4 haematological toxicities due solely to lymphopenia.

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

Figure 1 Instruction schemes for dose modifications



DMT: Dose modifying toxicity

Other reasons to consider temporary interruption of Lutathera/Lutathera CA treatment include intercurrent illnesses (e.g. urinary tract infection) which the physician considers could increase the risks associated with Lutathera/Lutathera CA administration, and which must therefore be resolved or stable before treatment is resumed, and major surgery, in which case treatment with Lutathera/Lutathera CA should be withheld for 12 weeks after surgery.

Special populations

Elderly patients

No difference in response has been observed between elderly patients and younger patients in clinical study results. However, since an increased risk of haematotoxicity has been described in elderly patients (≥ 70 years old), close follow-up allowing for prompt dose adaptation in this population is advisable.

Patients with renal impairment

The activity to be administered must be carefully considered in patients with renal impairment due to the possibility of increased radiation exposure. The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with baseline severe or end-stage renal failure have not been studied. Treatment with Lutathera/Lutathera CA is contraindicated in patients with severe renal impairment with a creatinine clearance < 30 ml/min (see “Contraindications”). Treatment with Lutathera/Lutathera CA in patients with a creatinine clearance < 40 ml/min at baseline (using Cockcroft-Gault formula) is not recommended. No dose adjustment is recommended for renally impaired patients with baseline creatinine clearance ≥ 40 ml/min. However, as this medicinal product is mainly excreted by the kidneys, renal function should be more frequently monitored during treatment as these patients may be at greater risk of toxicity.

For additional information on the management of patients with renal toxicity see “Dosage/Administration” (**Table 3**) and “Warnings and precautions”.

Patients with hepatic impairment

The activity to be administered must be carefully considered in patients with hepatic impairment due to the possibility of increased radiation exposure. The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with baseline severe hepatic impairment (total bilirubin > 3 times upper limit of normal regardless of AST levels) have not been studied. Therefore, treatment with Lutathera/Lutathera CA is not recommended in these patients. Patients with baseline hepatic impairment with either total bilirubin > 3 times the upper limit of normal or albuminaemia < 30 g/l and INR > 1.5 should only be treated with Lutathera/Lutathera CA after careful benefit-risk assessment. For the procedure to follow in patients with hepatotoxicity, see **Table 3** under “Dosage/Administration” and “Warnings and precautions”.

Paediatric population

There is no relevant use of Lutathera/Lutathera CA in children and adolescents in the indication of GEP-NETs (excluding neuroblastoma, neuroganglioblastoma and pheochromocytoma). Lutathera/Lutathera CA is not approved for use in the paediatric population.

Premedication

Antiemetics

Antiemetic premedication must be administered leaving a sufficient interval before the start of amino acid solution infusion. Please refer to the full prescribing information for the antiemetics for administration instructions.

If severe nausea or vomiting occurs during infusion of the amino acid solution despite prior administration of an antiemetic, an antiemetic of a different pharmacological class may be administered.

Concomitant use of somatostatin analogues

Before initiating Lutathera/Lutathera CA treatment: Interrupt administration of long-acting somatostatin analogues (e.g. octreotide long-acting release [LAR]) at least 4 to 6 weeks prior to initiating Lutathera/Lutathera CA. If necessary, administer short-acting octreotide up to 24 hours prior to initiating Lutathera/Lutathera CA (see “Interactions”).

During Lutathera/Lutathera CA treatment: Do not administer octreotide LAR in the 4 to 6 weeks prior to each Lutathera/Lutathera CA infusion. To control disease symptoms during treatment with Lutathera/Lutathera CA, short-acting octreotide may be administered to the patient, but must be withheld for at least 24 hours before each Lutathera/Lutathera CA dose.

Following Lutathera/Lutathera CA treatment: Continue intramuscular administration of 30 mg octreotide LAR every 4 weeks after the end of Lutathera/Lutathera CA treatment if clinically indicated.

Method of administration

Lutathera/Lutathera CA is intended for intravenous administration. It is a ready-to-use radiopharmaceutical medicinal product for single use only.

Administration instructions

The gravity method, the peristaltic pump method or the syringe pump method may be used to administer the recommended dose. Treating healthcare professionals may use other methods deemed appropriate and safe, particularly when dose reduction is required.

When using the gravity method or the peristaltic pump method, Lutathera/Lutathera CA should be infused directly from its original container. The peristaltic pump method or the syringe pump method should be used when administering a reduced dose of Lutathera/Lutathera CA following dose modification for an adverse reaction (see **Table 3**). Using the gravity method to administer a reduced dose of Lutathera/Lutathera CA may result in the delivery of an incorrect amount of Lutathera/Lutathera CA if the dose is not adjusted prior to administration. During administration the standard radiation protection precautions should be taken regardless of the infusion method (see “Notes on handling/radioprotection”).

Lutathera/Lutathera CA must not be infused as a bolus.

Soon after the start of the infusion, the radioactivity emitted from the patient should be monitored with a calibrated radioactivity measurement system to ensure that the dose is being delivered. During the infusion, the radioactivity emitted from the patient should steadily increase, while that emitted from the Lutathera/Lutathera CA vial should decrease.

Careful monitoring of the patient's vital signs during the infusion is recommended.

Table 4 summarises the necessary procedures during a treatment course with Lutathera/Lutathera CA.

Table 4 Administration procedure for antiemetics, amino acid solution and Lutathera/Lutathera CA

Administered agents	Start time (min)	Infusion rate (ml/h)	Duration
Antiemetics	Sufficient interval before 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	250-500 depending on volume	4 hours
Lutathera/Lutathera CA with sodium chloride 9 mg/ml (0.9%) solution for injection	30	Up to 400	30 ± 10 minutes

For instructions on handling the medicinal product before administration see "Other information".

For instructions on preparing the patient see "Warnings and precautions".

For recommendations in case of extravasation see "Warnings and precautions".

Intravenous methods of administration

Instructions for gravity infusion (using a tubing clamp or an infusion pump)

1. Insert a 2.5 cm, 20 gauge needle (short needle) into the Lutathera/Lutathera CA vial and connect via a catheter to 500 ml sterile 0.9% sodium chloride solution (used to transport the Lutathera/Lutathera CA solution during the infusion). Ensure that the short needle does not touch the Lutathera/Lutathera CA solution in the vial. The short needle must not be connected directly to the patient. The sodium chloride solution must not flow into the Lutathera/Lutathera CA vial prior to initiation of the Lutathera/Lutathera CA infusion. The Lutathera/Lutathera CA solution must not be injected directly into the sodium chloride solution.

2. Insert a 9 cm, 18 gauge needle (long needle) into the Lutathera/Lutathera CA vial, ensuring that this long needle touches and is secured to the bottom of the Lutathera/Lutathera CA vial during the entire infusion. Connect the long needle to the patient via an intravenous catheter that is connected to 0.9% sterile sodium chloride solution and used for the Lutathera/Lutathera CA infusion into the patient.
3. Use a roller clamp or an infusion pump to regulate the flow of the sodium chloride solution via the short needle into the Lutathera/Lutathera CA vial. The sodium chloride solution entering the vial through the short needle will carry the Lutathera/Lutathera CA solution from the vial to the patient via the intravenous catheter connected to the long needle over a total duration of 30 ± 10 minutes, at an infusion rate of up to 400 ml/h. The infusion should start at a lower rate of <100 ml/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.
4. During the infusion, ensure that the level of solution in the Lutathera/Lutathera CA vial remains constant by repeated direct visual control when a transparent shielded container is used or handling the vial with a pair of tongs when a lead shipping container is used.
5. The flow of Lutathera/Lutathera CA from the vial to the patient must be monitored throughout the infusion.
6. The infusion must be stopped (disconnect the vial from the long needle line and clamp the saline line) once the level of radioactivity remains stable for at least five minutes.
7. Following the infusion, the patient is given 25 ml of sterile 0.9% sodium chloride solution intravenously via the venous catheter.

