1.6 外国における使用状況等に関する資料

1.6 外国における使用状況等に関する資料

Advanced Accelerator Applications 社は， 2017 年 9 月に欧州経済領域 (European Economic Area：EEA) の 31 ヶ国で最初に本剤の承認を取得し，続いて，2018 年 1 月に米国，2019 年 1 月にカナダ，2019 年 5 月にイスラエル，2019 年 6 月にスイスで承認を取得している。なお，オーストラリアでは未承認である (2020 年 6 月末現在で，本剤の開発は行われていない) 。効能又は効果は，いずれの国又は地域においても，ソマトスタチン受容体陽性の胃腸膵神経内分泌腫瘍である。承認された順で，欧州，米国の添付文書を添付する。

表 1.6-1 に欧米等 6 ヶ国 (米・英・独・仏・加・豪) における承認状況及び効能・効果を示す。

表 1.6-1. 欧米等 6 ヵ国（米・英・独・仏・加・豪）における
承認状況及び効能・効果一覧

国名	承認年月	効能・効果
米国	2018 年 1 月	成人における前腸，中腸及び後腸神経内分泌腫瘍を含む，ソマトスタチン受容体陽性の胃腸膵神経内分泌腫瘍
英国	2017 年 9 月	成人における切除不能又は転移性，進行性，高分化型（G1 及び G2），ソマトスタチン受容体陽性の胃腸膵神経内分泌腫瘍
ドイツ		
フランス		
カナダ	2019 年 1 月	成人における進行した切除不能又は転移性，高分化型，ソマトスタチン受容体陽性の胃腸膵神経内分泌腫瘍
オーストラリア	未承認	

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lutathera 370 MBq/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The total amount of radioactivity per single dose vial is 7,400 MBq at the date and time of infusion. Given the fixed volumetric activity of 370 MBq/mL at the date and time of calibration, the volume of the solution is adjusted between 20.5 mL and 25.0 mL in order to provide the required amount of radioactivity at the date and time of infusion.

Lutetium (^{177}Lu) has a half-life of 6.647 days. Lutetium (^{177}Lu) decays by β^- emission to stable Hafnium (^{177}Hf) with the most abundant β^- (79.3%) having a maximum energy of 0.497 MeV. The average beta energy is approximately 0.13 MeV. Low gamma energy is also emitted, for instance at 113 keV (6.2%) and 208 keV (11%).

Excipient with known effect
Each mL of solution contains 0.14 mmol (3.2 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Lutathera should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

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

Posology

Adults

The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7,400 MBq each. The recommended interval between each administration is 8 weeks which could be extended up to 16 weeks in case of dose modifying toxicity (DMT) (see Table 5).

For renal protection purpose, an amino acid solution must be administered intravenously during 4 hours. The infusion of the amino acid solution should start 30 minutes prior to start of Lutathera infusion.

Amino acid solution

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

Table 1. Composition of the standard amino acid solution

Compound	**Amount**
Lysine	25 g
Arginine	25 g
Sodium chloride 9 mg/mL (0.9%) solution for injection	1 L

Alternatively, some commercially available amino acid solutions can be used if compliant with the specification described in Table 2.

Table 2. Specification of commercially available amino acid solutions

Characteristic	**Specification**
Lysine content	Between 18 and 24 g
Arginine content	Between 18 and 24 g
Volume	1.5 L to 2.2 L
Osmolarity	< 1,050 mOsmol

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 total volume to be infused and lower osmolarity.

Treatment monitoring

Before each administration and during the treatment, biological tests are required to re-assess the patient's condition and adapt the therapeutic protocol if necessary (dose, infusion interval, number of infusions).

The minimum laboratory tests needed before each infusion are:

- Liver function (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], albumin, bilirubin)
- Kidney function (creatinine and creatinine clearance)
- Haematology (Haemoglobin [Hb], white blood count, platelet count)

These tests should be performed at least once within 2 to 4 weeks prior to administration and shortly before the administration. It is also recommended to perform these tests every 4 weeks for at least 3 months after the last infusion of Lutathera and every 6 months thereof, in order to be able to detect possible delayed adverse reactions (see section 4.8). Dosing may need to be modified based on the tests results.

Dose modification
In some circumstances, it might be necessary to temporarily discontinue treatment with Lutathera, adapt the dose after the first administration or even discontinue the treatment (see Table 3 - Table 5 and Figure 1).

Table 3. Criteria for permanent discontinuation of treatment with Lutathera

Discontinue Lutathera administrations in patients who have experienced or are at risk of any of the following conditions during treatment:
Severe heart failure (defined as grade III or IV of the New York Heart Association (NYHA) classification)
Pregnancy
Hypersensitivity to the active substance or to any of the excipients of this medicinal product
When specific adverse reactions to this medicinal product persist or reoccur, such as delayed grade 3-4 (G3-G4) hematotoxicity (see Table 5).

