PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

LUTATHERA®

lutetium (^{177}Lu) oxodotreotide

Sterile Solution for Intravenous Infusion

370 MBq/mL at calibration

Therapeutic Radiopharmaceutical

Advanced Accelerator Applications
57 E Willow Street
Millburn, NJ 07041, USA

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LUTATHERA® (lutetium (^{177}Lu) oxodotreotide) is indicated for the treatment of unresectable or metastatic, well-differentiated, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults with progressive disease.

It is important to read through all dosing and administration sections prior to LUTATHERA use. LUTATHERA dosing instructions includes use of concomitant medications for renal protection and mitigation of nausea and vomiting. Provisions for patient monitoring and dose modifications are also provided. See **DOSAGE AND ADMINISTRATION (4)**.

This product should be administered under the supervision of a qualified health professional who is experienced in the use of therapeutic radiopharmaceuticals.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Of the 1325 patients treated with LUTATHERA® in clinical trials, 438 patients (33%) were 65 years and older [see **Geriatrics** (**10.5**)].

2 CONTRAINDICATIONS

- Severe renal impairment (creatinine clearance < 30 mL/min)
- Established or suspected pregnancy (when pregnancy has not been excluded)
- Hypersensitivity to the active substance or to any of the excipients listed [see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** (**7**)]

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

Acute and chronic renal toxicity can occur in patients treated with LUTATHERA® [see **WARNINGS AND PRECAUTIONS (9.4)**]. Cases of severe and life-threatening renal injury have been reported. Do not administer LUTATHERA to patients with severe renal impairment (creatinine clearance < 30 mL/min) [see **CONTRAINDICATIONS (2)**].

Myelodysplastic syndrome (MDS) and Acute Leukaemia (AL): Late-onset MDS and AL have been reported following treatment with LUTATHERA [see **WARNINGS AND PRECAUTIONS (9.3)**].

4 DOSAGE AND ADMINISTRATION

4.1 Important Safety Instructions

LUTATHERA® is a radiopharmaceutical; handle with appropriate safety measures to minimize radiation exposure [see **WARNINGS AND PRECAUTIONS (9.1)**]. Use waterproof gloves and effective radiation shielding when handling LUTATHERA. 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.

Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA [see **WARNINGS AND PRECAUTIONS (9.7)** and **SPECIAL POPULATIONS (10.1)**].

4.2 Dosing Considerations

LUTATHERA® dosing instructions include provisions for

- Use of concomitant medications for renal protection and mitigation of nausea and vomiting
- Dose modifications due to toxicity

4.3 Dosage

The recommended LUTATHERA® dose in adults is 7.4 GBq (200 mCi) as an intravenous infusion over 30 minutes every 8 weeks for a total of 4 doses.

Dose Modifications

Recommended dose modifications of LUTATHERA in the case of adverse reactions are provided in Table 1.

Table 1. Recommended Dose Modifications of LUTATHERA® for Adverse Reactions[1]

Adverse Reaction	Severity of Adverse Reaction[1]	Dose Modification
Thrombocytopenia [see **WARNINGS AND PRECAUTIONS (9.2)]**	Grade 2, 3, or 4	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume LUTATHERA at 3.7 GB (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 2, 3 or 4	Permanently discontinue LUTATHERA.
Anaemia and Neutropenia [see **WARNINGS AND PRECAUTIONS (9.2)]**	Grade 3 or 4	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 anaemia or neutropenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher anaemia or neutropenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4.	Permanently discontinue LUTATHERA.

Renal Toxicity [see **WARNINGS AND PRECAUTIONS (9.4)**]	Defined as: • Creatinine clearance less than 40 mL/min; 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. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution. 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 [see **WARNINGS AND PRECAUTIONS (9.5)]**	Defined as: • Bilirubinaemia greater than 3 times the upper limit of normal (Grade 3 or 4), or • Hypoalbuminaemia less than 30 g/L with a decreased prothrombin ratio less than 70%	Withhold dose until complete resolution. Resume LUTATHERA at 3.7GBq (100 mCi) in patients with complete resolution. 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-Haematologic Toxicity	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue LUTATHERA.

[1] National Cancer Institute, Common Toxicity Criteria for Adverse Events, version 4.03

4.4 Administration

Administer an antiemetic and the recommended amino acid solution prior to LUTATHERA® [see **DOSAGE AND ADMINISTRATION (4.4)**, *Pre and concomitant medications*). Do not administer LUTATHERA as an intravenous bolus.

Pre and concomitant medications

1) *Cold Somatostatin Analogs*
   - Before initiating LUTATHERA: Discontinue long-acting somatostatin analogs (e.g., long-acting octreotide) for at least 4 weeks prior to initiating LUTATHERA. Administer short-acting octreotide as needed; discontinue at least 24 hours prior to initiating LUTATHERA [see **DRUG INTERACTIONS (12.1**)].
   - During LUTATHERA treatment: Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each LUTATHERA dose. Do not administer long-acting octreotide within 4 weeks of each subsequent LUTATHERA dose. Short-acting octreotide may be given for symptomatic management during LUTATHERA treatment but must be withheld for at least 24 hours before each LUTATHERA dose.
   - Following LUTATHERA treatment: Continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing LUTATHERA until disease progression or for up to 18 months following treatment initiation.

2) *Pre-Treatment Anti-emetic*
   Administer antiemetics 30 minutes before the recommended amino acid solution.

3) *Amino Acid Solution*

   For renal protection, initiate an intravenous amino acid solution containing L-lysine and L-arginine (see Table 2 and Table 3) 30 minutes before administering LUTATHERA. The amino acid solution should not be administered in the same arm as LUTATHERA. Continue the infusion during, and for at least 3 hours after LUTATHERA infusion. Do not decrease the dose of the amino acid solution if the dose of LUTATHERA is reduced [see **WARNINGS AND PRECAUTIONS (9.4**)].

   The amino acid solution can be prepared as a compounded product, in compliance with hospital's sterile medicinal product preparation good practices and according to the composition specified in Table 2.

Table 2. Composition of the standard amino acid solution

Compound	**Amount**
Lysine HCl	25 g
Arginine HCl	25 g
Sodium chloride 2.25 mg/mL (0.225%) solution for injection	1 L

   Alternatively, some commercially available amino acid solutions can be used if compliant with the specification listed in Table 3.

Table 3. Specification of commercially available amino acid solutions

Item	Specification
L-Lysine content	Between 18 and 24 g
L-Arginine content	Between 18 and 24 g
Volume	1.5 L to 2.2 L
Osmolarity	< 1050 mOsmol/L

Considering the high quantity of amino acids and the significant volume that commercially available solutions may require to meet the above specifications, the compounded solution is considered the medicinal product of choice, due to its lower volume to be infused and lower osmolarity.

Administration Instructions

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 an amino acid solution administered by contralateral intravenous infusion. This medicinal product must not be injected as a bolus.

Premedication with antiemetics should be injected 30 minutes before the start of amino acid solution infusion.

The recommended infusion method for administration of LUTATHERA is the gravity method. During the administration the recommended precaution measures should be undertaken [see **DOSAGE AND ADMINISTRATION (4.4)**, *Pre and concomitant medications*].

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

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

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

Room and equipment preparation:
- Administration room:

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

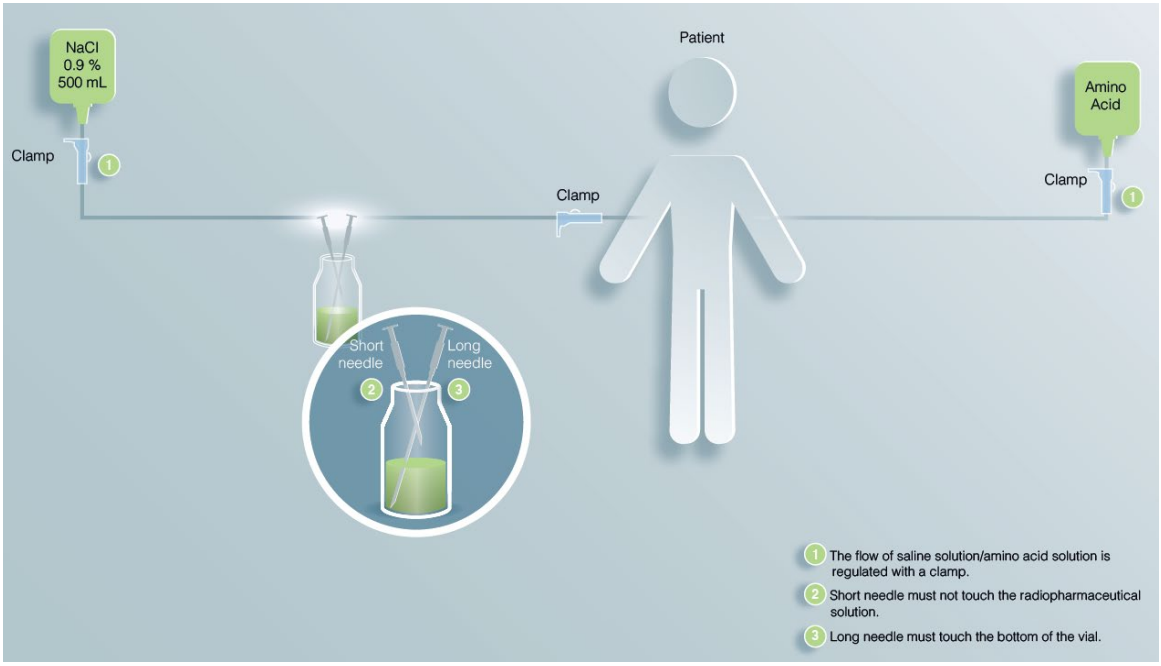
- Medicinal products to be administered:
  - One vial of LUTATHERA
  - One bag of sodium chloride 9 mg/mL (0.9%) solution for injection (500 mL)
  - Amino acid solution bag(s)
  - Antiemetics

- Care supplies and equipment:
  - Two (2) infusion poles
  - One (1) Long needle (90 – 100 mm)
  - One (1) Short needle
  - 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 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 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 30 minutes before 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 550 mL/h (depending on the solution type). Amino acid solution should be administered over 4 hour span. Rates lower than 320 mL/h are not recommended for commercial solutions. In case of severe nausea or vomiting during amino acid solution infusion, an antiemetic of a different pharmacological class can be administered.
5. Radioactivity in the LUTATHERA vial should be measured immediately before infusion using a calibrated radioactivity measurement system.
6. LUTATHERA infusion should start 30 minutes after the beginning of the amino acid solution infusion, with the infusion rate of approximately 400 mL/h (this infusion rate is the reference rate and can be adapted depending on the patient's venous status). LUTATHERA should be administered over 20 to 30 minute time span. Constant intra-vial pressure should be maintained 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.
10. 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.
11. 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.
12. 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 4. Administration procedure of antiemetic amino acid solution and LUTATHERA®

Administered agents	**Start time (min)**	**Infusion rate (mL/h)**	**Duration**
Antiemetic	0	-	bolus
Amino acid solution, either extemporaneously compounded (1 L) or commercial (1.5 L to 2.2 L)	30	250 – 550 (not < 320 mL/h for commercial solutions)	4 hours
LUTATHERA with sodium chloride 9 mg/mL (0.9%) solution for injection	60	400	20 to 30 minutes

4.5 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 5 [see **RADIATION DOSIMETRY (5)**].