Instructions for device-assisted infusion with peristaltic pump

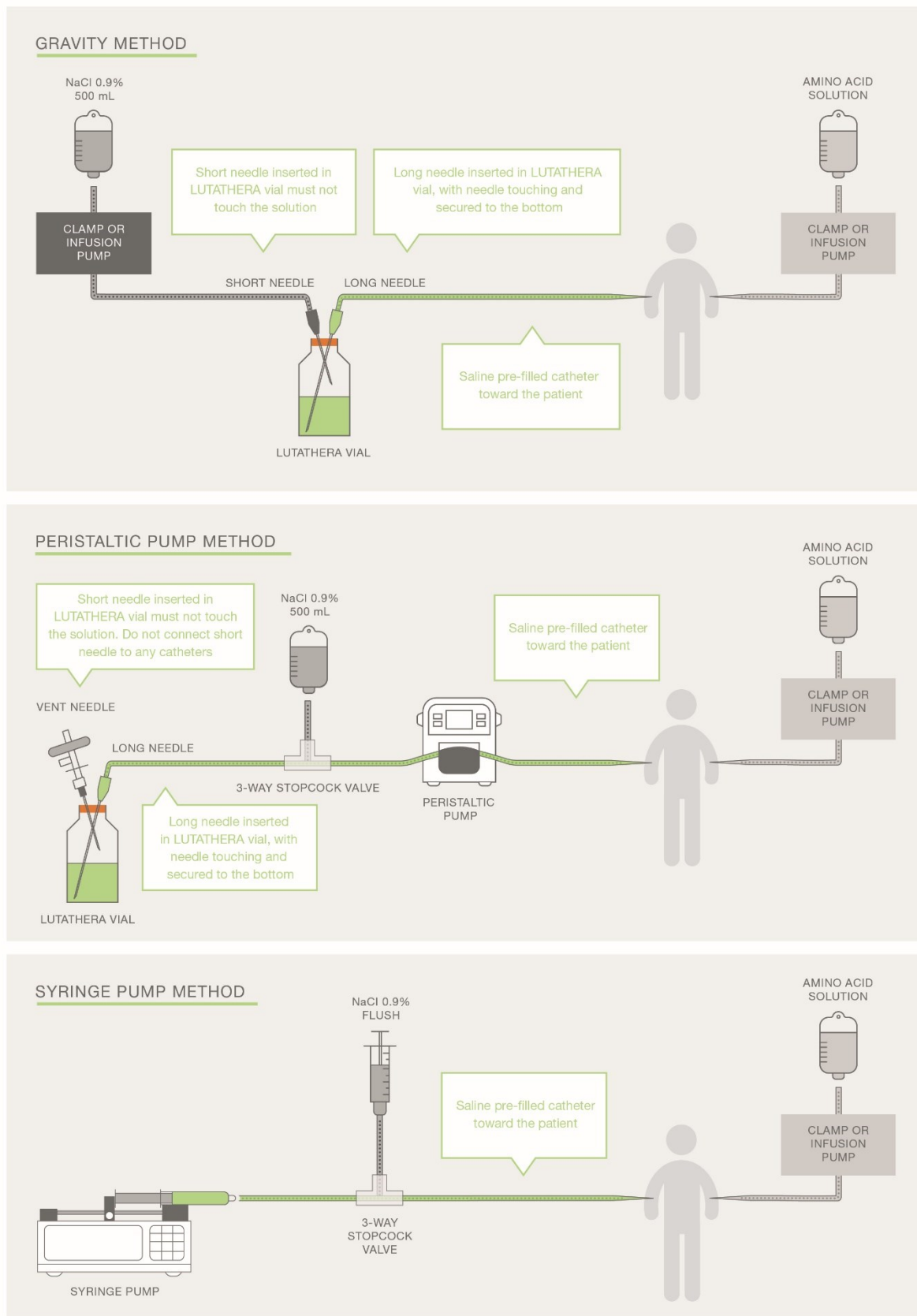
1. Insert a filtered 2.5 cm, 20 gauge needle (short venting needle) into the Lutathera/Lutathera CA vial. Ensure that the short needle does not touch the Lutathera/Lutathera CA solution in the vial. The short needle must not be connected directly to the patient or to the peristaltic pump.
2. Insert a 9 cm, 18 gauge needle (long needle) into the Lutathera/Lutathera CA vial, ensuring that this long needle touches and is secured to the bottom of the Lutathera/Lutathera CA vial during the entire infusion. Connect the long needle to a 3-way stopcock valve and a 0.9% sterile sodium chloride solution via appropriate tubing.
3. Connect the outlet of the 3-way stopcock valve to tubing installed on the inlet side of the peristaltic pump, following the pump manufacturer's instructions.
4. Prime the line by opening the 3-way stopcock valve and pumping the Lutathera/Lutathera CA solution through the tubing until it reaches the valve outlet.
5. Prime the intravenous catheter that will be connected to the patient by opening the 3-way stopcock valve to allow the 0.9% sterile sodium chloride solution to flow. The 0.9% sterile sodium chloride solution is pumped until it exits the end of the catheter tubing.
6. Connect the primed intravenous catheter to the patient and set the 3-way stopcock valve so that the Lutathera/Lutathera CA solution is in line with the peristaltic pump.

7. Administer an appropriate volume of Lutathera/Lutathera CA solution by infusion over a 30 ± 10 -minute period to deliver the desired radioactivity.
8. Once the desired Lutathera/Lutathera CA radioactivity has been delivered, stop the peristaltic pump and then change the position of the 3-way stopcock valve so that the peristaltic pump is connected to the 0.9% sterile sodium chloride solution. Restart the peristaltic pump and administer an intravenous flush of 25 ml of 0.9% sterile sodium chloride solution to the patient through the venous catheter.

Instructions for device-assisted infusion with syringe pump

1. Withdraw an appropriate volume of Lutathera/Lutathera CA solution to deliver the desired radioactivity by using a disposable syringe fitted with a syringe shield and a 9 cm, 18 gauge disposable sterile needle (long needle). To aid withdrawal of the solution, a filtered 2.5 cm, 20 gauge needle (short venting needle) can be used to reduce the resistance from the pressurised vial. Ensure that the short needle does not touch the Lutathera/Lutathera CA solution in the vial.
2. Fit the syringe into the shielded pump and include a 3-way stopcock valve between the syringe and an intravenous catheter that is filled with 0.9% sterile sodium chloride solution and used to administer Lutathera/Lutathera CA to the patient.
3. Administer an appropriate volume of Lutathera/Lutathera CA solution by infusion over a 30 ± 10 -minute period to deliver the desired radioactivity.
4. Once the desired Lutathera/Lutathera CA radioactivity has been delivered, stop the syringe pump and then change the position of the 3-way stopcock valve so as to flush the syringe with 25 ml of sterile 0.9% sodium chloride solution. Restart the syringe pump.
5. After the syringe flush has been completed, perform an intravenous flush with 25 ml of sterile 0.9% sodium chloride solution through the intravenous catheter to the patient.

Figure 2 Overview of methods of administration



Radiation exposure

Dosimetric analyses performed during clinical studies of Lutathera/Lutathera CA led to the following conclusions:

- The critical organ is the bone marrow. However, using the recommended cumulative dose of 29,600 MBq (4 administrations of 7,400 MBq), no correlation between haematological toxicity and the total radioactivity administered or bone marrow-absorbed dose has been observed in either the Erasmus phase I/II study or the NETTER-1 phase III study.
- The kidney is not a critical organ if co-infusion of an appropriate amino acid solution is performed.