Table 4. Criteria for temporary discontinuation treatment with Lutathera

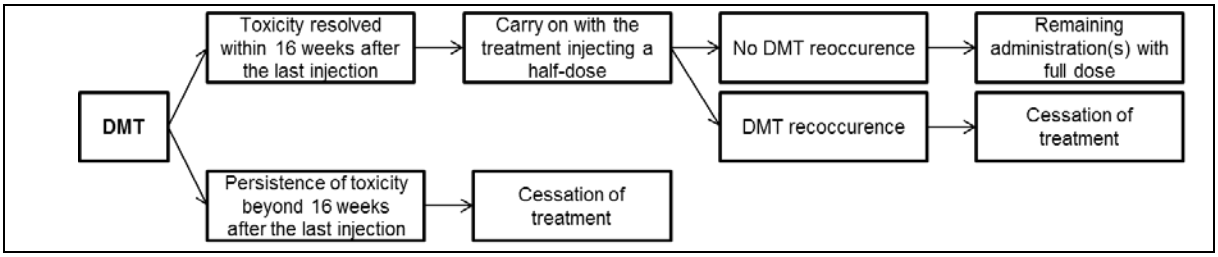
Temporarily discontinue treatment with Lutathera in the following conditions:	
Criterion	**Action**
Occurrence of an intercurrent disease (e.g. urinary tract infection), which according to the physician could increase the risks associated to Lutathera administration.	Temporarily discontinue the treatment until resolution or stabilisation. Treatment can be resumed after resolution or stabilisation.
Major surgery.	Wait 12 weeks after the date of surgery to administer Lutathera.
Major or some specific adverse reactions to Lutathera.	See Table 5.

Table 5. Instructions for dose modifications

Adjust Lutathera dosing for the following severe adverse reactions:	
Severe adverse reactions **Dose-modifying toxicity (DMT) criteria**	**Action**
Thrombocytopenia of grade 2 or superior (CTCAE)**.	1. Temporarily discontinue the treatment. 2. Monitor biological parameters every 2 weeks, and treat appropriately if needed; in case of renal failure, good hydration is recommended if not otherwise contraindicated. a. **<u>If the observed toxicity continues</u>** beyond 16 weeks after the last infusion, treatment with Lutathera must be definitively stopped. b. **<u>If the observed toxicity resolves</u>** within 16 weeks after the last infusion, it is possible to continue the treatment with Lutathera by infusing a half dose (3,700 MBq)*. 3. If the half dose is well tolerated (i.e. no DMT reoccurrence), the next remaining treatment administration(s) should continue with full dose (i.e. 7,400 MBq); but, if DMT recurs after treatment with a half dose, treatment with Lutathera must be definitively stopped.
Any haematological toxicity of grade 3 or superior (CTCAE)**, except lymphopenia.	
Renal toxicity defined as an estimated creatinine clearance < 40 mL/min, or a 40% increase compare to the baseline serum creatinine level with a decrease of over 40% compared to the baseline creatinine clearance.	
Liver toxicity defined as either: • Bilirubinemia > 3 times the upper limit of normal, • Or hypoalbuminemia < 30 g/L with a decreased prothrombin ratio < 70%.	
Any other CTCAE grade 3 or grade 4 toxicity** possibly related to Lutathera.	

* The concomitant amino acids infusion is always administered at full dose (see section 4.4).
** CTCAE: Common Terminology Criteria for Adverse Events, National Cancer Institute

Figure 1. Scheme of instructions for dose modifications



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

Renal impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. The pharmacokinetic profile of lutetium (^{177}Lu) oxodotreotide in patients with severe renal impairment (creatinine clearance < 30 mL/min) has not been studied, therefore treatment with Lutathera in those patients is contraindicated (see section 4.3). As this medicinal product is known to be substantially excreted by the kidneys, patients with mild to moderate impaired renal function should be more frequently monitored during the treatment.
For additional details about the treatment of patient with renal impairment see Table 5 in section 4.2 and section 4.4.

Hepatic impairment
Careful consideration of the activity to be administered to patients with hepatic impairment is required since an increased radiation exposure is possible in these patients. The pharmacokinetic profile of lutetium (^{177}Lu) oxodotreotide in patients with severe hepatic impairment has not been studied, therefore treatment with Lutathera in those patients is not recommended.
For additional details about the treatment of patient with mild to moderate hepatic impairment, see Table 5 and section 4.4.

Paediatric population
There is no relevant use of Lutathera in the paediatric population in the indication of treatment of GEP-NETs (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma).

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

Lutathera must be administered by slow intravenous infusion over approximately 30 minutes, concomitantly with amino acid solution administered by contralateral intravenous infusion. 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 section 6.6).

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.