5 RADIATION DOSIMETRY

Dosimetry and pharmacokinetics of lutetium (^{177}Lu) oxodotreotide have been studied in a subset of 20 patients enrolled in the Phase III NETTER-1 substudy, in order to define the pharmacokinetic profile of lutetium (^{177}Lu) oxodotreotide and to calculate whole body and organ radiation dosimetry, with particular focus on the absorbed radioactive dose to critical organs (e.g., kidney and bone marrow). The absorbed organ doses based on whole body planar images following the first (n=9) and the second/third (n=11) lutetium (^{177}Lu) oxodotreotide administrations were estimated with OLINDA/EXM (Version 1.1, 2005). Absorbed dose to each organ can be influenced by tumour burden. Consequently, the dosimetry is likely influenced by the disease process.

The estimated radiation absorbed doses for adults receiving LUTATHERA® are shown below**.**

Table 5. Estimated Radiation Absorbed Dose for LUTATHERA® in NETTER-1 Trial

	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)

In patients receiving a cumulative dose of 29.6 GBq, the mean ±SD estimated absorbed dose to tumours was 210 ± 210 Gy (range 7-984 Gy, n=19, excluding a patient outlier).

6 OVERDOSAGE

Overdose is unlikely with LUTATHERA® as this medicinal product is supplied as a “single dose” and “ready to use” product containing a predefined amount of radioactivity. In the case of overdose, an increase in the frequency of adverse reactions related to radiotoxicity is expected.

7 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 6. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Sterile solution for Intravenous Injection 370 MBq/mL at calibration	Sodium chloride 6.85 mg/mL Ascorbic acid 2.8 mg/mL Sodium acetate 0.66 mg/mL Sodium hydroxide 0.65 mg/mL Gentisic acid 0.63 mg/mL Acetic acid 0.48 mg/mL Diethylene triamine pentaacetic acid (DTPA) 0.05 mg/mL

LUTATHERA® Injection containing 370 MBq/mL (10 mCi/mL) of lutetium (^{177}Lu) oxodotreotide is a sterile, preservative-free and clear, colorless to slightly yellow solution for intravenous use supplied in a colorless Type I glass 30 mL single-dose vial containing 7.4 GBq (200 mCi) ± 10% of lutetium (^{177}Lu) oxodotreotide at the time of injection. The solution volume in the vial is adjusted from 20.5 mL to 25 mL to provide a total of 7.4 GBq (200 mCi) of radioactivity.

The product vial is in a lead shielded container placed in a plastic sealed container. The product is shipped in a Type A package.

8 DESCRIPTION

Physical Characteristics

Lutetium (Lu 177) decays to stable hafnium (Hf 177) with a half-life of 6.647 days, by emitting beta radiation with a maximum energy of 0.498 MeV and photonic radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (6.4%). The main radiations are detailed in Table 7.

Table 7. Radionuclide properties of ^{177}Lu

Radiation Type	Energy (keV)	Iβ%	Iγ%
β^-	176.5	12.2	
β^-	248.1	0.05	
β^-	384.9	9.1	
β^-	497.8	78.6	
γ	71.6		0.15
γ	112.9		6.40
γ	136.7		0.05
γ	208.4		11.0
γ	249.7		0.21
γ	321.3		0.22

External Radiation
Table 8 summarizes the radioactive decay properties of ^{177}Lu.

Table 8. Physical Decay Chart: Lutetium Lu 177 Half-life = 6.647 days

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1.000	48 (2 days)	0.812
1	0.996	72 (3 days)	0.731
2	0.991	168 (7 days)	0.482
5	0.979	336 (14 days)	0.232
10	0.958	720 (30 days)	0.044
24 (1 day)	0.902	1080 (45 days)	0.009

9 WARNINGS AND PRECAUTIONS

9.1 Risk of Radiation Exposure

LUTATHERA® contributes to a patient's overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures [see **DOSAGE AND ADMINISTRATION (4.1)**].

9.2 Haematologic

Myelosuppression was observed in the majority of patients treated with LUTATHERA® [see **Clinical Trial Adverse Reactions (11.2)**, *Adverse Reactions of Special Interest*]. Most of the cytopenic events were mild or moderate and transient. Patients with cytopenia ≥ Grade 2 at baseline are at higher risk of haematologic toxicity during LUTATHERA treatment.

Haematological evaluation of patients must be performed at baseline and prior to every dose of LUTATHERA. Withhold or reduce dose or permanently discontinue LUTATHERA based on severity of cytopenia [see **DOSAGE AND ADMINISTRATION (4.3)** *Dose Modifications*]. Patients with severely impaired haematological function at baseline prior to LUTATHERA therapy should not start treatment (e.g. Hb < 4.9 mmol/L or 8 g/dL, platelets < 75 G/L or 75 x 10^3/mm^3, or leukocytes <2 G/L or 2000/mm^3).

9.3 Carcinogenesis and Mutagenesis

Late-onset myelodysplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with LUTATHERA® [see **Clinical Trial Adverse Reactions (11.2),** *Adverse Reactions of Special Interest*]. Patients who may be at increased risk for developing MDS/AL are those who are > 70 years old, have impaired renal function, have pre-existing cytopenias, or had prior exposure to chemo or radiation therapy.

9.4 Renal Toxicity

Renal dysfunction can develop gradually during and after treatment with LUTATHERA®. In most patients, the kidney function impairment is mild or subclinical and acute. 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 **Clinical Trial Adverse Reactions (11.2)**, *Adverse Reactions of Special Interest*]. Cases of renal failure have occurred 3-36 months following treatment with LUTATHERA.

LUTATHERA is almost exclusively eliminated through the kidneys; therefore, concomitant administration of an amino acid solution containing L-lysine and L-arginine is necessary before, during and after LUTATHERA [see **DOSAGE AND ADMINISTRATION (4.4)**] to decrease reabsorption of lutetium (^{177}Lu) oxodotreotide through the proximal tubules and decrease the radiation dose to the kidneys. Do not decrease the dose of the amino acid solution if the dose of LUTATHERA is reduced.

Advise patients to urinate frequently during and after administration of LUTATHERA.

Renal function as determined by serum creatinine and calculated creatinine clearance must be assessed at baseline, during treatment and at least for the first year after treatment. Withhold or reduce dose, or permanently discontinue LUTATHERA based on severity of reaction [**DOSAGE AND ADMINISTRATION (4.3),** *Dose Modifications*].

Patients with baseline renal impairment, urinary tract obstruction, or predisposing risk factors such as diabetes or hypertension may be at greater risk of toxicity; perform more frequent assessments of renal function in patients with mild or moderate impairment. LUTATHERA has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min). Treatment with LUTATHERA in patients with creatinine clearance < 40 mL/min is not recommended.

9.5 Hepatic/Biliary/Pancreatic

Hepatotoxicity in patients treated with LUTATHERA® was mostly mild and reversible, without requiring inpatient treatment, but rare serious events including hepatic encephalopathy, cholecystitis, cholestasis, hepatic tumour haemorrhage, and necrosis, have occurred but may be due to underlying disease rather than treatment related effect [see **Clinical Trial Adverse Reactions (11.2)**, *Adverse Reactions of Special Interest*]. Patients with hepatic metastasis or pre-existing advanced hepatic impairment may be at increased risk of hepatotoxicity due to radiation exposure. Administration of LUTATHERA is not recommended in patients with liver impairment with either total bilirubinaemia > 3 times the upper limit of normal or albuminaemia < 30 g/L and prothrombin ratio decreased < 70%.

Monitor transaminases, bilirubin and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of reaction [see **DOSAGE AND ADMINISTRATION (4.3),** *Dose Modifications*].

9.6 Endocrine and Metabolism

Neuroendocrine hormonal crises, due to excessive release of hormones or bioactive substance may occur following treatment with LUTATHERA®, therefore observation of patients by overnight hospitalization should be considered in some cases. Hormonal crisis typically occurred during or within 24 hours following the initial LUTATHERA dose [see **Clinical Trial Adverse Reactions (11.2)**, *Adverse Reactions of Special Interest*].

Monitor patients for flushing, diarrhoea, hypotension, bronchoconstriction or other signs and symptoms of tumour-related hormonal release. Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.

9.7 Embryo-Fetal Toxicity

Based on its mechanism of action, LUTATHERA® can cause fetal harm [see **ACTION AND CLINICAL PHARMACOLOGY (13.1)**]. There are no available data on the use of LUTATHERA in pregnant women. No animal studies using lutetium (^{177}Lu) oxodotreotide have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm.

Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA [see **DOSAGE AND ADMINISTRATION (4.1)**].

Advise females and males of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose [see **SPECIAL POPULATIONS (10.1, 10.3)**].

9.8 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 **RADIATION DOSIMETRY (5)** and **SPECIAL POPULATIONS (10.3)**].

10 SPECIAL POPULATIONS

10.1 Pregnant Women

Risk Summary

Based on its mechanism of action, LUTATHERA® can cause fetal harm [see **ACTION AND CLINICAL PHARMACOLOGY (13.1)**]. There are no available data on LUTATHERA use in pregnant women. No animal studies using lutetium (^{177}Lu) oxodotreotide have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all

radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm. Advise pregnant women of the risk to a fetus.

In the Canadian general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is estimated at 3.85% and 5%, respectively.

10.2 Lactation

Risk Summary
There are no data on the presence of lutetium (^{177}Lu) oxodotreotide in human milk, 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, advise women not to breastfeed during treatment with LUTATHERA® and for 2.5 months after the final dose.

10.3 Females and Males of Reproductive Potential

Pregnancy Testing:
Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA® [see **SPECIAL POPULATIONS (10.1)**].

Contraception
Females
LUTATHERA can cause fetal harm when administered to a pregnant woman [see **SPECIAL POPULATIONS (10.1)**]. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the final dose of LUTATHERA.

Males
Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of LUTATHERA [see **ACTION AND CLINICAL PHARMACOLOGY (13.1) and NON-CLINICAL TOXICOLOGY (18**)].

Infertility
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 **RADIATION DOSIMETRY (5)**].

10.4 Pediatrics (<18 years):

The safety and effectiveness of LUTATHERA® have not been established in pediatric patients.

10.5 Geriatrics

Of the 1325 patients treated with LUTATHERA® in clinical trials, 438 patients were 65 years of age and older. The proportion of patients with serious adverse events was similar to that of younger subjects.

However, since increased risk of toxicity has been described in elderly patients (≥70 years old), close monitoring to allow for prompt dose modification in this population is advisable.

10.6 Renal Impairment

Patients with mild or moderate renal impairment may be at greater risk of toxicity. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. Perform more frequent assessments of renal function in patients with mild to moderate impairment. The 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. Treatment with LUTATHERA in patients with creatinine clearance < 40 mL/min is not recommended. [See **WARNINGS AND PRECAUTIONS (9.4)** and **DOSAGE AND ADMINISTRATION (4.3),** *Dose Modifications*].

10.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The safety of LUTATHERA® in patients with severe hepatic impairment (total bilirubin > 3 times upper limit of normal and any AST) has not been studied. It is not recommended to start LUTATHERA treatment in patients with liver impairment with either total bilirubinaemia > 3 times the upper limit of normal or albuminaemia < 30 g/L and prothrombin ratio decreased <70% [see **WARNINGS AND PRECAUTIONS (9.5**)].

11 ADVERSE REACTIONS

11.1 Adverse Reaction Overview

The data in this overview reflect LUTATHERA® exposure in 111 patients with advanced, progressive midgut neuroendocrine tumours (NETTER-1). Safety data in Warnings and Precautions section were also based on experience of an additional 22 patients participating in a non-randomized pharmacokinetic substudy of NETTER-1 and in a subset of patients (811 of 1214) with advanced somatostatin receptor positive tumours enrolled in ERASMUS [see **WARNINGS AND PRECAUTIONS (9)**].

The most serious adverse drug reactions reported with LUTATHERA use were myelosuppression, secondary myelodysplastic syndrome and leukaemia, renal toxicity, hepatotoxicity and neuroendocrine hormonal crisis [see **WARNINGS AND PRECAUTIONS (9)** and **ADVERSE REACTIONS** (**11.2**) *Adverse Reactions of Special Interest*].

The most frequently observed adverse drug reactions (≥ 10%) in patients receiving LUTATHERA compared to controls in the NETTER-1 trial were nausea (65% vs 12%), vomiting (53% vs 10%), fatigue (38% vs 26%), and decreased appetite (21% vs 11%). The most common Grade 3-4 adverse reactions occurring with a greater frequency among patients receiving LUTATHERA with octreotide compared to patients receiving high-dose octreotide include: lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea and elevated AST (5% each), and increased ALT, hyperglycaemia and hypokalaemia (4% each).

11.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

NETTER-1

The safety data described below are from NETTER-1, which randomized (1:1) patients with progressive, somatostatin receptor-positive midgut carcinoid tumours to receive LUTATHERA® 7.4 GBq (200 mCi) administered every 8 to 16 weeks concurrently with a commercial amino acid solution and with long-acting octreotide (30 mg administered by intramuscular injection within 24 hours of each LUTATHERA dose) (n = 111), or high-dose octreotide (defined as long-acting octreotide 60 mg by intramuscular injection every 4 weeks) (n = 112) [see **CLINICAL TRIALS** (**17**)]. Among patients receiving LUTATHERA with octreotide, 79% received a cumulative dose > 22.2 GBq (> 600 mCi) and 76% of patients received all four planned doses. Ten patients (8.9%) in the LUTATHERA arm experienced 12 adverse events that lead to dose modification, 14 patients (12.5%) reported 26 adverse events leading to a permanent discontinuation of the LUTATHERA treatment and 3 patients (2.7%) experienced 4 adverse events leading to a dosing delay. Five patients discontinued LUTATHERA for renal-related events and 4 discontinued for haematological toxicities. The median duration of follow-up was 24 months for patients receiving LUTATHERA with octreotide and 20 months for patients receiving high-dose octreotide.

Table 9 and Table 10 summarize the incidence of adverse reactions and laboratory abnormalities, respectively. The most common Grade 3-4 adverse reactions occurring with a greater frequency among patients receiving LUTATHERA with octreotide compared to patients receiving high-dose octreotide include: lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea and elevated AST (5% each), and increased ALT, hyperglycaemia and hypokalaemia (4% each).

Table 9. Adverse Reactions Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA® with Octreotide in NETTER-1[1]

Adverse Reaction[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Cardiac disorders				
Atrial fibrillation	5	1	0	0
Palpitations	5	0	5	0
Gastrointestinal disorders				
Nausea	65	5	12	2
Vomiting	53	7	10	0
Abdominal pain	26	3	19	3
Diarrhoea	26	3	18	1
Abdominal distension	16	0	13	0
Constipation	10	0	5	0
Dyspepsia	6	0	6	0
Flatulence	5	0	5	0
Abdominal pain upper	5	0	2	0
Gastritis	5	1	1	0
General disorders				
Fatigue	38	1	26	2
Peripheral oedema	16	0	9	1
Pyrexia	8	0	3	0
Asthenia	7	1	7	0
Influenza like illness	5	0	4	0
Chest pain	5	0	2	0
Investigations				
Decreased weight	8	1	7	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	11	3
Dehydration	5	2	3	2
Musculoskeletal and connective tissue disorders				
Back pain	13	2	10	0
Arthralgia	11	0	10	0
Pain in extremity	11	0	5	0
Muscle spasms	6	0	2	0
Musculoskeletal pain	5	0	5	0
Myalgia	5	0	0	0
Neck Pain	5	0	0	0
Musculoskeletal chest pain	5	1	3	1
Nervous system disorders				
Headache	17	0	5	0
Dizziness	17	0	8	0

Adverse Reaction[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Dysgeusia	8	0	2	0
Syncope	6	3	3	2
Infections and Infestations				
Urinary tract infection	6	0	6	1
Nasopharyngitis	5	0	5	0
Bronchitis	5	0	3	0
Psychiatric disorders				
Anxiety	12	1	5	0
Renal and urinary disorders				
Renal failure*	13	3	4	1
Radiation-related urinary tract toxicity**	8	0	3	0
Haematuria	6	0	2	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	1	6	0
Dyspnoea	11	0	8	0
Skin and subcutaneous tissue disorders				
Alopecia	12	0	2	0
Vascular disorders				
Flushing	14	1	9	0
Hypertension	12	2	7	2
Hypotension	5	0	2	0
Ear and Labyrinth Disorders				
Vertigo	5	0	1	0

[1] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

* Includes the terms: Glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotaemia, renal disorder, renal failure, renal impairment

**Includes the terms: Dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain and urinary incontinence

Other clinically relevant treatment emergent adverse events occurring with LUTATHERA with an incidence of <5% and affecting at least 2 patients include:

Gastrointestinal Disorders: ascites, dry mouth, abdominal discomfort, stomatitis, dysphagia, rectal haemorrhage, small intestinal obstruction

General Disorders and Administration Site Conditions: injection site pain, injection site reaction, non-cardiac chest pain, administration site pain, chills, chest discomfort, general physical health deterioration, swelling

Investigations: electrocardiogram QT prolonged, protein urine

Metabolism and Nutrition Disorders: hypomagnesaemia, Vitamin D deficiency

Musculoskeletal and Connective Tissue Disorders: bone pain, flank pain

Nervous System Disorders: lethargy, parosmia, somnolence, tremor, paraesthesia

Infections and Infestations: respiratory tract infection, diverticulitis, Clostridium difficile infection

Vascular Disorders: hot flush

Respiratory, Thoracic, and Mediastinal Disorders: pleural effusion, wheezing, dysphonia

Blood and Lymphatic System Disorders: pancytopenia

Psychiatric Disorders: insomnia, depression, confusional state, sleep disorder, agitation, delirium, panic attack

Renal and Urinary Disorders: proteinuria, urinary incontinence, dysuria, nephrolithiasis, calculus uretic

Skin and Subcutaneous Tissue Disorders: rash, pruritis, erythema, dry skin

Cardiac Disorders: Angina pectoris

Injury, Poisoning and Procedural Complications: fall, contusion, ligament sprain, femur fracture

Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps): malignant neoplasm progression