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

Table 5 Absorbed dose estimates for lutetium (¹⁷⁷Lu) oxodotreotide from NETTER-1 phase III study (Olinda output)

Organ	Organ absorbed dose (mGy/MBq) (n=20)	
	Mean	SD
Adrenals	0.037	0.016
Brain	0.027	0.016
Breasts**	0.027	0.015
Gallbladder wall	0.042	0.019
Lower large intestine wall	0.029	0.016
Small intestine	0.031	0.015
Stomach wall	0.031	0.015
Upper large intestine wall	0.032	0.015
Heart wall	0.032	0.015
Kidneys	0.654	0.295
Liver*	0.199	0.226
Lungs	0.031	0.015
Muscle	0.029	0.015
Ovaries***	0.031	0.013
Pancreas	0.038	0.016
Red marrow	0.035	0.029
Osteogenic cells	0.151	0.268
Skin	0.027	0.015
Spleen	0.846	0.804

Organ	Organ absorbed dose (mGy/MBq) (n=20)	
	Mean	SD
Testes**	0.026	0.018
Thymus	0.028	0.015
Thyroid	0.027	0.016
Bladder wall	0.437	0.176
Uterus***	0.032	0.013
Total body	0.052	0.027

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

**n=11 (male patients only)

***n=9 (female patients only)

The radiation dose to specific organs that are not necessarily target organs of therapy can be greatly influenced by pathophysiological changes resulting from the disease process. This must be taken into consideration when using these data.

Contraindications

- Evidence of hypersensitivity to the active substance or any of the excipients mentioned under "Composition".
- Established or suspected pregnancy or when pregnancy cannot be excluded (see "Pregnancy/Breast-feeding").
- Severe renal impairment with creatinine clearance <30 ml/min.

Warnings and precautions

Risks associated with radiation exposure

Lutathera/Lutathera CA contributes to a patient's overall long-term cumulative exposure to ionising radiation. Long-term cumulative radiation exposure is associated with an increased risk of cancer.

Myelosuppression

In the NETTER-1 study, cases of myelosuppression were observed more frequently in patients receiving Lutathera/Lutathera CA with octreotide LAR than patients receiving high-dose octreotide LAR (all grades/grade 3 or 4): anaemia (81%/0) versus (54%/1%); thrombocytopenia (53%/1%) versus (17%/0); and neutropenia (26%/3%) versus (11%/0). In the NETTER-1 study, the median time to platelet nadir was 5.1 months after 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. 15 of the 19 patients in whom platelet recovery was not documented

had post-nadir platelet counts. Of these 15 patients, 5 recovered to grade 1, 9 to grade 2 and 1 to grade 3.

Patients with reduced bone marrow function and patients who have received prior chemotherapy or external beam radiotherapy may be at higher risk of haematological toxicity during Lutathera/Lutathera CA treatment. Initiation of treatment is not recommended in patients who have severely impaired haematological function before and during Lutathera/Lutathera CA use (e.g. Hb <4.9 mmol/l or 8 g/dl, platelet count <75 G/l or leukocytes <2 G/l), unless solely due to lymphopenia. Monitor blood counts at the start of treatment and before each dose of Lutathera/Lutathera CA. Temporarily suspend treatment, adjust the dosage or permanently discontinue treatment based on the severity of adverse effects (see "Modification of treatment" under "Dosage/Administration").

Secondary myelodysplastic syndrome and acute leukaemia

Late-onset myelodysplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with Lutathera/Lutathera CA (see "Adverse effects"). In the NETTER-1 study, after a median follow-up time of 76 months in the main study, cases of myelodysplastic syndrome (MDS) were reported in 3 patients (2 patients from the main study and 1 patient from the dosimetry sub-study; 2.3%) receiving Lutathera/Lutathera CA and octreotide LAR, but not in patients receiving high-dose octreotide LAR. In the Erasmus study, 16 patients (2.0%) developed MDS and 4 (0.5%) developed acute leukaemia. The median time to onset was 29 months (9 to 45 months) for MDS and 55 months (32 to 125 months) for AL. The aetiology of these therapy-related secondary myeloid neoplasms has not been clearly established. Factors such as age >70 years, renal impairment, baseline cytopenias, prior number of therapies, prior exposure to chemotherapeutic agents (specifically alkylating agents) and prior radiotherapy constitute potential risks and/or predictive factors for MDS/AL.

Renal toxicity

In the Erasmus study, 8 patients (<1%) developed renal failure 3 to 36 months after administration of Lutathera/Lutathera CA. Two of these patients had underlying renal impairment or risk factors for renal failure (particularly diabetes or hypertension) and required dialysis.

The amino acid solution must be administered before, during and after Lutathera/Lutathera CA use (see "Amino acid solution" under "Dosage/Administration") to decrease reabsorption of lutetium (¹⁷⁷Lu) oxodotreotide through the proximal tubules and hence radiation exposure to the kidneys. Patients should be encouraged to remain hydrated and empty their bladder as frequently as possible before, on the day of and the day after Lutathera/Lutathera CA administration. Serum creatinine and calculated creatinine clearance must be monitored.

Temporarily suspend treatment, adjust the dosage or permanently discontinue treatment based on the severity of adverse effects (see "Modification of treatment" under "Dosage/Administration").

The risk of toxicity may be increased in patients with pre-existing renal impairment or with renal or urinary tract abnormalities.

For patients with a creatinine clearance <50 ml/min, an increased risk of transient hyperkalaemia must also be taken into consideration (see “Warnings and precautions regarding the renal protective amino acid solution”).

Hepatotoxicity

In the Erasmus study, hepatic tumour haemorrhage, oedema or necrosis was observed in 2 patients (0.25%), one of whom (0.12%) developed congestion and intrahepatic cholestasis. Since Lutathera/Lutathera CA is indicated in many patients with hepatic metastasis, it is common to observe altered baseline liver function in these patients. An increased risk of hepatotoxicity due to exposure to ionising radiation may be observed in these patients.

Monitor concentrations of transaminases, bilirubin and serum albumin during treatment (see “Dosage/Administration”).

Temporarily suspend treatment, adjust the dosage or permanently discontinue treatment based on the severity of adverse effects (see “Modification of treatment” under “Dosage/Administration”).

Hypersensitivity

Cases of hypersensitivity reactions (including isolated angioedema events) have been reported in the post-marketing setting in patients treated with Lutathera/Lutathera CA (see “Adverse effects”). In the event of serious hypersensitivity reactions, treatment with Lutathera/Lutathera CA must be discontinued immediately. Appropriate medications and equipment to manage such reactions should be available for immediate use.

Neuroendocrine hormonal crises

Neuroendocrine hormonal crises due to the excessive release of hormones or bioactive substances manifesting as flushing, diarrhoea, bronchospasm and hypotension occurred in 2 patients (0.25%) in the Erasmus study, typically during treatment with Lutathera/Lutathera CA or in the 24 hours following administration. Furthermore, cases of hypercalcaemia were reported in 2 patients (0.25%). Therefore, observation of patients by overnight hospitalisation must be considered in some cases (e.g. patients with poor pharmacological control of symptoms).

Patients must be monitored if flushing, diarrhoea, hypotension, bronchoconstriction or any other signs and symptoms of tumour-related neuroendocrine disease occur. High doses of somatostatin analogues, corticosteroids and intravenous rehydration solution are to be administered as required.

Nausea and vomiting

To prevent treatment-related nausea and vomiting, intravenous antiemetics must be administered leaving a sufficient interval before the start of amino acid solution infusion (see “Dosage/Administration”).

Concomitant use of somatostatin analogues

Concomitant use of cold somatostatin analogues may be necessary for disease symptom control (see “Dosage/Administration”).