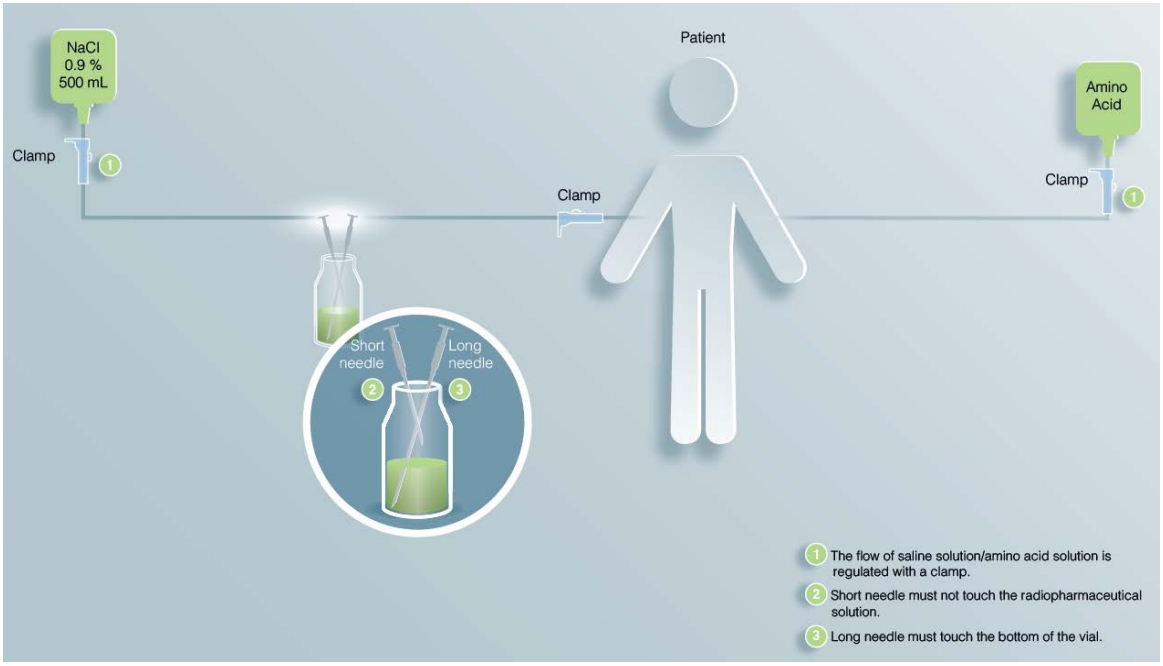
Room and equipment preparation:
- Administration room:
  - The floor and the furniture should be covered with tissue paper to avoid any accidental contamination

- 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 2):
- 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 2. 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 time 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.
   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).
7. 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.

8. To ensure complete administration, the Lutathera vial should be kept under even pressure. The level of solution in the vial should remain constant during the entire infusion.
   Visual controls of the solution levels should be repeated during the administration by direct visual control (when PMMA container is used) or using a pair of tongs to handle the vial when the lead shipping container is used.
9. 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.
10. 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 summarises the required procedures during a treatment course with Lutathera using the gravity method:

Table 6. 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

For instructions on the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.
For recommendations in case of extravasation, see section 4.4.

4.3 Contraindications

- Hypersensitivity to the active substance, to any of the excipients listed in section 6.1.
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).
- Kidney failure with creatinine clearance < 30 mL/min

4.4 Special warnings and precautions for use

Patients with risk factors
A patient presenting with any of the conditions below is more prone to develop adverse reactions. Therefore, it is recommended to monitor those patients more frequently during the treatment. Please see Table 5 in case of dose modifying toxicity.

- Renal or urinary tract morphological abnormalities;
- Urinary incontinence;
- Mild to moderate chronic kidney disease with creatinine clearance ≥ 50 mL/min;
- Previous chemotherapy;
- Hematologic toxicity greater or equal to grade 2 (CTCAE) before treatment other than lymphopenia;
- Bone metastasis;

- Previous oncologic radiometabolic therapies with ^{131}I-compounds or any other therapy using unshielded radioactive sources;
- History of other malignant tumours unless the patient is considered to be in remission for at least 5 years.

Given the mechanism of action and the tolerance profile of Lutathera (see section 4.8), it is not recommended to start treatment in the following cases:
- Previous external beam radiotherapy involving more than 25% of the bone marrow;
- Severe heart failure defined as class III or IV in the NYHA classifications;
- Kidney failure with creatinine clearance < 50 mL/min;
- Impaired haematological function with either Hb < 4.9 mmol/L (8 g/dL), platelets < 75 G/L ($75x10^3/mm^3$), or leucocytes < 2 G/L ($2,000/mm^3$) (except lymphopenia);
- Liver impairment with either total bilirubinemia > 3 times the upper limit of normal or albuminemia < 30 g/L and prothrombin ratio decreased < 70%;
- Patients with somatostatin receptor negative or mixed visceral lesions (tumour uptake score < 2) according to somatostatin receptor imaging.

Nevertheless, if the physician decides to start the treatment, clear information should be given to the patient regarding the risks associated with the administration of Lutathera. The posology can be adapted according to the patient's status at the discretion of the physician.

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

Renal protection and renal impairment

Because lutetium (^{177}Lu) oxodotreotide is almost exclusively eliminated through the renal system, it is mandatory to concomitantly administer an amino acid solution containing the amino acids L-lysine and L-arginine. The amino acids solution will help to decrease reabsorption of lutetium (^{177}Lu) oxodotreotide through the proximal tubules, resulting in a significant reduction in the kidney radiation dose (see section 4.2). When the recommended concomitant amino acids infusion is delivered over a 4 hour time span, a mean reduction in kidney radiation exposure of about 47% has been reported.
It is not recommended to decrease the amount of amino acid solution in case of Lutathera dose adaptation.
Patients should be encouraged to empty their bladder as frequently as possible during the administration of amino acids and the hours after administration.
Renal function as determined by serum creatinine and calculated creatinine clearance must be assessed at baseline, during and at least for the first year after treatment (see section 4.2).
For information on the use in patients with renal impairment, see section 4.2.