Hepatobiliary Disorders: cholestasis

Eye Disorders: diplopia

Endocrine Disorders: hypothyroidism, Diabetes mellitus, secondary hypothyroidism

Ear and Labyrinth Disorders: tinnitus

Reproductive System and Breast Disorders: gynaecomastia

Immune System Disorders: hypersensitivity

Table 10. Laboratory Abnormalities Occurring in ≥5% (All Grades) of Patients Receiving LUTATHERA® with Octreotide in NETTER-1[*1]

Laboratory Abnormality[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N= 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All grades %	Grade 3-4 %	All grades %	Grade 3-4 %
Haematology				
Lymphopenia	90	44	39	5
Anaemia	81	0	55	1
Leukopenia	55	2	20	0
Thrombocytopenia	53	1	17	0
Neutropenia	26	3	11	0
Renal/Metabolic				
Creatinine increased	85	1	73	0
Hyperglycaemia	82	4	67	2
Hypoalbuminaemia	29	0	29	0
Hyperuricaemia	34	6	30	6
Hypocalcaemia	32	0	14	0
Hypokalaemia	26	4	21	2
Hyperkalaemia	19	0	11	0
Hyponatraemia	19	2	18	4
Hypernatraemia	17	0	7	0
Hypoglycaemia	15	0	8	0
Hypercalcaemia	12	0	9	0
Hepatic				
GGT increased	66	20	67	16
Alkaline phosphatase increased	65	5	55	9
AST increased	50	5	35	0
ALT increased	43	4	34	0
Blood bilirubin increased	30	2	28	0

*Values are worst grade observed after randomization
[1]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Lymphocytosis was the only other clinically relevant laboratory abnormality observed with LUTATHERA when considering an incidence of <5% and affecting at least 2 patients.

ERASMUS

Safety data are available from 1214 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with somatostatin receptor-positive tumours (neuroendocrine and other primaries). Patients received LUTATHERA® 7.4 GBq (200 mCi) administered every 6 to 13 weeks with or without octreotide. Retrospective medical record review was conducted on a subset of 811 patients to document serious adverse reactions. Eighty-one (81%) percent of patients in the subset received a cumulative dose ≥ 22.2 GBq (≥ 600 mCi). The rates of serious adverse reactions in this section were based on a median follow-up time of more than 4 years.

Table 11. Serious Adverse Events ≥1% of patients receiving lutetium (^{177}Lu) oxodotreotide in ERASMUS[1,2]

Serious Adverse Event[1]	lutetium (^{177}Lu) oxodotreotide (N=811)[3]
Blood and lymphatic system disorders	
Pancytopenia	10.1%
Anaemia	5.3%
Thrombocytopenia	3.3%
Surgical and medical procedures	
Cholescystectomy	2.2%
Abdominal cavity drainage	2.1%
Transfusion	1.7%
Stent placement	1.2%
High frequency ablation	1.1%
Gastrointestinal disorders	
Diarrhoea	6.4%
Abdominal pain	5.8%
Vomiting	4.1%
Nausea	3.6%
Constipation	3.0%
Ascites	2.1%
Ileus	1.5%
Abdominal pain upper	1.4%
Intestinal obstruction	1.0%
Melaena	1.0%
Metabolism and nutrition disorders	
Dehydration	3.5%
Hypercalcaemia	1.6%
Respiratory, Thoracic and Mediastinal disorders	
Dyspnoea	3.0%
Infections and infestations	
Pneumonia	3.0%
Urinary tract infection	1.2%
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Myelodysplastic syndrome	1.8%
Metastasis to central nervous system	1.0%
Vascular disorders	
Hypotension	1.2%
Cardiac disorders	
Cardiac failure	1.5%
Myocardial infarction	1.1%
Investigations	
Weight decreased	1.5%
Renal and urinary disorders	
Renal failure	1.0%

Serious Adverse Event[1]	lutetium (^{177}Lu) oxodotreotide (N=811)[3]
Renal impairment	1.2%
Hepatobiliary Disorders	
Cholelithiasis	1.2%
Jaundice	1.1%
Injury and Poisoning	
Fall	1.2%
General disorders and administration site	
Death	5.1%
Pyrexia	4.3%
Malaise	3.3%
Pain	2.3%

[1]ERASMUS study collected Serious Adverse Events only
[2]ERASMUS involved delivery of lutetium (^{177}Lu) oxodotreotide in an investigational formulation similar to LUTATHERA
[3]Data in Table 11 is derived from 811 Dutch patients participating in ERASMUS

Serious Adverse Events reported at ≥ 5% incidence were pancytopenia (10.1%), anaemia (5.3%), diarrhoea (6.4%), abdominal pain (5.8%).

Other treatment-emergent adverse events occurring with LUTATHERA with an incidence of < 1% and affecting more than one patient include:

Blood and Lymphatic System Disorders: leukopenia, bone marrow failure, febrile neutropenia

Cardiac Disorders: atrial fibrillation, tricuspid valve incompetence, angina pectoris, arrhythmia, bradycardia, cardiomyopathy, sinus tachycardia

Endocrine Disorders: carcinoid crisis, carcinoid syndrome

Gastrointestinal Disorders: haematemesis, abdominal discomfort, small intestinal obstruction, subileus, gastrointestinal haemorrhage, abdominal pain lower, gastric haemorrhage, gastric perforation, ileus paralytic, inguinal hernia, Mallory-Weiss syndrome, pancreatitis

Surgical and Medical Procedures: enterostomy, cytoreductive surgery, gastrointestinal tube insertion, pancreaticoduodenectomy, therapeutic embolization, tricuspid valve replacement, tumour excision, abscess drainage, knee arthroplasty, mastectomy, radiotherapy, splenectomy, bile duct stent insertion, gallbladder operation, gastrointestinal surgery, hepatectomy, hepatic embolization, pancreatectomy, venous stent insertion, brain tumour operation, cardioversion, catheter placement, colectomy, coronary angioplasty, coronary arterial stent insertion, duodenal sphincterotomy, hip arthroplasty, hospitalization, intestinal anastomosis, intestinal operation, lymphadenectomy, nephrostomy, polypectomy, pulmonary valve replacement, renal stone removal, Salpingo-oophorectomy, stent removal, thoracic cavity drainage

General Disorders and Administration Site Conditions: peripheral oedema, oedema, asthenia, chest pain, fatigue, device occlusion, chills, gait disturbance, general physical health deterioration, local swelling

Hepatobiliary Disorders: cholangitis, cholecystitis, cholestasis, hepatic failure, hepatic function abnormal, hyperbilirubinaemia, cholecystitis acute, bile duct stenosis, hepatic pain

Immune System Disorders: hypersensitivity

Infections and Infestations: infection, sepsis, urosepsis, cystitis, device related infection, gastroenteritis, abdominal abscess, cholecystic infective, Herpes zoster, influenza, localized infection

Investigations: blood bilirubin increased, blood alkaline phosphatase increased, endoscopic retrograde cholangiopancreatography, haemoglobin decreased, hepatic enzyme abnormal, biopsy bone marrow, colonoscopy, diagnostic procedure, hepatic enzyme increased, liver function test abnormal

Metabolism and Nutrition Disorders: cachexia, decreased appetite, hyponatraemia, hypoglycaemia, Diabetes Mellitus, hypocalcaemia, hypokalaemia, tumour lysis syndrome, hyperglycaemia, hypoalbuminaemia, hypophagia, malnutrition

Musculoskeletal and Connective Tissue Disorders: back pain, flank pain, musculoskeletal pain, pain in extremity

Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps): acute myeloid leukaemia, acute leukaemia, chronic myeloid leukaemia, chronic myelomonocytic leukaemia, malignant neoplasm progression, metastases to liver, metastatic pain, tumour pain, metastases to bone, neoplasm progression, prostate cancer, tumour compression

Injury, Poisoning and Procedural Complications: hip fracture, wound dehiscence, wrist fracture, ankle fracture, clavicle fracture, fat embolism, rib fracture, road traffic accident, upper limb fracture

Nervous System Disorders: dizziness, syncope, transient ischaemic attack, cerebral infarction, epilepsy, headache, somnolence, cerebral haemorrhage, cerebrovascular accident, cerebrovascular disorder, spinal cord compression

Psychiatric Disorders: delirium, disorientation

Renal and Urinary Disorders: hydronephrosis, haematuria, renal disorder, urinary retention, acute kidney injury, urinary incontinence

Respiratory, Thoracic and Mediastinal Disorders: pleural effusion, pulmonary embolism, cough, epistaxis, haemoptysis, pneumothorax

Vascular Disorders: haemorrhage, flushing, thrombosis, embolism, deep vein thrombosis

Congenital, Familial and Genetic Disorders: exomphalos

Adverse Reactions of Special Interest

Myelosuppression (Anaemia, Thrombocytopenia, and Neutropenia) [see **WARNINGS AND PRECAUTIONS (9.2)**]
In the NETTER-1 trial, myelosuppression occurred more frequently in patients receiving LUTATHERA® with long-acting octreotide compared to patients receiving high-dose long-acting octreotide (all grades): anaemia (81% vs 54%), thrombocytopenia (53% vs 17%), and neutropenia (26% vs 11%). Most of the cytopenic events were mild or moderate, and reversible. For those that did not experience full recovery, improvement in grade was noted. In the ERASMUS trial, serious adverse haematologic events were reported: pancytopenia (10.5%), anaemia (5.3%) and thrombocytopenia (3.3%).

The nadir usually occurs 4-6 weeks after the treatment; the toxicity is mild and reverses without supportive treatment within a few weeks of the LUTATHERA dose.

Secondary Myelodysplastic Syndrome and Leukaemia **[see WARNINGS AND PRECAUTIONS (9.3)]**
Treatment with LUTATHERA is associated with increased risk of developing blood cancer. Late-onset myelodysplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with LUTATHERA. MDS was reported in 2.7% of patients who received LUTATHERA in the NETTER-1 trial. In the ERASMUS trial, 15 patients (1.8%) developed MDS and 4 patients (0.5%) developed acute leukaemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukaemia.