Tumour lysis syndrome

Tumour lysis syndrome has been reported following therapy with medicinal products containing lutetium (^{177}Lu). Patients with a history of renal impairment and a high tumour burden may be at greater risk and must be treated with caution. Renal function and electrolyte balance should be assessed before and during treatment.

Radioprotection guidelines

Therapy must take place in a facility licensed by the Swiss Federal Office of Public Health (FOPH) for the therapeutic use of unsealed source radiation.

Radiation exposure to patients and medical personnel must be minimised during and after treatment with Lutathera/Lutathera CA and patient contact with other people limited as per institutional good radioprotection practices and patient management procedures.

The treated person must be kept in a separate, specially equipped room during administration of Lutathera/Lutathera CA. Hospitalisation and discharge after treatment with radioactive substances must be performed in accordance with the Swiss Radiological Protection Ordinance, the Swiss FDHA Ordinance on the Use of Radioactive materials and the guidelines of the Swiss Federal Office of Public Health (FOPH).

Patients must be instructed to drink substantial quantities of water (e.g. at least 1 glass of water every hour) on the day before infusion, on the day of infusion and the day after to promote urinary elimination. The patient must also be encouraged to defecate every day and to use a laxative if needed. Urine and faeces must be disposed of according to national requirements (regulations and guidelines). Unless the patient's skin has been contaminated by infusion leakage or urinary incontinence, no radioactive contamination is expected on the skin or in the vomit. However, when conducting standard care or treatments with medical devices or other equipment that comes into contact with the skin (e.g. electrocardiogram [ECG]), basic protective measures must still be taken, such as wearing gloves, applying equipment and electrodes before the start of the radioactive infusion, changing the equipment and electrodes after the measurement and possibly measuring the radioactivity of the equipment after use.

In accordance with the requirements of the Swiss Radiological Protection Ordinance, before the patient is discharged, the nuclear medicine specialist must explain to the patient, on a one-on-one basis, the rules for interacting with family members and third parties in terms of radioprotection and the general precautions to follow during daily activities after treatment in order to minimise radiation exposure to others.

After each administration, the following general recommendations must be considered along with national, local and institutional procedures and regulations:

- Close contact (closer than 1 metre) with other people should be restricted for 7 days.
- For children and/or pregnant women close contact (closer than 1 metre) should be limited to less than 15 minutes per day for 7 days.
- Patients must sleep in a separate bedroom from other people for 7 days; they should sleep in a separate bedroom from children and/or pregnant women for 15 days.

Radioactivity can be detected in the urine for up to 30 days following Lutathera/Lutathera CA administration.

Recommended measures in case of extravasation

Wear disposable, waterproof gloves. Infusion of the medicinal product must be immediately stopped and the administration device (catheter, etc) removed. The nuclear medicine physician and radiation protection officer must be informed.

The administration materials must be kept in order to measure the residual radioactivity and determine the activity actually administered and possibly the absorbed dose. The extravasation area must be delimited with an indelible pen and a photo should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated.

To continue the Lutathera/Lutathera CA infusion, it is mandatory to use a new catheter, placing it in a contralateral vein. No other medicinal product must be administered to the same side where the extravasation occurred.

To accelerate dispersion of the medicinal product and prevent its stagnation in tissue, blood flow should be increased by elevating the affected arm. Depending on the case, aspiration of extravasated fluid, flush injection of sodium chloride 9 mg/ml (0.9%) solution or application of warm compresses or a heating pad to the infusion site may be considered in order to accelerate vasodilation.

Symptoms, especially inflammation and/or pain, must be treated. Depending on the situation, the nuclear medicine specialist must inform the patient about the risks linked to extravasation and advise them on potential treatment and follow-up requirements. The extravasation area must be monitored until the patient is discharged from the hospital. Depending on its severity, this event must be declared as an adverse effect.

Patients with urinary incontinence

It is recommended to monitor patients with urinary incontinence more frequently during treatment. In patients with urinary incontinence it is advisable to take special precautions after administration of Lutathera/Lutathera CA to avoid radioactive contamination. This includes the handling of any materials potentially contaminated with urine.

Patients with brain metastases

No efficacy data are available in patients with brain metastases. Therefore, the benefit-risk ratio must be assessed individually for these patients.

Secondary malignant neoplasms

Exposure to ionising radiation may favour the development of cancer and hereditary abnormalities. The radiation burden resulting from therapeutic exposure may result in a higher incidence of cancer and genetic mutations. In any case it must be ensured that the risks associated with radiation exposure are lower than the risks from the disease itself.

For precautions to take in connection with environmental risks, see “Other information”.

Other patients with risk factors

Patients with any of the conditions below are at increased risk of experiencing adverse effects. These patients should therefore be monitored more frequently during treatment. Refer to **Table 3** in case of dose-dependent toxicity.

- Bone metastases;
- Previous oncological radiometabolic therapies with ^{131}I -labelled radiopharmaceuticals or any other therapy using unshielded radioactive sources;
- History of other malignant tumours unless the patient has been in remission for at least 5 years.

Warnings and precautions regarding the renal protective amino acid solution

Hyperkalaemia associated with the amino acid solution

Potassium levels may transiently rise in patients receiving arginine and lysine, but usually return to normal within 24 hours of starting the infusion of the amino acid solution. Patients with reduced creatinine clearance may be at increased risk of transient hyperkalaemia (see “Renal toxicity”). The patient’s serum potassium levels must be determined before each administration of amino acid solution. In case of hyperkalaemia, the patient’s history of hyperkalaemia and concomitant medication should be reviewed. Hyperkalaemia must be corrected before starting the infusion.

In case of pre-existing clinically significant hyperkalaemia, a second check prior to amino acid solution infusion must confirm that potassium levels have been successfully corrected. The patient must be monitored closely for signs and symptoms of hyperkalaemia, e.g. dyspnoea, weakness, numbness, chest pain and cardiac manifestations (conduction disorders and arrhythmias). An electrocardiogram (ECG) should be performed prior to patient discharge.

Vital signs must be monitored during the infusion regardless of baseline serum potassium levels. Patients should be encouraged to drink plenty of fluids (i.e. at least 1 glass of water each hour) on the day before the infusion, on the infusion day itself and on the following day in order to be adequately hydrated and to aid elimination of excess potassium from the serum.

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

Heart failure

Given the risk of clinical complications due to volume overload, special caution is required when using arginine and lysine in patients with severe heart failure (class III or IV according to the New York Heart Association [NYHA] classification). Patients with severe (NYHA class III or IV) heart failure may only be treated after careful benefit-risk assessment, taking into consideration the volume and osmolality of the amino acid solution.

Metabolic acidosis

Metabolic acidosis has been observed when administering complex amino acid solutions as part of total parenteral nutrition (TPN). Shifts in acid-base balance alter the balance between extra- and intracellular potassium, and emergent acidosis may be accompanied by a rapid increase in plasma potassium levels.

Sodium content

This medicinal product contains up to 3.5 mmol (81.1 mg) of sodium per dose, equivalent to 4% of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

Interactions

Somatostatin and its analogues competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera/Lutathera CA. Therefore, treatment with long-acting somatostatin analogues must be discontinued 4 to 6 weeks before Lutathera/Lutathera CA treatment. If necessary, patients may be treated with short-acting somatostatin analogues up to 24 hours preceding Lutathera/Lutathera CA infusion.

There is evidence that glucocorticoids can induce down-regulation of subtype 2 somatostatin receptors (SSTR2). Therefore, as a matter of caution, repeated administration of high doses of glucocorticoids should be avoided during Lutathera/Lutathera CA treatment. Patients who have received prolonged treatment with glucocorticoids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known whether the intermittent use of glucocorticoids for the prevention of nausea and vomiting during Lutathera/Lutathera CA administration could induce SSTR2 down-regulation. As a matter of caution, glucocorticoids should therefore be avoided as preventive antiemetic treatment. Should the treatment administered to prevent nausea and vomiting before the amino acid solution infusion prove insufficient, a single glucocorticoid dose can be given, provided this is not done before or within one hour after the end of Lutathera/Lutathera CA infusion.