Hepatic impairment

Since many patients referred for Lutathera therapy have hepatic metastasis, it may be common to observe patients with altered baseline liver function. Therefore, it is recommended to monitor ALAT, ASAT, bilirubin and albumin serum during treatment (see section 4.2).
For information on the use in patients with hepatic impairment, see section 4.2.

Nausea and vomiting

To avoid treatment-related nausea and vomiting, an intravenous bolus of an antiemetic medicinal product should be injected 30 minutes before the start of amino acid solution infusion (see section 4.2).

Concomitant use of somatostatin analogues

Concomitant use of cold somatostatin analogues may be needed for disease symptoms control. Administration of long acting somatostatin analogues should be avoided within 30 days prior to the administration of Lutathera. If necessary, patients may be treated with short acting somatostatin analogues during the 4 weeks preceding Lutathera administration, until 24 hours before the administration of Lutathera.

Bone marrow function and/or blood count disorders
Because of the potential for undesirable effects, blood counts must be monitored at baseline and during treatment, and until resolution of any eventual toxicity (see section 4.2).

Myelodisplastic syndrome and acute leukaemia
Late-onset myelodisplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with Lutathera (see section 4.8), occurring approximately 28 months (9 – 41) for MDS and 55 months (32 - 125) for AL after the end of treatment. Etiology of this therapy related secondary myeloid neoplasms (t-MNs) is unclear. Factors such as age >70 years, impaired renal function, baseline cytopenias, prior number of therapies, prior exposure to chemotherapeutic agents (specifically alkylating agents), and prior radiotherapy are suggested as potential risks and/or predictive factors for MDS/AL.

Hormonal crises
Crises due to excessive release of hormones or bioactive substances may occur following treatment with Lutathera, therefore observation of patients by overnight hospitalisation should be considered in some cases (e.g. patients with poor pharmacologic control of symptoms). In case of hormonal crises, recommended treatments are: intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting.

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

Radioprotection rules
Lutathera should always be infused through an intravenous catheter placed exclusively for its infusion. The adequate position of the catheter should be checked before and during infusion.

The patient treated with Lutathera should be kept away from others during the administration and up to reaching the radiation emission limits stipulated by applicable laws, usually within the 4-5 hours following medicinal product administration. The nuclear medicine physician should determine when the patient can leave the controlled area of the hospital, i.e. when the radiation exposure to third parties does not exceed regulatory thresholds.

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

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

Before the patient is released, the nuclear physician should explain the necessary radioprotection rules of interacting with family members and third parties, and the general precautions the patient must follow during daily activities after treatment (as given in next paragraph and the package leaflet) to minimize radiation exposure to others.
Close contact with other people should be restricted during 7 days following an administration of Lutathera, and for children and pregnant women it should be limited to less than 15 minutes for each

day while keeping a distance of at least 1 meter. Patients should sleep in a separate bedroom for 7 days, what should be extended to 15 days in case of pregnant partners or children.

Recommended measures in case of extravasation
Disposable waterproof gloves should be worn. The infusion of the medicinal product must be immediately ceased and the administration device (catheter, etc.) removed. The nuclear medicine physician and the radiopharmacist should be informed.
All the administration device materials should be kept in order to measure the residual radioactivity and the activity actually administered and eventually the absorbed dose should be determined. The extravasation area should be delimited with an indelible pen and a picture should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated. To continue Lutathera infusion, it is mandatory to use a new catheter possibly placing it in a contralateral venous access.

No additional medicinal product can be administered to the same side where the extravasation occurred.
In order to accelerate medicinal product dispersion and to prevent its stagnation in tissue, it is recommended to increase blood flow by elevating the affected arm. Depending on the case, aspiration of extravasation fluid, sodium chloride 9 mg/mL (0.9%) solution for injection flush injection, or applying warm compresses or a heating pad to the infusion site to accelerate vasodilation should be considered.

Symptoms, especially inflammation and/or pain, should be treated. Depending on the situation, the nuclear medicine physician should inform the patient about the risks linked to extravasation injury, and give advice about potential treatment and necessary follow-up requirements. The extravasation area must be monitored until the patient is discharged from the hospital. Depending upon its seriousness, this event should be declared as an adverse reaction.

Patients with urinary incontinence
During the first 2 days following administration of this medicinal product, special precautions should be taken with patients with urinary incontinence to avoid spread of radioactive contamination. This includes the handling of any materials possibly contaminated with urine.

Patients with brain metastases
There is no efficacy data in patients with known brain metastases therefore individual benefit-risk must be assessed in these patients.

Secondary malignant neoplasms
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation exposure are less than from the disease itself.

Specific warnings
This medicinal product contains up to 3.5 mmol (81.1 mg) sodium per dose. This should be taken into consideration in patient on controlled sodium diet.