Renal Toxicity [see **WARNINGS AND PRECAUTIONS (9.4)**]
Renal dysfunction can develop gradually during and after treatment with LUTATHERA. In ERASMUS, 8 patients (1%) developed renal failure 3 to 36 months following LUTATHERA. Two of these patients had underlying renal impairment or risk factors for renal failure (e.g., diabetes or hypertension) and required dialysis. In NETTER-1, acute kidney injury was reported in 2.7% of LUTATHERA treated patients, including one Grade 5 event.

Hepatotoxicity [see **WARNINGS AND PRECAUTIONS (9.5)]**
In NETTER-1, treatment emergent serious adverse events of hepatic encephalopathy, hepatocellular injury, cholecystitis, and cholestasis were reported in 4 patients (3.6%). In ERASMUS, 2 patients (<1%) were reported to have hepatic tumour haemorrhage, oedema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis.

Neuroendocrine Hormonal Crisis [see **WARNINGS AND PRECAUTIONS (9.6)**]
Hormonal crisis occurred in 1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose. Two (<1%) patients were reported to have hypercalcaemia.

Adverse reactions related to amino-acid co-infusion
The amino acid infusion contributes to some adverse reactions described for the LUTATHERA safety profile. Adverse reactions possibly related to the co-infusion of amino acids during LUTATHERA treatment are nausea, vomiting, and transient increased heart rate.

11.3 Clinical Trial Adverse Reactions (Pediatrics)

No data on use of LUTATHERA® in pediatric patients is available.

12 DRUG INTERACTIONS

12.1 Overview

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA®. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended [see **DOSAGE AND ADMINISTRATION** (**4.4**)].

Some evidence exists that corticosteroids can induce down-regulation of SST2 receptors. As a caution, repeated administration of high-doses of glucocorticosteroids should be avoided during LUTATHERA therapy. Patients with history of chronic glucocorticosteroids use should be carefully evaluated for sufficient SST2 receptor expression. It is not known if there is interaction between glucocorticosteroids used intermittently for prevention of nausea/vomiting during LUTATHERA therapy. Glucocorticosteroids should be avoided as preventative antiemetic treatment.

13 ACTION AND CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Lutetium (^{177}Lu) oxodotreotide binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSRT2). Upon binding to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumours, the compound is internalized. The beta emission from Lu 177 induces cellular damage by formation of free radicals in somatostatin receptor-positive cells and in neighboring cells.

13.2 Pharmacodynamics

Lutetium Lu 177 exposure-response relationships and the time course of pharmacodynamics response are unknown.

In vitro metabolism studies and plasma protein binding studies performed on lutetium (^{175}Lu) oxodotreotide showed an absence of significant inhibitory or induction effects on human CYP450 enzymes, no potential P-gp specific interactions, absence of significant inhibitory effects on human transporters, and that lutetium (^{175}Lu) oxodotreotide is not a highly-protein

bound compound. Therefore, LUTATHERA® has a low risk for clinically relevant drug-drug interactions due to metabolism or protein transporter mechanisms.

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 tumours. No clinically relevant changes in the mean QTc interval (i.e., >20 ms) were detected.

A transient increased heart rate in patients treated with LUTATHERA and commercial amino acid solution was observed.

13.3 Pharmacokinetics

The pharmacokinetics (PK) of lutetium (^{177}Lu) oxodotreotide was characterized in 20 patients with progressive, somatostatin receptor-positive neuroendocrine tumours. The PK parameters are shown in Table 12.

Table 12. Summary of LUTATHERA® pharmacokinetic parameters in patients with progressive somatostatin receptor positive neuroendocrine tumours*

	$C_{max\ (ng/mL)}$	$T_{max\ (h)}$	$t_{½}$ (h)	$AUC_{0-\infty}$	CL (L/h)	Vd (L)
Single dose mean	10 ± 5	0.48 ± 0.26	71.2 ± 28.1	41.3 ± 14.7	4.5 ± 1.4	460 ± 246

*Mean ±SD values are shown. Cmax = the value of the maximum blood concentration; Tmax = time after start of infusion at which Cmax is found; Vz= distribution volume during the terminal phase; Cl = clearance; t1/2 = terminal half-life

Distribution

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

Within 4 hours after administration, lutetium (^{177}Lu) oxodotreotide distributes in kidneys, tumour 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 (^{177}Lu) oxodotreotide by 36%.

The non-radioactive form of lutetium (^{177}Lu) oxodotreotide is 43% bound to human plasma proteins.

Elimination

The mean clearance (CL) is 4.5 L/h (CV 31%) for lutetium (^{177}Lu) oxodotreotide. The mean (± standard deviation) effective blood elimination half-life is 3.5 (±1.4) hours and the mean terminal blood half-life is 71 (± 28) hours.

Metabolism

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

Excretion
Lutetium (^{177}Lu) oxodotreotide is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following LUTATHERA® administration. Prolonged elimination of lutetium (^{177}Lu) oxodotreotide in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium (^{177}Lu) oxodotreotide, greater than 99% will be eliminated within 14 days after administration of LUTATHERA [see **WARNINGS AND PRECAUTIONS** (**9.1**)].

14 STORAGE, STABILITY AND DISPOSAL

Store between 2 to 27 ºC (35.6 to 80.6 ºF) in the original lead shielding packaging.
The shelf life is 72 hours. Discard appropriately at 72 hours.

15 SPECIAL HANDLING INSTRUCTIONS

Radiopharmaceuticals should be received, used, administered and disposed of only by authorized persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organization.

Always use the principles of time, distance and shielding (reducing the manipulation of the vial and using the material already supplied by the manufacturer) to minimize the radiation dose, especially to the person administering.

Recommended protective measures:

- Use disposable plastic, latex or rubber gloves.
- Wear a lab coat, which must be monitored before leaving the laboratory.
- Wear safety glasses.
- Minimize handling time.
- Use tongs to handle unshielded sources and potentially contaminated vessels.
- Use disposable absorbent liners on trays
- Use isolated treatment room

Radiation shielding information:

Physical data[3]

Gamma constant: 0.028 mrem/hr per mCi at 1.0 meter [7.636E-6 mSv/hr per MBq at 1.0 meter]
Specific Activity: 1.1E5 Ci/g [4.1E15 Bq/g] max

Shielding:

Photons*

Lead [Pb] Half Value Layer [HVL]: 0.6 mm (0.02 inches)
Tenth Value Layer [TVL]: 2.1 mm (0.08 inches)

Betas

Plexiglas Half Value Layer [HVL]: 0.135 cm

(*Photons calculated based on maximum beta energy; assume beta range = 159 mg/cm² & Plexiglas density = 1.18 g/cm³)

PART II: SCIENTIFIC INFORMATION

16 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: lutetium (^{177}Lu) oxodotreotide

Chemical name: lutetium (Lu 177)-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 and molecular mass: $C_{65}H_{87}N_{14}O_{19}S_2{}^{177}Lu$, 1609.6 g/mol

Structural formula:

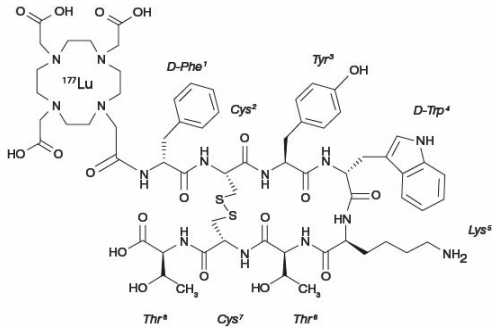


Figure 2. lutetium (^{177}Lu) oxodotreotide chemical structure

Physicochemical properties: Lutetium (^{177}Lu) decays to stable hafnium (^{177}Hf) with a half-life of 6.647 days, by emitting β^- radiation with a maximum energy of 0.498 MeV and photonic radiations (γ) of 0.208 MeV (11.0%) and 0.113 MeV (6.4%).

Product Characteristics
LUTATHERA® Injection containing 370 MBq/mL (10 mCi/mL) of lutetium (^{177}Lu) oxodotreotide is a sterile, preservative-free and clear, colorless to slightly yellow solution for intravenous use supplied in a colorless Type I glass 30 mL single-dose vial containing 7.4 GBq (200 mCi) ± 10% of lutetium (^{177}Lu) oxodotreotide at the time of injection. The solution volume in the vial is adjusted from 20.5 mL to 25 mL to provide a total of 7.4 GBq (200 mCi) of radioactivity. The final pH is 4.5 to 8.5.

The product vial is in a lead shielded container placed in a plastic sealed container. The product is shipped in a Type A package.

17 CLINICAL TRIALS

17.1 Trial Design and Study Demographics

The safety and efficacy of LUTATHERA® was examined in two clinical studies as described in Table 13.

Table 13. Summary of Patient Demographics for Clinical Trials with LUTATHERA®

Study I.D.	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age years (Range)	Sex (male/female)
NETTER-1	Randomized, multicenter, open label, active controlled phase III study in patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumours	**LUTATHERA arm:** 4 LUTATHERA administrations x 200 mCi each (7.4 GBq) i.v. q 8 weeks + long-acting octreotide 30 mg every 4 weeks **Control arm**: high dose long-acting octreotide 60 mg every 4 weeks	116 LUTATHERA arm 113 control arm	64.0 (28-84) 65.0 (34-87)	63/53 53/60
ERASMUS	Phase I/II open, non-randomized, single arm study to evaluate the efficacy and safety of lutetium (^{177}Lu) oxodotreotide treatment in somatostatin receptor positive GEP-NETs	lutetium (^{177}Lu) oxodotreotide ***:** 4 x 200 mCi (7.4 GBq) i.v. every 6-13 weeks	1214 360** - 183 midgut - 133 pancreatic - 19 bronchial - 13 hindgut - 12 foregut (other than bronchial and pancreatic)	59.0 (16-90) 60.0 (30-85)	658/556 183/177

*Note, the drug product used for the ERASMUS study used the same active pharmaceutical ingredient as LUTATHERA, but the formulation was slightly different.
**A total of 360 patients with long-term follow-up and baseline tumour assessment had GEP-NET tumours (midgut 183, pancreatic 133, bronchial 19, hindgut 13, foregut other than bronchial and pancreatic 12)

17.2 Study Results

NETTER-1 Study

The efficacy of LUTATHERA® in patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumours was established in NETTER-1 (NCT01578239), a randomized, multicenter, open-label, active-controlled trial. Key eligibility criteria included Ki67 index ≤ 20%, Karnofsky performance status ≥ 60, confirmed presence of somatostatin receptors on all lesions (OctreoScan uptake ≥ normal liver), creatinine clearance ≥ 50 mL/min, no prior treatment with peptide receptor radionuclide therapy (PRRT), and no prior external radiation therapy to more than 25% of the bone marrow.