Pregnancy/Breast-feeding

Women of childbearing potential

Before the use of Lutathera/Lutathera CA, pregnancy must be excluded using an appropriate/validated test.

Contraception in males and females

Lutathera/Lutathera CA may be harmful to the fetus if administered to a pregnant woman. Appropriate measures must be taken to prevent female patients from becoming pregnant during treatment with Lutathera/Lutathera CA and for at least 7 months after stopping treatment. Appropriate measures must be taken to avoid pregnancy in female partners of male patients during treatment with Lutathera/Lutathera CA and for at least 4 months after cessation of treatment.

Pregnancy

No animal studies have been conducted to determine the effects of lutetium (^{177}Lu) oxodotreotide on reproduction in women and embryo-fetal development.

Nuclear medicine examinations in pregnant women also involve irradiation of the fetus. Due to the risk associated with ionising radiation, the use of Lutathera/Lutathera CA is contraindicated during confirmed or suspected pregnancy or when pregnancy has not been excluded (see "Contraindications"). Pregnant women should be informed of the risk to the fetus.

Breast-feeding

It has not been established whether lutetium (^{177}Lu) oxodotreotide is excreted in breast milk.

A risk to the breast-fed infant associated with ionising radiation cannot be excluded. Breast-feeding should be avoided during treatment with this medicinal product. If treatment with Lutathera/Lutathera CA during breast-feeding proves to be necessary, the infant must be weaned and breast-feeding must be interrupted.

Fertility

No studies have been conducted in animals to determine the effects of lutetium (^{177}Lu) oxodotreotide on female or male fertility. Ionising radiation from lutetium (^{177}Lu) oxodotreotide may have toxic effects on female and male gonads, leading to temporary or permanent infertility. A genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm or eggs can be proposed as an option to patients before treatment.

Effects on ability to drive and use machines

Lutathera/Lutathera CA has no or negligible influence on the ability to drive or use machines.

Nevertheless, the general condition of the patient and possible adverse effects of treatment must be taken into account before driving or using machines.

Adverse effects

Summary of the safety profile

The overall safety profile of Lutathera/Lutathera CA is based on pooled data from patients from clinical studies (NETTER-1 phase III and Erasmus phase I/II Dutch patients) and from the compassionate use programme.

The most common adverse effects in patients receiving Lutathera/Lutathera CA were nausea and vomiting, which occurred at the start of the infusion in 58.9% and 45.5% of patients, respectively. The causality of nausea and vomiting is difficult to determine because of the nausea-inducing effects of the concomitant infusion of amino acid solutions to protect the kidneys.

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

Fatigue (27.7%) and loss of appetite (13.4%) were reported as other very common adverse effects. At the time of the final analysis of the NETTER-1 study, after a median follow-up duration of 76 months in each study arm, the safety profile remained consistent with that previously reported.

Tabulated summary of adverse effects

Adverse effects are listed in **Table 6** according to frequency and system organ class (MedDRA). Frequencies have been categorised according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and frequency undetermined (cannot be estimated from the available data).

Table 6 Frequency of adverse effects reported in clinical studies and during post-marketing surveillance

MedDRA system organ class	Very common	Common	Uncommon	Frequency not known
Infections and infestations			Conjunctivitis Respiratory tract infection Cystitis Pneumonia Herpes zoster Ophthalmic herpes zoster Influenza Staphylococcal infections Streptococcal bacteraemia	
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Refractory cytopenia with multilineage dysplasia (myelodysplastic syndrome)	Acute myeloid leukaemia Acute leukaemia Chronic myelomonocytic leukaemia	
Blood and lymphatic system disorders	Thrombocytopenia (25%) ² Lymphopenia (22.3%) ³ Anaemia (13.4%) ⁴ Pancytopenia (10.2%)	Leukopenia ⁵ Neutropenia ⁶	Refractory cytopenia with multilineage dysplasia Nephrogenic anaemia Bone marrow failure Thrombocytopenic purpura	
Immune system disorders			Hypersensitivity	Angioedema ¹²
Endocrine disorders		Secondary hypothyroidism	Hypothyroidism Diabetes mellitus Carcinoid crisis Hyperparathyroidism	
Metabolism and nutrition disorders	Decreased appetite (13.4%)	Hyperglycaemia Dehydration Hypomagnesaemia Hyponatraemia	Hypoglycaemia Hypernatraemia Hypophosphataemia Tumour lysis syndrome Hypercalcaemia Hypocalcaemia Hypoalbuminaemia Metabolic acidosis	

Prescribing information for human medicines

MedDRA system organ class	Very common	Common	Uncommon	Frequency not known
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		QT prolongation in electrocardiogram	Atrial fibrillation Palpitations Myocardial infarction Angina pectoris Cardiogenic shock	
Vascular disorders		Hypertension ⁷ Flushing Hot flushes Hypotension	Vasodilation Peripheral coldness Pallor Orthostatic hypotension Phlebitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Oropharyngeal pain Pleural effusion Increased sputum Feeling of pressure	

Prescribing information for human medicines

MedDRA system organ class	Very common	Common	Uncommon	Frequency not known
Gastrointestinal disorders	Nausea (58.9%) Vomiting (45.5%)	Abdominal distension Diarrhoea Abdominal pain Constipation Upper abdominal pain Dyspepsia Gastritis	Dry mouth Flatulence Ascites Gastrointestinal pain Stomatitis Haematochezia Intestinal discomfort Intestinal obstruction Colitis Acute pancreatitis Rectal haemorrhage Melaena Lower abdominal pain Haematemesis Haemorrhagic ascites Ileus	
Hepatobiliary disorders		Hyperbilirubinaemia ⁹	Decreased pancreatic enzymes Hepatocellular injury Cholestasis Hepatic congestion Hepatic failure	
Skin and subcutaneous tissue disorders		Alopecia	Skin rash Dry skin Swelling of face Hyperhidrosis Generalised pruritus	
Musculoskeletal, connective tissue and bone disorders		Musculoskeletal pain ⁸ Muscle spasms		
Renal and urinary disorders		Acute kidney injury Haematuria Renal failure Proteinuria	Leukocyturia Urinary incontinence Decreased glomerular filtration rate Renal disorder Acute pre-renal failure Kidney damage	

Prescribing information for human medicines

MedDRA system organ class	Very common	Common	Uncommon	Frequency not known
General disorders and administration site conditions	Fatigue (27.7%) ¹	Injection site reaction ¹¹ Peripheral oedema Administration site pain Chills Influenza-like illness	Injection site mass Chest discomfort Chest pain Pyrexia Malaise Pain Death Abnormal sensation	

Prescribing information for human medicines

MedDRA system organ class	Very common	Common	Uncommon	Frequency not known
Investigations		<p>Increased blood creatinine [Renal and urinary disorders]</p> <p>Increased GGT* [Hepatobiliary disorders]</p> <p>Increased ALT** [Hepatobiliary disorders]</p> <p>Increased AST*** [Hepatobiliary disorders]</p> <p>Increased ALP**** [Hepatobiliary disorders]</p>	<p>Decreased serum potassium [Renal and urinary disorders]</p> <p>Increased blood urea [Renal and urinary disorders]</p> <p>Increased glycosylated haemoglobin [Metabolism and nutrition disorders]</p> <p>Decreased haematocrit [Blood and lymphatic system disorders]</p> <p>Proteinuria [Renal and urinary disorders]</p> <p>Weight loss [General disorders and administration site conditions]</p> <p>Increased serum creatine phosphokinase [Musculoskeletal and connective tissue disorders]</p> <p>Increased serum lactate dehydrogenase [Musculoskeletal and systemic disorders]</p> <p>Increased blood catecholamines [Endocrine disorders]</p> <p>Increased C-reactive protein [Infections and infestations]</p>	
Injury, poisoning and procedural complications			Clavicle fracture	