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Somatostatin and its analogues competitively bind to somatostatin receptors. Therefore, administration of long acting somatostatin analogues should be avoided within 30 days prior to the administration of this medicinal product. If necessary, patients may be treated with short acting somatostatin analogues during the 4 weeks until 24 hours preceding Lutathera administration.

There is some evidence that corticosteroids can induce down-regulation of SST2 receptors. Therefore, as a matter of cautiousness, repeated administration of high-doses of glucocorticosteroids should be avoided during Lutathera treatment. Patients with a history of chronic use of glucocorticosteroids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known if there is of interaction between glucocorticosteroids used intermittently for the prevention of nausea and vomiting during Lutathera administration. Therefore, glucocorticosteroids should be avoided as preventive anti-emetic treatment. In the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of Lutathera infusion.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in any doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient. Before the use of Lutathera, pregnancy should be excluded using an adequate/validated test.

Contraception in males and females
During treatment with Lutathera and for a minimum of the following 6 months after the end of the treatment, appropriate measures must be taken to avoid pregnancy; this applies to patients of both genders.

Pregnancy
No studies on animal reproductive function have been conducted with lutetium (^{177}Lu) oxodotreotide. Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. The use of Lutathera is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk associated with the ionizing radiation (see section 4.3).

Breast-feeding
It is unknown whether lutetium (^{177}Lu) oxodotreotide is excreted in breast milk. A risk to the suckling child associated with ionising radiation cannot be excluded. Breast-feeding should be avoided during treatment with this medicinal product. If treatment with Lutathera during breast-feeding is necessary, the child must be weaned.

Fertility
No animal studies have been performed to determine the effects of lutetium (^{177}Lu) oxodotreotide on the fertility of either gender. Ionizing radiations of lutetium (^{177}Lu) oxodotreotide may potentially have temporary toxic effects on female and male gonads. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm or eggs can be discussed as an option to patients before the treatment.

4.7 Effects on ability to drive and use machines

Lutathera has no or negligible influence on the ability to drive and use machines. Nevertheless, the general condition of the patient and the possible adverse reactions to treatment must be taken into account before driving or using machines.

4.8 Undesirable effects

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

The most common adverse reactions in patients receiving Lutathera treatment were nausea and vomiting which occurred at the beginning of the infusion in 58.9% and 45.5% of patients, respectively. The causality of nausea / vomiting is confounded by the emetic effect of the concomitant amino acids infusion administered for renal protection.

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

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

Tabulated list of adverse reactions
The adverse reactions are listed in Table 7 according to the frequency and the MedDRA System Organ Class (SOC). The frequencies are categorized as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 7. Frequency of adverse reactions reported from clinical trials and from post-marketing surveillance

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
Infections and infestations			Conjunctivitis Respiratory tract infection Cystitis Pneumonia Herpes zoster Ophthalmic herpes zoster Influenza Staphylococcal infections Streptococcal bacteraemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome)	Acute myeloid leukaemia Acute leukaemia Chronic myelomonocytic leukaemia
Blood and lymphatic system disorders	Thrombocytopenia[2] Lymphopenia[3] Anaemia[4] Pancytopenia	Leukopenia[5] Neutropenia[6]	Refractory cytopenia with unilineage dysplasia Nephrogenic anaemia Bone marrow failure Thrombocytopenic purpura
Immune system disorders			Hypersensitivity
Endocrine disorders		Secondary hypothyroidism	Hypothyroidism Diabetes mellitus Carcinoid crisis Hyperparathyroidism
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia Dehydration Hypomagnesaemia Hyponatremia	Hypoglycaemia Hypernatremia Hypophosphatemia Tumor lysis syndrome Hypercalcaemia Hypocalcaemia Hypoalbuminaemia Metabolic acidosis
Psychiatric disorders		Sleep disorders	Anxiety Hallucination

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon
			Disorientation
Nervous system disorders		Dizziness Dysgeusia Headache[10] Lethargy Syncope	Formication Hepatic encephalopathy Paraesthesia Parosmia Somnolence Spinal cord compression
Eye disorders			Eye disorders
Ear and labyrinth disorders			Vertigo
Cardiac disorders		Electrocardiogram QT prolonged	Atrial fibrillation Palpitations Myocardial infarction Angina pectoris Cardiogenic shock
Vascular disorders		Hypertension[7] Flushing Hot flush Hypotension	Vasodilatation Peripheral coldness Pallor Orthostatic hypotension Phlebitis
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Oropharyngeal pain Pleural effusion Sputum increased Choecking sensation
Gastrointestinal disorders	Nausea Vomiting	Abdominal distension Diarrhoea Abdominal pain Constipation Abdominal pain upper Dyspepsia Gastritis	Dry mouth Flatulence Ascities Gastrointestinal pain Stomatitis Haematochezia Abdominal discomfort Intestinal obstruction Colitis Pancreatitis acute Rectal haemorrhage Melaena Abdominal pain lower Haematemesis Haemorrhagic ascites Ileus
Hepatobiliary disorders		Hyperbilirubinaemia[9]	Pancreatic enzymes decreased Hepatocellular injury Cholestasis Hepatic congestion Hepatic failure
Skin and subcutaneous tissue disorders		Alopecia	Rash Dry skin Swelling face Hyperhidrosis Pruritus generalized
Musculoskeletal and connective tissue disorders		Musculoskeletal pain[8] Muscle spasms	
Renal and urinary disorders		Acute kidney injury Haematuria Renal failure Proteinuria	Leukocyturia Urinary incontinence Glomerular filtration rate decreased Renal disorder Acute prerenal failure Renal impairment
General disorders and administration site conditions	Fatigue[1]	Injection site reaction[11] Oedema peripheral Administration site pain Chills Influenza like illness	Injection site mass Chest discomfort Chest pain Pyrexia Malaise Pain Deaths Feeling abnormal
Investigations		Blood creatinine increased	Blood potassium decreased