Two hundred twenty-nine (229) patients were randomized (1:1) to receive either LUTATHERA 7.4 GBq (200 mCi) every 8 weeks for up to 4 administrations (maximum cumulative dose of 29.6 GBq) or high-dose long-acting octreotide (defined as 60 mg by intramuscular injection every 4 weeks). Patients in the LUTATHERA arm also received long-acting octreotide 30 mg as

an intramuscular injection 4 to 24 hours after each LUTATHERA dose and every 4 weeks after completion of LUTATHERA treatment until disease progression or until week 76 of the study. Patients were co-infused with a commercial amino acid solution. Long-acting octreotide was withheld for at least 4 weeks before each LUTATHERA dose. Patients in both arms could receive short-acting octreotide for symptom management; short-acting octreotide was withheld for at least 24 hours before each LUTATHERA dose. Randomization was stratified by OctreoScan tumour 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). The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee (IRC) per RECIST v1.1. Additional efficacy outcome measures were overall response rate (ORR) by IRC, duration of response, and overall survival (OS).

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, 74% had an illial primary, 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 tumour 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. Efficacy results for NETTER-1 are presented in Table 14 and Figure 3.

At the time of analysis (30 June 2016), the number of centrally confirmed disease progressions or deaths was 27 events in the LUTATHERA group, and 78 events in the octreotide LAR group. Median PFS was not yet reached in the LUTATHERA group, while for octreotide LAR group it was 8.5 months (hazard ratio of 0.21 [95% CI: 0.13, 0.32]), indicating a 79% reduction in the risk for a patient to progress or die under LUTATHERA compared to octreotide LAR.

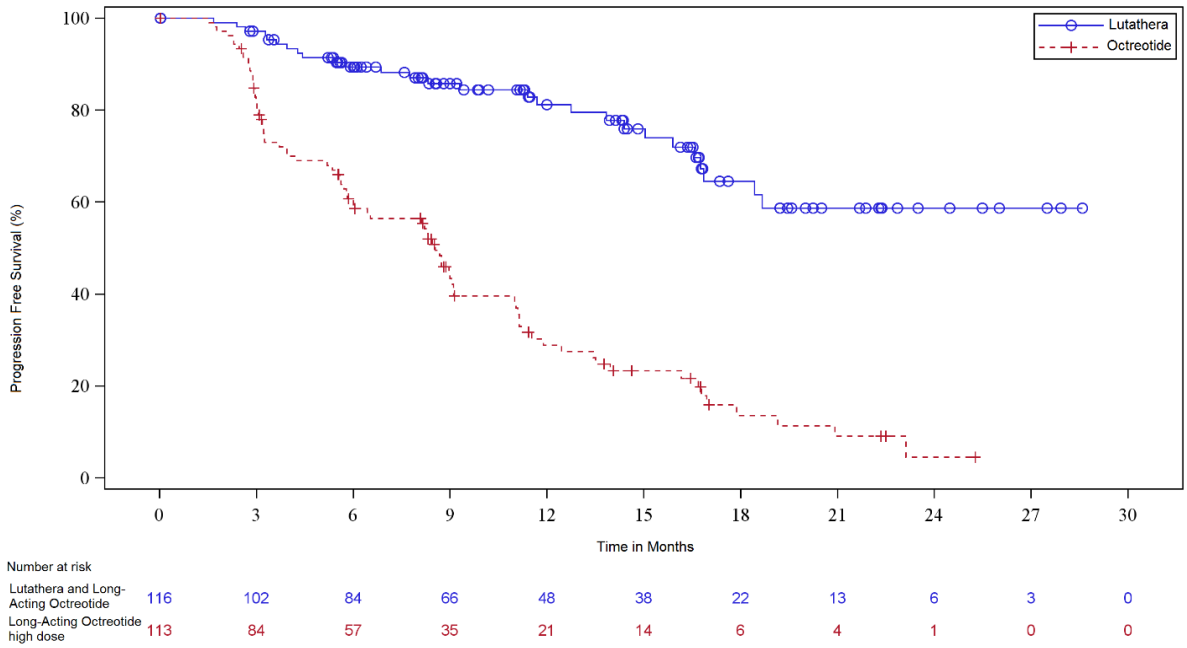
At a pre-specified interim (24 July 2015) analysis of OS, there were 17 deaths in the LUTATHERA arm and 31 in the octreotide LAR arm. Statistical significance was not demonstrated at this time. At the time of the updated analysis, there were 27 deaths in the LUTATHERA arm and 43 in the octreotide LAR arm. Median OS was not reached in the LUTATHERA group, and 27.4 months in the octreotide LAR group (hazard ratio of 0.52). The final OS analysis will be conducted after 158 deaths occur, or 5 years have passed. ORR by independent review for LUTATHERA was 13% (7%, 19%), while only 4% (0.1%, 7%) for the octreotide LAR ($p<0.0148$).

Table 14. Efficacy Results in NETTER-1

	LUTATHERA® and Long-Acting Octreotide (30 mg) N=116	Long-Acting Octreotide (60 mg) N=113
PFS by IRC		
Events (%)	27 (23%)	78 (69%)
Progressive disease, n (%)	15 (13%)	61 (54%)
Death, n (%)	12 (10%)	17 (15%)
Median in months (95% CI)	NR[c] (NE, NE)	8.5 (6.0, 9.1)
Hazard ratio[a] (95% CI)	0.21 (0.13, 0.32)	
P-Value[b]	< 0.0001	
OS (Updated)		
Deaths (%)	27 (23%)	43 (38%)
Median in months (95% CI)	NR (31.0, NE)	27.4 (22.2, NE)
Hazard ratio[a,d]	0.52	
ORR by IRC		
ORR, % (95% CI)	13% (7%,19%)	4% (0.1%, 7%)
Complete response rate, n (%)	1 (1%)	0
Partial response rate, n (%)	14 (12%)	4 (4%)
P-Value[e]	0.0148	
Duration of response, median in months (95% CI)	NR (2.8, NE)	1.9 (1.9, NE)

a: Hazard ratio based on the unstratified Cox model
b: Unstratified log rank test
c: Median follow-up 10.5 months at time of primary analysis of PFS (range: 0 to 29 months)
d: Interim analysis of OS not statistically significant based on pre-specified significance criteria
e: Fisher's Exact test
NR: Not reached; NE: Not evaluable

Figure 3. Kaplan-Meier Curves for Progression-Free Survival in NETTER-1



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 1214 patients received LUTATHERA in ERASMUS, of which 360 patients had long-term follow-up and baseline tumour assessment and GEP-NET tumours. 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 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; hence, it should be interpreted with caution. Out of the 360 subjects, 19 subjects had bronchial tumours, 133 had pancreatic tumours, 12 had foregut tumours, 183 had midgut tumours, and 13 had hindgut tumours. Subjects had their tumours assessed using either the RECIST 1.1 criteria (145 subjects, 40%) or the SWOG assessment which was retrospectively algorithmically converted to RECIST 1.1 (215 subjects, 60%). The overall investigator assessed ORR was 45% (95% CI 40, 50), median 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 is 41% (95% CI 33, 50), and median DOR is 35 months (95% CI: 17, 38), and in the subset of 215 patients who were evaluated by the investigators using the converted SWOG criteria, the ORR is 47% (95% CI 41, 54), and median DOR is 18.5 months (95% CI 15, 24).

Table 15. Best response, ORR and DoR observed in the Erasmus phase I/II study in Dutch patients with GEP and bronchial NETs – (FAS, N=360)†

	N	CR		PR		SD		ORR				DoR (months)		
Tumour type		n	%	n	%	N	%	n	%	95%CI		Median	95%CI	
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 subjects 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

18 NON-CLINICAL TOXICOLOGY

General toxicology (single and repeat dose studies)

- An acute toxicity study was conducted in female rats using a non-radioactive form of lutetium (^{177}Lu) oxodotreotide (lutetium (^{175}Lu) oxodotreotide). The compound was given intravenously, as a bolus, to three groups of three animals each at increasing doses (1.2, 4.8 and 20.5 mg/kg respectively) at an administration volume of 5 mL/kg. The administered doses were about 40, 170 and 700 fold the recommended human dose. Animals were observed for 11 to 14 days after the treatment.

  The results of the study showed that the compound was well tolerated after single i.v. administration, without inducing any toxicity signs, up to the highest tested dose. Therefore, the Maximum Tolerated Dose (MTD) in female rats is higher than 20.5 mg/kg.

- In the maximum tolerated dose (MTD) study conducted in male and female dogs, lutetium (^{175}Lu) oxodotreotide formulation was administered intravenously, as a bolus, at ascending doses from 0.4 to 3.2 mg/kg (0.4, 0.8, 1.6 and 3.2 mg/kg, that is about 50 to 400 fold the recommended human dose) to a group of 1 male and 2 female dogs, and as single doses of 6.4 mg/kg and 10 mg/kg (about 800 and 1200 fold the intended human dose) to two groups of 1 male and 1 female dog each. The administration volume was 2.5 mL/kg. Animals were observed for a 13 to 15 day period following administration.