Prescribing information for human medicines

MedDRA system organ class	Very common	Common	Uncommon	Frequency not known
Surgical and medical procedures		Transfusion	Abdominal cavity drainage Dialysis Gastric tube insertion Stent placement Abscess drainage Bone marrow harvest Polypectomy	
Social circumstances			Physical disability	

¹ Includes asthenia and exhaustion

² Includes thrombocytopenia and decreased platelet count

³ Includes lymphopenia and decreased lymphocyte count

⁴ Includes anaemia and decreased haemoglobin

⁵ Includes leukopenia and decreased white blood cell count

⁶ Includes neutropenia and decreased neutrophil count

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 increased blood bilirubin and hyperbilirubinaemia

¹⁰ Includes headache and migraine

¹¹ Includes injection site reaction, injection site hypersensitivity, injection site induration, injection site swelling

¹² Post-marketing report

* Increased gamma-glutamyltransferase

** Alanine aminotransferase

*** Aspartate aminotransferase

**** Alkaline phosphatase

Adverse effects from spontaneous reports (frequency not known)

The following adverse effects have been derived from post-marketing experience with Lutathera/Lutathera CA via spontaneous case reports (see **Table 6**). As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorised as “not known”. Adverse effects are listed according to MedDRA system organ class. Within each system organ class, adverse effects are listed in order of decreasing seriousness.

Immune system disorders

Angioedema

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal EIViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

In case of overdose, an increase in the frequency of radiotoxicity-related adverse effects is expected. If an overdose of Lutathera/Lutathera CA has been given, the radiation dose absorbed by the patient should be reduced as much as possible by increasing the elimination of the radionuclide from the body by forced diuresis, frequent micturition and increased fluid intake during the first 48 hours after the infusion. The effective dose administered should be estimated.

It is recommended that the following laboratory tests be performed weekly for the next 10 weeks:

- Haematological monitoring: white blood cell count, platelets and haemoglobin
- Biochemical monitoring: serum creatinine and blood glucose

Properties/Actions

ATC code

V10XX04

Physical properties

Lutathera/Lutathera CA containing lutetium (^{177}Lu) decays to stable hafnium (^{177}Hf) with a half-life of 6.647 days and primarily emits β^- radiation at a maximum energy of 0.498 MeV. The average beta energy is 0.13 MeV. Photon radiation (γ) is also emitted at 0.113 MeV (6.2%) and 0.208 MeV (11%). Lutathera CA is prepared using ^{176}Lu that contains a small amount of the nuclear isomer metastable lutetium ($^{177\text{m}}\text{Lu}$). The $^{177\text{m}}\text{Lu}$ isomer has a half-life of 160.44 days. The $^{177\text{m}}\text{Lu}$ isomer decays partly (22.8%) by isomeric transition with emission of gamma radiation and conversion electrons to the ground state of Lu-177 and partly (77.2%) by emission of beta radiation (40.8 keV) to metastable hafnium-177 ($^{177\text{m}}\text{Hf}$), which immediately decays by multiple gamma emissions and conversion electrons to stable ^{177}Hf . With all radioactive waste resulting from the use of lutetium (^{177}Lu) oxodotreotide, the presence and amount of this specific isomer must be taken into account to ensure proper disposal.

Mechanism of action

Lutetium (^{177}Lu) oxodotreotide has a high affinity for subtype 2 somatostatin receptors (sst2). It binds specifically to malignant cells which overexpress sst2 receptors.

Lutetium-177 is a beta-minus emitting radionuclide with a maximum penetration range in tissue of about 2.2 mm (mean penetration range of 0.67 mm) that induces the death of targeted tumour cells with limited effect on neighbouring normal cells.

Pharmacodynamics

At the concentration used (about 10 µg/ml in total for both free and radiolabelled forms), the peptide oxodotretotide does not exert any clinically relevant pharmacodynamic effect.

Clinical efficacy

NETTER-1 study

The NETTER-1 phase III study was a randomised, multicentre, open-label, active-controlled study comparing treatment with Lutathera CA (4 doses of 7,400 MBq, one dose every 8 weeks [± 1 week]) co-administered with an amino acid solution plus best supportive care (30 mg octreotide long-acting release [LAR] after each Lutathera CA dose and every 4 weeks after completion of Lutathera CA treatment for symptom control, replaced by short-acting octreotide in the 4 to 6 weeks before Lutathera CA administration) to high-dose, octreotide LAR (60 mg every 4 weeks) in patients with inoperable, progressive, somatostatin receptor-positive midgut carcinoid tumours. The primary endpoint of the study was progression-free survival (PFS) evaluated by response evaluation criteria in solid tumours (RECIST V.1.1) and based on blinded independent radiological review. Secondary efficacy endpoints included objective response rate (ORR), overall survival (OS), time to tumour progression (TTP), safety and tolerability of the medicinal product and health-related quality of life (HRQoL).

At the time of the primary analysis 229 patients were randomised to receive either Lutathera CA (n=116) or a high dose (60 mg) of octreotide LAR (n=113). Randomisation was stratified by OctreoScan® scintigraphy score (grade 2, 3 or 4) and the longest duration of constant-dose octreotide most recently received prior to randomisation (≤6 or >6 months). Demographics as well as patient and disease characteristics were balanced between the two arms, with a median age of 64 years and 82.1% Caucasians in the overall population.

The final per-protocol analysis results (cut-off date 24 July 2015) are presented in **Table 7**.

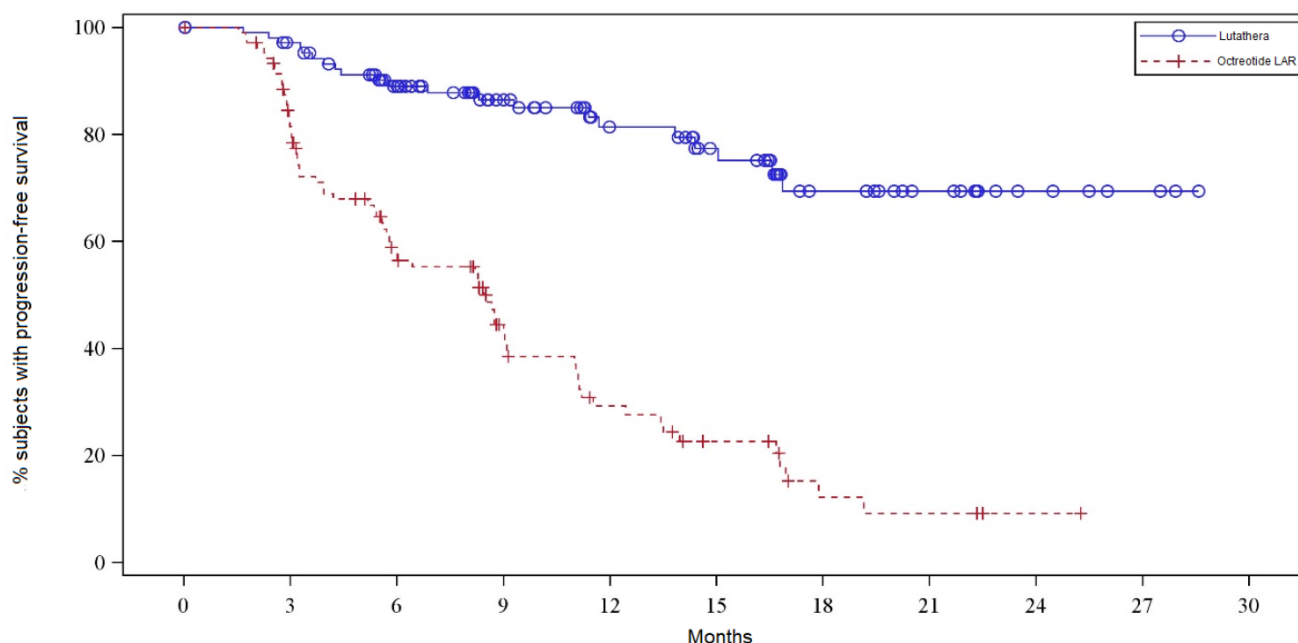
Table 7 PFS observed in the NETTER-1 phase III study in patients with a progressive midgut carcinoid tumours – (full analysis set (FAS), N=229)