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

[1] Includes Asthenia and Fatigue
[2] Includes Thrombocytopenia and Platelet count decreased
[3] Includes Lymphopenia and Lymphocyte count decreased
[4] Includes Anaemia and Haemoglobin decreased
[5] Includes Leukopenia and White blood cell count decreased
[6] Includes Neutropenia and Neutrophil count decreased
[7] Includes Hypertension and Hypertensive crisis
[8] Includes Arthralgia, Pain in extremity, Back pain, Bone pain, Flank pain, Musculoskeletal chest pain and Neck pain
[9] Includes Blood bilirubin increased and Hyperbilirubinaemia
[10] Includes Headache and migraine
[11] Includes injection site reaction, injection site hypersensibility, injection site induration, injection site swelling
* Gamma-glutamyltransferase increased
**Alanine amino transferase
*** Aspartate amino transferase
**** Alkaline phosphatase

Description of selected adverse reactions

Bone marrow toxicity

Bone marrow toxicity (myelo-/hematotoxicity) manifested with reversible / transient reductions in blood counts affecting all lineages (cytopenias in all combinations, i.e., pancytopenia, bicytopenias, isolated monocytopenias – anemia, neutropenia, lymphocytopenia, and thrombocytopenia). In spite of an observed significant selective B-cell depletion, no increase in the rate of infectious complications occurs after PRRT.

Cases of irreversible hematological pathologies, i.e., premalignant and malignant blood neoplasms (i.e., myelodysplastic syndrome and acute myeloid leukemia, respectively) have been reported following Lutathera treatment.

Nephrotoxicity

Lutetium (^{177}Lu) oxodotreotide is excreted by the kidney.

The long-term trend of progressive glomerular filtration function deterioration demonstrated in the clinical studies confirms that Lutathera-related nephropathy is a chronic kidney disease that develops progressively over months or years after exposure. An individual benefit-risk assessment is recommended prior to treatment with Lutathera in patients with mild and moderate renal impairment, for additional details see section 4.2 (Table 3) and section 4.4. The use of Lutathera is contraindicated in patients with severe kidney failure (see section 4.3).

Hormonal crises
Hormonal crises related to bioactive substances release (probably due to lysis of the neuroendocrine tumour cells) have rarely been observed and resolved after appropriate medical treatment (section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom: Yellow Card Scheme - Website: www.mhra.gov.uk/yellowcard

Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

Malta: ADR Reporting - Website: www.medicinesauthority.gov.mt/adrportal .

4.9 Overdose

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 the adverse reactions related to radiotoxicity is expected.

In the event of administration of a radiation overdose with Lutathera, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding during the first 48 hours after infusion. It is helpful to estimate the effective dose that was applied.

The following checking should be carried out every week, for the next 10 weeks:
- Hematologic monitoring: white blood cells, platelets, and haemoglobin
- Blood chemistry monitoring: serum creatinine and glycaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10XX04

Mechanism of action
Lutetium (^{177}Lu) oxodotreotide has a high affinity for subtype 2 somatostatin receptors (sst2). It binds to malignant cells which overexpress sst2 receptors.
Lutetium-177 (^{177}Lu) is a β^- emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumour cells with a limited effect on neighbouring normal cells.

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

Clinical efficacy and safety
NETTER-1 phase III study was a multicentre stratified, open labelled, randomized, comparator-controlled, parallel-group study comparing treatment with Lutathera (4 doses of 7,400 MBq every 8 weeks) co-administered with amino acid solution plus best supportive care (BSC; octreotide long acting release [LAR] 30 mg every 4 weeks for symptoms control, replaced by short acting octreotide in the 4 weeks interval before Lutathera administration) to high dose octreotide LAR (60 mg every 4 weeks) in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours. The primary endpoint for the study was progression-free survival (PFS) evaluated

by response evaluation criteria in solid tumours (RECIST 1.1), based on independent radiology assessment. Secondary endpoints included objective response rate (ORR), overall survival (OS), time to tumour progression (TTP), safety and tolerability of the medicinal product and quality of life (QoL). Two hundred thirty-one (231) patients have been randomized to receive either Lutathera (n=117) or octreotide LAR (n=114). Demographics as well as patients and disease characteristics were very balanced between groups with median age of 64 years and 82.1% Caucasian in the general population.