  The results of this MTD study in dogs show that intravenous bolus of lutetium (^{175}Lu) oxodotreotide did not induce mortality and any evident drug-related signs of toxicity in male and female Beagle dogs, except for soft to liquid faeces observed on the days following treatment at all doses, and spread red (at 0.4 to 3.2 mg/kg) or dark red (at 6.4 and 10 mg/kg) areas on the mucosa of the gastro-intestinal tract (jejunum, duodenum or rectum). No changes on haematology, coagulation and clinical chemistry parameters were observed. Based on the results of this study, the doses chosen for the repeated dose toxicity study in dogs were 0.08, 0.5 and 3.2 mg/kg.

- In the repeat dose toxicity study in rats lutetium (^{175}Lu) oxodotreotide formulation was administered intravenously at 1.25, 5 or 20 mg/kg (that is, 40, 170, and 700 fold the recommended human dose) for four times, once every two weeks, to mimic the schedule applied in human but with a reduced time between treatments to increase the possibility of occurrence of any toxic effects linked to the non-radioactive compound. The treatment groups were composed of 10 male and 10 female rats. The study included additional animals (5 males and 5 females) administered with the vehicle and with the highest dose, in order to study the reversibility, persistence or delayed occurrence of toxic effects for 3 months post-treatment.

  The compound induced no mortality and no major signs of toxicity. The primary target organ was the pancreas, a high SSTR2 expressing organ. Pancreatic acinar apoptosis occurred at lutetium (^{175}Lu) oxodotreotide intermediate and high doses (≥ 5 mg/kg). These findings were consistent with high uptake of the peptide in the pancreas in animal biodistribution studies.

Therefore, the NOEL corresponds to 1.25 mg/kg, that is around 40 times the human dose.

- A repeated dose toxicity study was also conducted in dogs. Lutetium (^{175}Lu) oxodotreotide formulation was administered intravenously four times, once every two weeks, at three different doses (0.08, 0.5 and 3.2 mg/kg, corresponding to about 10, 65 and 400 fold the recommended human dose).

  The compound induced no mortality and no major signs of toxicity at any dose tested. The signs observed (salivation, vocalisation and soft to liquid faeces, associated at the highest dose to slight increase in body temperature and a slight decrease of food consumption) were mild and reversible. As for rats, the primary target organ was the pancreas. Moderate and reversible pancreatic acinar apoptosis occurred in few animals at doses ≥ 0.5 mg/kg.

  At recovery sacrifice there was no incidence of pancreatic acinar apoptosis in the 4 male dogs of the control group and male dogs of group treated with the highest dose. In female dogs there was a single case of pancreatic acinar apoptosis in highest dose group and also in the control group, both at minimal degree, confirming the reversible nature of this change.

  Acinar apoptosis was the only histological change observed in the high dose group. Therefore, considering also the reversibility of this change after recovery, 3.2 mg/kg was considered to be the NOAEL in the repeated dose toxicology study in dogs, which is equivalent to 400 times the human dose.

Carcinogenesis

No long term animal studies have been performed to evaluate carcinogenic potential of LUTATHERA®. However, radiation is a carcinogen and mutagen.

Mutagenesis

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

Lutetium (^{175}Lu) oxodotreotide formulation was examined for the ability to induce gene mutations in tester strains of *Salmonella typhimurium* and *Escherichia coli*, as measured by reversion of auxotrophic strains to prototrophy. The five tester strains TA1535, TA1537, TA98, TA100 and WP2 uvrA were used. Experiments were performed both in the absence and presence of metabolic activation, using liver S9 fraction from rats.

Lutetium (^{175}Lu) oxodotreotide formulation was also assayed for its ability to induce mutations (5-trifluorothymidine resistance) in L5178Y TK+/- mouse lymphoma cells after in vitro treatment, in the absence and presence of S9 metabolizing system, using a fluctuation method.

These genotoxicity studies showed that lutetium (^{175}Lu) oxodotreotide formulation does not induce mutation at the TK locus of L5178Y mouse lymphoma cells in vitro, nor reverse mutation

in *Salmonella typhimurium* or *Escherichia coli* in the absence or presence of S9 metabolic activation.

Impairment of Fertility
No long term animal studies have been performed to evaluate whether LUTATHERA affects fertility in males and females.

Cardiac Safety Study

The effects of lutetium (^{175}Lu) oxodotreotide on blood pressure, heart rate, body temperature and electrocardiogram (duration of PR, PQ, QT and QRS) after single i.v. administration were investigated in dogs. The compound did not show any effect on cardiac conduction times or body temperature and did not cause arrhythmia at the doses tested (from 0.08 to 0.8 mg/kg).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

LUTATHERA®

lutetium (^{177}Lu) oxodotreotide

Read this carefully before you start taking **LUTATHERA®** and before each dose. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LUTATHERA**.

Serious Warnings and Precautions

LUTATHERA® should be used by health professionals who are appropriately trained in use of radiopharmaceuticals.

Kidney impairment can occur in patients treated with LUTATHERA. Tell your physician about any kidney condition prior to receiving LUTATHERA.

Secondary blood cancer (myelodysplastic syndrome or acute leukaemia) can rarely occur several years after you have completed LUTATHERA treatment.]

What is LUTATHERA® used for?

LUTATHERA is a radiopharmaceutical medicine used for the treatment of certain tumours (gastroenteropancreatic neuroendocrine tumours) that have somatostatin receptors, which cannot be completely removed from your body by surgery, have spread in your body (metastatic) and no longer responds to your current treatment.

How does LUTATHERA® work?

The tumour needs to have certain proteins (somatostatin receptors) on the surface of its cells in order for the medicine to work. LUTATHERA binds to these receptors, delivering radioactivity directly to the tumour cells, causing their death.

The use of LUTATHERA involves exposure to radioactivity. Your doctor and nuclear medicine doctor have considered that the clinical benefit that you will obtain from LUTATHERA outweighs the risk of toxicity due to radiation.

LUTATHERA® must not be used if

- If you are allergic to lutetium (^{177}Lu) oxodotreotide or to any of the other ingredients in this medicine
- If you are pregnant
- If your kidneys are seriously impaired

What are the ingredients in LUTATHERA®?
- The active substance is lutetium (^{177}Lu) oxodotreotide.
- The other ingredients are: acetic acid (to adjust acid content), sodium acetate (to adjust acid content), gentisic acid (for stability), ascorbic acid (for stability), diethylene triamine pentaacetic acid (DTPA) (removes unwanted chemical substances from the solution), sodium chloride (adjusts concentration of the substances in the product), water for injection (see section 2 "LUTATHERA contains sodium").

LUTATHERA® comes in the following dosage forms:
Solution for Intravenous Injection, 370 MBq/mL. MBq is a measure of radioactivity.

BEFORE you are given LUTATHERA®, talk to your doctor if:
- You are under 18 years of age
- You are pregnant or plan to become pregnant. Exposure to radiation during pregnancy may harm your unborn baby. Women who are able to become pregnant should use effective contraception and avoid getting pregnant during treatment with LUTATHERA and for 7 months after your last dose of LUTATHERA.
- You are breastfeeding or plan to breastfeed. It is not known if LUTATHERA passes into your breast milk. Breast feeding must be stopped. If treatment with LUTATHERA during breast feeding is necessary, the child must be weaned.
- You have mild to moderate chronic kidney disease
- You suffer from urinary incontinence (uncontrollable urination)
- You have a kidney or urinary tract abnormality, including urinary track obstruction
- You have mildly altered blood cell counts. LUTATHERA can lead to a decrease in the number of your red blood cells (responsible for transporting the oxygen from the lungs to the different organs), platelets (cells that help the blood to clot), and other blood cells such as white blood cells (helps to fight infection). Before starting treatment and before each subsequent treatment, your doctor will perform blood tests. Depending on the results of these tests your doctor will decide if the treatment can be started, can be continued, or needs to be adjusted, postponed or discontinued.
- You previously received anti-cancer treatment (chemotherapy, radiation therapy)
- You have previously received any radionuclide therapy (therapy with a radioactive medicine)
- You had any other type of cancer within the last 5 years

LUTATHERA® contains sodium
This medicine contains 0.14 mmol (3.2 mg) of sodium per mL. To be taken into consideration by patients on controlled sodium diet.

Other warnings you should know about:
Talk to your doctor before you are given LUTATHERA® as it may cause:
- Secondary blood cancer (myelodysplastic syndrome or acute leukaemia) which can rarely occur several years after you have completed LUTATHERA treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LUTATHERA®

- Somatostatin analogues (drugs similar to LUTATHERA)– you may be asked to stop and/or adapt your treatment for a short period of time while receiving LUTATHERA.

How to take LUTATHERA®:

LUTATHERA will be administered intravenously (into your arm) under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

There are strict laws on the use, handling and disposal of radiopharmaceutical products like LUTATHERA. It will only be used in special controlled areas. Your physician will inform you when you can leave the controlled area or hospital.

Usual dose:

The recommended dose to be administered is 7.4 GBq (gigabecquerel, the unit used to express radioactivity) of LUTATHERA® in a single infusion into your vein, which is given at 4 times once every 8 weeks.

In addition to the LUTATHERA injection, an infusion with amino acids (substances present in many foods and in muscles) will be given to you in order to protect your kidneys. This might cause nausea and vomiting; you will also receive an injection before the start of treatment to reduce these symptoms.

Duration of procedure:

Your physician will inform you about the usual duration of the procedure. The LUTATHERA® infusion takes 20 to 30 minutes; but the complete administration procedure will take approximately 5 hours.

Treatment monitoring:

Treatment with LUTATHERA® can have an impact on blood cells, liver and kidneys. Your doctor will ask you to have regular blood tests in order to detect any side effects as early as possible. Based on the results, your physician may decide to delay or stop your treatment with this medicine.

After administration of LUTATHERA®:

Drink a sufficient amount of water (1 glass every hour) necessary to urinate every hour on the day of infusion and the day after. Try to defecate every day, use a laxative if necessary. These steps are needed to help remove the medicine from your body.

Because this medicine is radioactive, you will have to follow the instructions described below to minimize radiation exposure to others.