	Treatment	
	Lutathera CA and octreotide LAR	High-dose octreotide LAR
N	116	113
Patients with events	21	70
Excluded patients	95	43
Median months (95% CI)	Not reached	8.5 (5.8; 9.1)
p-value of log-rank test	<0.0001	
Hazard ratio (95% CI)	0.177 (0.108; 0.289)	

N: number of patients, CI: confidence interval, LAR: long-acting release.

The PFS Kaplan-Meier graph for the full analysis set (FAS) is depicted in **Figure 3**.

Figure 3 PFS Kaplan-Meier curves for patients with progressive midgut carcinoid tumours (NETTER-1 phase III study; FAS, N=229)



The OS results from the interim analysis (cut-off date 24 July 2015) and the final analysis (cut-off date 18 January 2021) are depicted in **Table 8**.

At the time of the final OS analysis, which occurred 5 years after the last patient was randomised (N=231, cut-off date 24 July 2015), the median follow-up duration was 76 months in each study arm. The final OS results did not reach statistical significance.

In the high-dose octreotide LAR arm, 22.8% of patients received subsequent radioligand therapy (including lutetium [¹⁷⁷Lu] oxodotretotide) within 24 months of randomisation and 36% of patients by

the final OS cut-off date, which, along with other factors, may have influenced the OS in this subset of patients.

Table 8 OS results from NETTER-1 phase III study in patients with progressive midgut carcinoid tumours (FAS)

	LUTATHERA CA and octreotide LAR	High-dose octreotide LAR
Interim OS analysis (24 July 2015) – N=229*		
Deaths (%)	17 (14.7 %)	31 (27.4 %)
Median in months (95% CI)	NR (NE, NE)	27.4 (20.1, NE)
Hazard ratio ^{a,b} (99.9915% CI)	0.46 (0.14, 1.51)	
Final OS analysis (18 January 2021) – N=231**		
Deaths (%)	73 (62.4 %)	69 (60.5 %)
Median in months (95% CI)	48.0 (37.4, 55.2)	36.3 (25.9, 51.7)
Hazard ratio ^{a,b,c} (95 % CI)	0.84 (0.60, 1.17)	
Final OS analysis by restricted mean survival time (RMST) at 60 months (18 January 2021 – N=231**)		
Deaths (%)	65 (55.6)	63 (55.3)
RMST (95% CI)	41.2 (37.6, 44.9)	36.1 (31.9, 40.4)
Difference (95% CI)	5.1 (-0.5, 10.7)	

a: Hazard ratio based on unstratified Cox model

b: Not statistically significant as per pre-specified significance criteria

c: HR based on non-proportional hazards

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

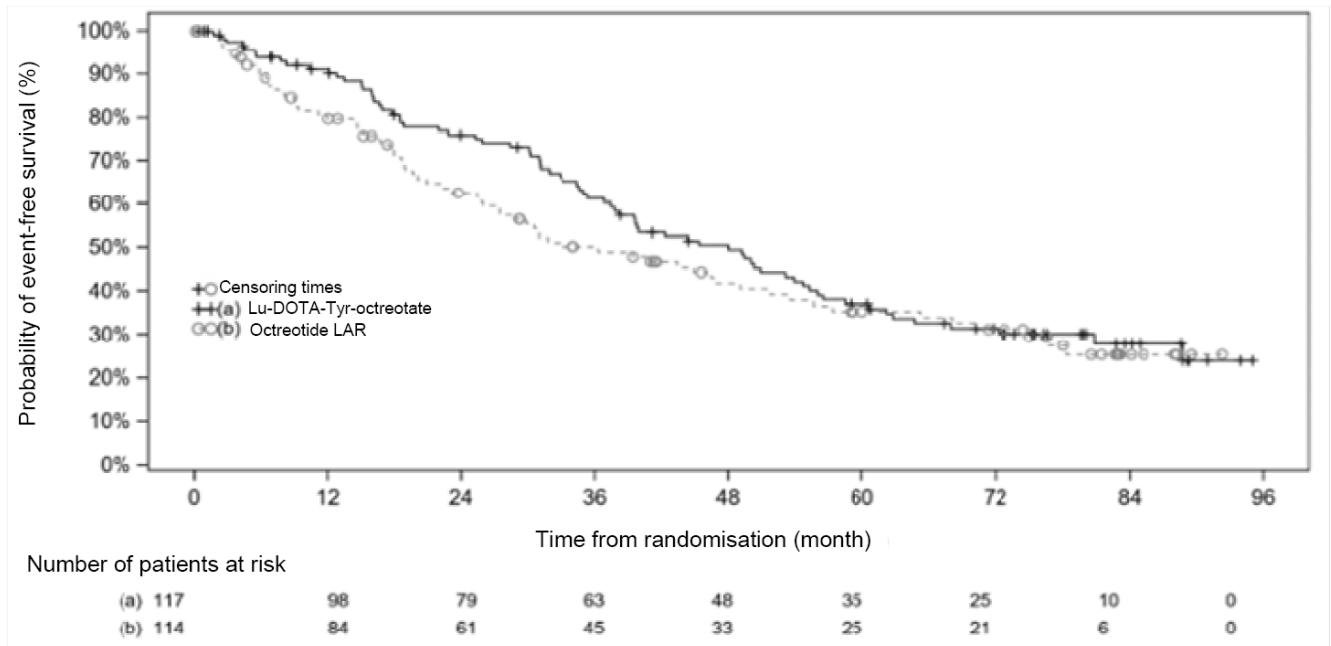
*** : Analysis performed on 117 patients in the Lutathera CA arm and 114 patients in the high-dose octreotide LAR arm (N=231).*

NR = not reached

NE = not estimable

The OS Kaplan-Meier graph for the full analysis set (FAS) at the cut-off date 18 January 2021 is depicted in **Figure 4**.

Figure 4 OS Kaplan-Meier curves for patients with progressive midgut carcinoid tumours – cut-off date 18 January 2021 (NETTER-1 phase III study; FAS, N=231)



In the presence of non-proportional hazards, an additional sensitivity analysis (restricted mean survival time) was performed at the time of the final OS analysis to further estimate the treatment effect (see **Table 8**).

Health-related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (generic instrument) and its neuroendocrine tumour module (EORTC QLQ-GI.NET 21).

The results indicate an improvement in the overall global health-related quality of life up to week 84 for patients in the Lutathera CA treatment arm versus the high-dose octreotide LAR treatment arm.