At the time of final per-protocol PFS statistical analysis (cut–off date 24 July 2015), the number of centrally confirmed disease progressions or deaths was 21 events in the Lutathera arm and 70 events in the octreotide LAR arm (Table 8). PFS differed significantly (p<0.0001) between the treatment groups. The median PFS for Lutathera was not reached at the time of analysis whereas the one of octreotide LAR was 8.5 months. The hazard ratio for Lutathera was 0.18 (95% CI: 0.11 - 0.29), indicating 82% reduction in the risk for a patient to progress or die under Lutathera compared to octreotide LAR.

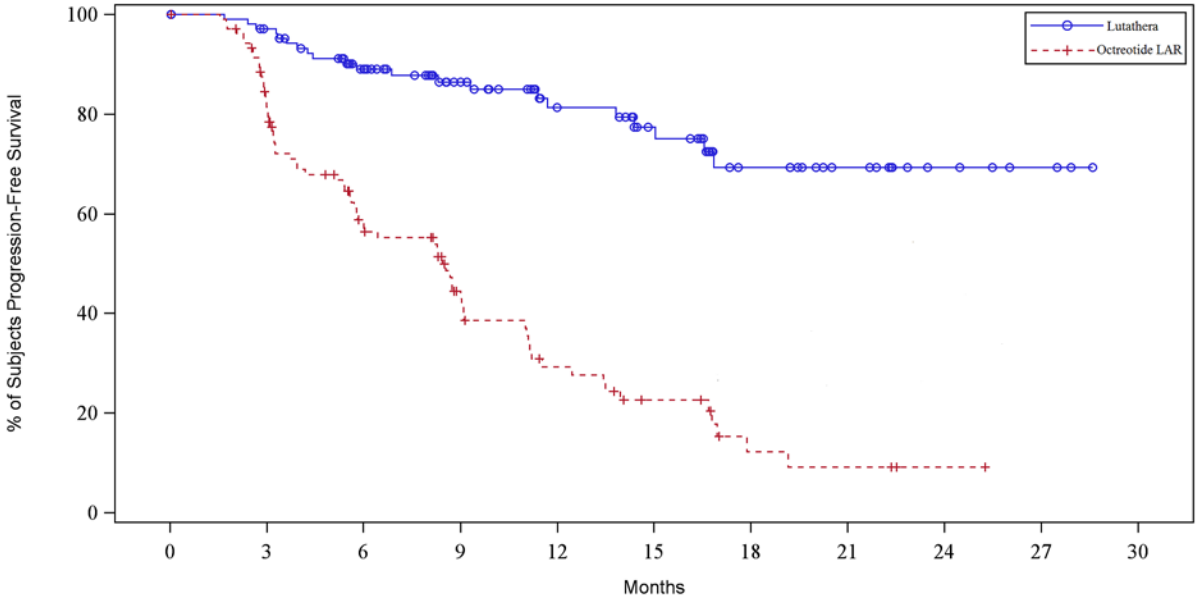
Table 8. PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumour – cut–off date 24 July 2015 (full analyses set (FAS), N=229)

	Treatment	
	Lutathera	**Octreotide LAR**
N	116	113
Patients with events	21	70
Censored patients	95	43
Median months (95%-CI)	Not reached	8.5 (5.8 ; 9.1)
p-value of Log-rank test	<0.0001	
Hazard ratio (95%-CI)	0.177 (0.108 ; 0.289)	

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut–off date 24 July 2015 is depicted in Figure 3.

Figure 3. PFS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - cut–off date 24 July 2015 (NETTER-1 phase III study; FAS, N=229)



At the cut-off date for post-hoc statistical analysis (30 June 2016), the number of centrally confirmed disease progressions or deaths was 30 events in the Lutathera arm and 78 events in the octreotide LAR arm (Table 9). PFS differed significantly (p<0.0001) between the treatment groups. The median PFS for Lutathera was 28.4 months whereas the one of octreotide LAR was 8.5 months. The hazard ratio for Lutathera was 0.21 (95% CI: 0.14 - 0.33), indicating 79% reduction in the risk for a patient to progress or die under Lutathera compared to octreotide LAR.

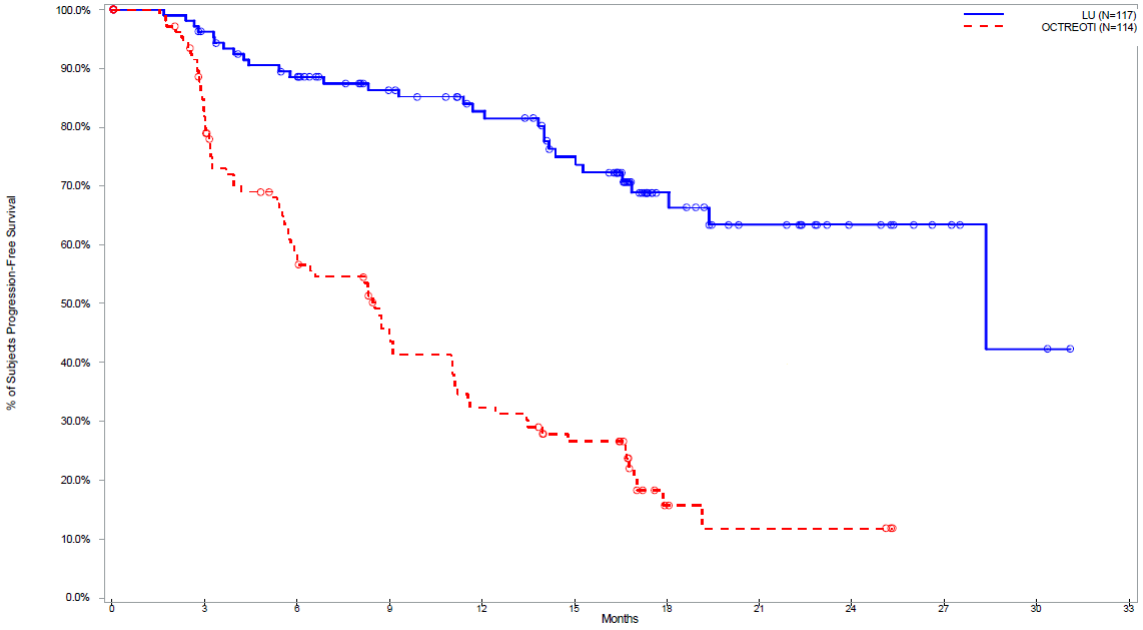
Table 9. PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumour - cut-off date 30 June 2016 (full analyses set (FAS), N=231)