<u>General rule:</u>

You must avoid close contact with people who live with you and should try to keep a distance of at least one meter for 7 days after you receive LUTATHERA. When together for a prolonged period, a distance of 2 meters or more should be maintained.

Use of toilets:
Toilets must be used in a seated position, even for men. It is absolutely necessary to use toilet paper each time. It is also important to wash your hands to avoid contaminating the door handles.

Contact with children and pregnant women
It is strongly recommended to limit contact with children and pregnant women for 7 days after you receive LUTATHERA.

Contact with spouse and people in the family circle
During 7 days after LUTATHERA administration, sleep in separate beds at a distance of at least 2 meters. If your partner is pregnant, extend this time to 15 days.

People who need extra assistance
People who are confined to bed or have reduced mobility will preferably receive assistance by a care provider. It is recommended that when providing assistance in the bathroom, the care provider wears disposable gloves for 7 days after administration. In the case of the use of special medical equipment such as catheters, colostomy bags, bedpan, water nozzle, or anything that could be contaminated by your body fluids, these must be emptied immediately in the toilet and then cleaned. If anyone helps you clean up vomit, blood, urine, or stool they should wear plastic gloves. The gloves should then be disposed of in a specific trash plastic bag (according to "Trash recommendations" below).

Dishes and bathroom accessories
Take special precautions during the 7 days after treatment:
- Flush all wipes and/or toilet paper down the toilet immediately after use,
- Always wash your hands well after using the toilet,
- Take a shower every day,
- Flush any tissues or any other items that contain anything from your body, such as blood, urine and faeces down the toilet. Items that cannot be flushed down the toilet, such as menstrual pads and bandages, must be placed in specific trash plastic bags (according to "Trash recommendations" below).
- Wash your underwear, pyjamas, sheets and any clothes that contain sweat, blood or urine separately from the laundry of other members of your household, using a standard washing cycle. You do not need to use bleach and do not need extra rinses.

Trash recommendations
Keep the specific plastic trash bags separated from the other trash. Keep the bags away from children and animals.

A member of the hospital staff will tell you how and when to get rid of these trash bags. You might be asked to bring the bag back to your treatment facility, or, after 70 days, the bag may be removed as the other household waste.

Hospitalisation and emergency care
If for any reason you require emergency medical assistance or an unplanned hospitalisation during the 3 months after your treatment, you should inform the medical providers that you have

been treated with LUTATHERA. You should carry your discharge letter with you at all times, so that you can provide information on the reason for use, date and dose of LUTATHERA.

Travel
Keep your discharge letter with you whenever you are travelling for at least 3 months after treatment.

Other precautions
The nuclear medicine physician will inform you if you need to take any other special precautions after receiving this medicine. Contact your nuclear medicine physician if you have any questions.

Overdose:
An overdose is unlikely because of how LUTATHERA® is packaged and administered. However, in the case of an overdose, you will receive the appropriate treatment.

Should you have any further question on the use of this medicine, please ask the nuclear medicine doctor who supervises the procedure.

What are possible side effects from using LUTATHERA®?
Like all medicines, this medicine can cause side effects, although not everybody gets them. LUTATHERA side effects are mainly linked to radioactivity and the amino acid co-infusion. Your physician will perform blood tests before starting treatment and before each treatment cycle to check your number of blood cells and platelets, kidney function, and liver function. It is important that you keep any appointments to give the blood samples needed for the tests.

Very common side effects (may affect more than 1 in 10 people):
- Nausea (usually during the first 24 hours)
- Vomiting (usually during the first 24 hours)
- Abdominal pain
- Diarrhoea
- Fatigue (possibly delayed for more than 24 hours after treatment)
- Decreased appetite
- Pain (including back pain, arms, legs, joints, chest, bone, side or neck)
- Headache
- Dizziness (vertigo)
- Fluid retention (peripheral oedema)
- Abdominal bloating (abdominal distension)
- Flushing
- Anxiety
- Increase in blood pressure (hypertension)
- Hair loss (alopecia)
- Decrease in red blood cells (anaemia)
- Decrease in blood lymphocytes (lymphopenia)
- Decrease in blood platelets (thrombocytopenia)

- Decrease in blood neutrophils (neutropenia)
- Decrease in white blood cells (leukopenia)
- Change in kidney function (decreased urine output, increased blood creatinine, increased potassium in blood, increase in blood urea or uric acid, change in urine color due to protein or blood in urine, renal failure)
- Cough
- Trouble breathing (dyspnoea)
- Increased blood sugar (hyperglycaemia)
- Decreased blood calcium (hypocalcaemia)
- Increased blood sodium (hypernatraemia)
- Decrease in blood sugar (hypoglycaemia)
- Increased blood potassium (hyperkalaemia)
- Decreased blood potassium (hypokalaemia)
- Increase in liver enzymes (alkaline phosphatase, Gamma-glutamyltransferase, Aspartate aminotransferase, Alanine aminotransferase)
- Increase in blood bilirubin

Common side effects (may affect up to 1 in 10 people):
- Constipation
- Indigestion (dyspepsia)
- Gas (flatulence)
- Fluid accumulation in the abdominal region (ascites) or around the lungs (pleural effusion)
- Pain in the upper abdomen
- Abdominal discomfort
- Inflammation of the stomach lining (gastritis)
- Sore mouth (stomatitis)
- Difficulty swallowing (dysphagia)
- Anal bleeding (rectal haemorrhage)
- Weakness (asthenia)
- Fever (pyrexia)
- Influenza like illness
- Injection site pain
- Muscle spasms
- Injection site reaction
- Chills
- Chest discomfort
- Swelling
- Weight loss
- Change in heart function (increase or decrease in heart rate, inability to pump enough blood)
- Increased blood lymphocyte count (lymphocytosis)
- Decreased blood sodium (hyponatraemia)
- Dehydration
- Sleepiness (somnolence)
- Shaking (tremor)

- Decrease in blood magnesium (hypomagnesaemia)
- Vitamin D deficiency
- Disturbed sense of taste (dysgeusia)
- Fainting/loss of consciousness (syncope)
- Lack of energy (lethargy)
- Disturbed sense of smell (parosmia)
- Tingling sensation (paraesthesia)
- Low blood pressure (hypotension)
- Hot flush
- Dry mouth
- Trouble sleeping (insomnia)
- Urinary incontinence
- Rash
- Skin itching (pruritus) and redness (erythema)
- Dry skin
- Chest pain (angina pectoris)
- Bruising (contusion)
- Reduced bile flow (cholestasis)
- Decreased thyroid function (hypothyroidism, secondary hypothyroidism)
- Diabetes mellitus
- Allergic reaction (hypersensitivity)
- Infections (includes pneumonia, herpes zoster, respiratory tract infection, influenza, urinary tract infection, nasopharyngitis, bronchitis, Clostridium difficile infection)
- Intestinal obstruction (including small intestine)
- Blood cancers (myelodysplastic syndrome, acute leukaemia)
- General decline in physical health
- Inflammation of small bulging pouches of the large intestine (diverticulitis)
- Wheezing or high-pitched whistling sound
- Change in voice (dysphonia)
- Depression
- Agitation
- Kidney stones
- Falls
- Sprains, fractures
- Tumour progression (malignancy)
- Double vision (diplopia)
- Ringing in the ears (tinnitus)
- Breast growth in men (gynecomastia)
- Inflammation of the gallbladder (cholecystitis)
- Increased blood calcium (hypercalcaemia)
- Cardiac failure (including myocardial infarction)
- Gallstones
- General feeling of discomfort, illness, abnormal or uneasiness (malaise)
- Death

Uncommon side effects (may affect up to 1 in 100 people):
- Bone marrow failure
- Carcinoid syndrome
- Gastrointestinal pain, bleeding
- Tear in gastrointestinal tract
- Lower abdominal pain
- Inguinal hernia
- Inflamed pancreas (pancreatitis)
- Blood in stool (melaena)
- Disturbance in walking
- Decreased blood albumin (hypoalbuminaemia)
- Decreased blood phosphate (hypophosphataemia)
- Blood potassium decreased (hypokalaemia)
- Liver failure
- Vomiting of blood (haematemesis)
- Bloody fluid accumulation (haemorrhagic ascites)
- Blood clots (including pulmonary embolism and deep vein thrombosis)
- Disruption of intestinal mobility (ileus)
- Spinal cord compression
- Confusion (disorientation)
- Delirium
- Panic attack
- Bleeding (including nose bleeds)

LUTATHERA contributes to your overall long-term cumulative radiation exposure (the amounts of radiation that an individual typically receives from different sources over a longer period of time). Long-term cumulative radiation exposure may increase your risk for developing new cancers and increase the chances for your future children to have hereditary (from a parent) abnormalities. LUTATHERA has been associated with an increased risk for blood cancers.

If you get any side effects talk to your physician. This includes any possible side effects not listed in this leaflet.

Symptom/effect	Talk to your healthcare professional	
	Only if severe	In all cases
VERY COMMON		
Anaemia (marked by weakness, paleness, shortness of breath, headaches, dizziness, heart palpitations)		X
Thrombocytopenia, Lymphopenia, Neutropenia, Leukopenia (marked by unusual bruising, more bleeding than usual after injury, fever, catching infections more frequently)		X
Kidney injury (marked by changes in urine output and blood biochemistry)		X

Liver changes (marked by changes in liver protein levels in the blood)		X
COMMON		
Chronic blood syndromes (myelodysplastic syndrome and acute leukaemia) (marked by feeling tired, dizzy, weak, shortness of breath, pale skin, infections and abnormal bleeding)		X
Neuroendocrine Hormonal Crisis (marked by flushing, diarrhoea, hypotension, difficulty breathing usually within 24 hours of LUTATHERA dose)		X

This is not a complete list of side effects. For any unexpected effects while taking LUTATHERA, talk to your healthcare provider.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

If you want more information about LUTATHERA®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or the manufacturer's website http://www.adacap.com.

This leaflet was prepared by Advanced Accelerator Applications

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