Somatostatin receptor-expressing gastroenteropancreatic neuroendocrine tumours (GEP-NETs)

The efficacy of Lutathera CA in patients with somatostatin receptor-expressing gastroenteropancreatic (GEP) and bronchial neuroendocrine tumours (NETs) was evaluated in the Erasmus clinical study, a monocentric, non-comparative, open-label study in which the therapeutic protocol of Lutathera CA consisted of 4 intravenous administrations of 7,400 MBq each co-administered with an amino acid solution. Lutathera CA was initially administered as part of a compassionate-use programme following a general protocol of peptide receptor radionuclide therapy (PRRT) at a single site in the Netherlands. Eight years after the start of this programme, a protocol specifically related to Lutathera CA was created that allowed retrospective data collection even if the total number of patients and the hypothesis tested are not precisely described. A total of 360 patients with gastroenteropancreatic and bronchial neuroendocrine tumours at baseline (a tumour of the midgut 183, pancreas 133, bronchi 19, hindgut 13, foregut without bronchi and pancreas 12) were followed long-term. The mean age was 60 years, 51% were male, 99.4% had an OctreoScan tumour

uptake score of ≥ 2 (5.6 % [2]/62.8% [3]/31.1% [4]), 71.4% had a Karnofsky performance status of ≥ 90 and 52% received concomitant somatostatin analogues. The investigator-assessed objective response rate, the major efficacy criterion, was 45% (95% CI: 40, 50). The median duration of response was 16.3 months (95% CI: 12.2, 17.8). The objective response rate was highest for pancreatic NET patients (61%, 95% CI: 52, 69) and lowest for midgut NET patients (33%, 95% CI: 27, 41).

Pharmacokinetics

Absorption

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

Distribution

An analysis performed on human plasma to determine the extent of plasma protein binding of the non-radioactive compound (lutetium [^{175}Lu] oxodotreotide) showed that about 50% of the compound is bound to plasma proteins.

Transchelation of lutetium from lutetium (^{175}Lu) oxodotreotide to serum proteins has not been observed.

Organ uptake

Within 4 hours after administration, the distribution pattern of lutetium (^{177}Lu) oxodotreotide shows rapid uptake in the kidneys, tumour lesions, liver and spleen and, in some patients, in the pituitary gland and thyroid. Co-administration of an amino acid solution decreases renal uptake, thus enhancing elimination of the radioactive product (see “Warnings and precautions”). Biodistribution studies show that lutetium (^{177}Lu) oxodotreotide is rapidly cleared from the bloodstream.

Metabolism

Biotransformation

The analysis of urine samples of 20 patients included in the NETTER-1 phase III dosimetry, pharmacokinetic and ECG substudy demonstrates that lutetium (^{177}Lu) oxodotreotide is poorly metabolised and is excreted mainly unchanged by the kidneys.

HPLC analyses performed on urine samples collected up to 48 hours post-infusion showed unchanged lutetium (^{177}Lu) oxodotreotide close to 100% in most samples analysed (with a minimum value above 92%), indicating that the product is eliminated in urine mainly in unchanged form.

These results confirm those previously observed in the Erasmus phase I/II study, in which HPLC analysis of urine specimens collected 1 hour post-administration from one patient receiving 1.85 MBq of lutetium (^{177}Lu) oxodotreotide indicated that the main portion (91%) was excreted unchanged.

These results are corroborated by *in vitro* metabolism data in human hepatocytes, in which no metabolic degradation of lutetium (^{175}Lu) oxodotreotide was observed.

Elimination

Based on the data collected during the Erasmus phase I/II and NETTER-1 phase III studies, lutetium (^{177}Lu) oxodotreotide is primarily eliminated renally: about 60% of the medicinal product is eliminated in the urine within 24 hours and about 65% within 48 hours following administration.

In vitro evaluation of interaction potential

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

Preclinical data

Toxicological studies performed in rats have demonstrated that a single intravenous injection of up to 4,550 MBq/kg was well tolerated and no deaths were observed. On testing the cold compound (non-radioactive lutetium [^{175}Lu] oxodotreotide) as a single intravenous injection in rats and dogs at doses up to 20,000 $\mu\text{g}/\text{kg}$ (rats) and 3,200 $\mu\text{g}/\text{kg}$ (dogs), it was found that the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) was well tolerated in both species and there were no deaths. No toxicity was observed with repeated administration of 4 doses of the cold compound once every 2 weeks at 1,250 $\mu\text{g}/\text{kg}$ in rats and 80 $\mu\text{g}/\text{kg}$ in dogs. This medicinal product is not intended for regular or continuous administration.

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

Preclinical data on the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) reveal no special hazard in humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

Other information

Incompatibilities

This medicinal product may only be mixed with the medicinal products mentioned under "Dosage/Administration".

Shelf life

This medicinal product may be stored for no more than 72 hours from the time of calibration.

Special precautions for storage

Do not store above 25°C. Do not freeze.

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

Do not use after the expiry date (= EXP) printed on the pack.

Storage of radiopharmaceuticals must be in accordance with national regulations on radioactive products.

Notes on handling/radioprotection

The use of radioactive substances in humans is regulated by the Swiss Radiological Protection Ordinance. A handling licence from the Swiss Federal Office of Public Health is required for the use of radioactive substances.

Lutathera/Lutathera CA must be received, used and administered only by authorised persons in licensed facilities. The receipt, storage, use, transport and disposal of Lutathera/Lutathera CA are subject to the radiation protection regulations and/or relevant approvals from the competent regulatory authorities.

Lutathera/Lutathera CA must be used with appropriate safety measures to minimise radiation exposure. Appropriate aseptic precautions must be taken.

The solution must be visually inspected for particles, discoloration and impurities before use. Only clear solutions free of particles may be used. The vial should be discarded if particles, discoloration or impurities are present. The visual inspection of the solution must be performed under a shielded screen for radioprotection purposes.

The packaging must be checked for damage, and the presence of radioactive contamination should be determined using a suitable activity meter. The product must not be used if the integrity of the vial or the lead container is compromised. Lutathera/Lutathera CA must not be injected directly into any other intravenous solution.

The amount of radioactivity in the vial must be measured before and after each infusion using a calibrated activity meter to ensure that the amount of radioactivity to be administered corresponds to the planned amount at the time of infusion.

Administration must be performed in a way that minimises the risk of medicinal product contamination and user exposure to radiation. Adequate shielding is mandatory and impervious gloves must be worn when handling this medicinal product.

The administration of radiopharmaceuticals represents a risk factor to other people due to radiation emitted by the patient or contamination from bodily fluids such as urine, stools, vomit, etc. Appropriate precautions must therefore be taken.

Healthcare personnel are advised to limit the time of close contact with patients who have received Lutathera/Lutathera CA. The use of a remote monitoring screen to monitor patients is recommended. Given the long half life of ^{177}Lu , it is especially important to avoid internal contamination. High-quality protective gloves (latex/nitrile) must be worn to avoid all direct contact with the radiopharmaceutical (vial/syringe). To minimise radiation exposure, the principles of time, distance and shielding must always be followed (by minimising vial handling and using the equipment supplied by the manufacturer).

Administration may result in significant radiation exposure to the environment.

This may be relevant to the immediate family of individuals undergoing treatment or the general public. Compliance with radioprotection requirements is therefore essential (see “Warnings and precautions”). To avoid any contamination, suitable precautions concerning the activity eliminated by patients must be taken in conformance with national regulations.

Waste disposal

Unused radioactive products or waste may only be disposed of in accordance with the applicable Swiss radiation protection regulations.

Lutathera

Lutetium-177 for Lutathera is produced using the stable isotope ytterbium-176 (non-carrier added).

Lutathera CA

Lutetium-177 for Lutathera CA is produced using the stable isotope lutetium-176 (carrier added) and, due to the presence of metastable lutetium-177 (^{177m}Lu), requires special attention in terms of waste disposal.

Swissmedic number

66580, 69776

Pack sizes

Clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and sealed with an aluminium capsule.

Each vial contains a volume ranging from 20.5 to 25.0 ml of solution, corresponding to an activity of 7,400 MBq at the date and time of infusion.

The vial is enclosed within a lead container for protective shielding.

Dispensing category A (available by non-renewable prescription only).

Marketing authorisation holder

Novartis Pharma Schweiz AG. Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

June 2024