	Treatment	
	Lutathera	**Octreotide LAR**
N	117	114
Patients with events	30	78
Censored patients	87	36
Median months (95%-CI)	28.4 (28.4; NE)	8.5 (5.8; 11.0)
p-value of Log-rank test	<0.0001	
Hazard ratio (95%-CI)	0.214 (0.139 ; 0.331)	

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut-off date 30 June 2016 is depicted in Figure 4.

Figure 4. PFS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - cut-off date 30 June 2016 (NETTER-1 phase III study; FAS, N=231)



With respect to overall survival OS, at the time of interim analysis (24 July 2015), there were 17 deaths in the Lutathera arm and 31 in octreotide LAR 60 mg arm and the hazard ratio was 0.459 in favour of Lutathera, but did not reach the level of significance for interim analysis (HR 99.9915% CI: 0.140, 1.506). OS median was 27.4 months in octreotide LAR arm and was not reached in Lutathera arm. An update conducted about one year after (30 June 2016) showed similar trend with 28 deaths in the Lutathera arm and 43 in octreotide LAR 60 mg arm, an HR of 0.536, and a median OS of 27.4 months in octreotide LAR arm and still not reached in Lutathera arm. The final OS analysis is foreseen after 158 cumulative deaths.

Health Related Quality of Life (HRQOL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (generic instrument) and its neuroendocrine tumour module (EORTC QLQ-GI.NET-21).
The results indicate an improvement in the overall global health-related quality of life up to week 84, for patients on Lutathera treatment as compared to patients on Octreotide LAR arm.

Erasmus phase I/II study was a monocentric single arm open-label study to evaluate the efficacy of Lutathera (7,400 MBq administered for 4 times every 8 weeks) co-administered with amino acid solution in patients with somatostatin receptor positive tumours. The mean age of patients enrolled in

the study was 58.4 years. Most patients were Dutch (811) with the remaining (403) residents of various European and non-European countries. The main analysis has been conducted on 811 Dutch patients with different somatostatin receptor positive tumour types. The ORR (including complete response (CR) and partial response (PR) according to RECIST criteria) and duration of response (DoR) for the FAS Dutch population with gastroenteropancreatic (GEP) and bronchial NETs (360 patients) as well as per tumour type are presented in Table 10.

Table 10. 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**	
All*	360	11	3%	151	42%	183	51%	162	45%	40%	50%	16.3	12.2	17.8
Bronchial	19	0	0%	7	37%	11	58%	7	37%	16%	62%	23.9	1.7	30.0
Pancreatic	133	7	5%	74	56%	47	35%	81	61%	52%	69%	16.3	12.1	21.8
Foregut**	12	1	8%	6	50%	4	33%	7	58%	28%	85%	22.3	0.0	38.0
Midgut	183	3	2%	58	32%	115	63%	61	33%	27%	41%	15.3	10.5	17.7
Hindgut	13	0	0%	6	46%	6	46%	6	46%	19%	75%	17.8	6.2	29.9

CR = Complete response; PR = Partial response; SD = Stable disease; ORR = Objective response (CR+PR); DoR = Duration of response
* Includes Foregut, Midgut and Hindgut; **Foregut NETs other than bronchial and pancreatic

The overall median PFS and OS for the FAS Dutch population with GEP and bronchial NETs (360 patients) as well as per tumour type are presented in Table 11.

Table 11. PFS and OS observed in the Erasmus phase I/II study in Dutch patients with GEP and bronchial NET – (FAS, N=360)

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

PFS = Progression free survival; OS = Overall survival
* Includes Foregut, Midgut and Hindgut; **Foregut NETs other than bronchial and pancreatic

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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Lutathera in all subsets of the paediatric population in the treatment of GEP-NETs (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma). See section 4.2.

5.2 Pharmacokinetic properties

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

Organ uptake
At 4 hours after administration, the distribution pattern of lutetium (^{177}Lu) oxodotreotide shows a rapid uptake in kidneys, tumour lesions, liver and spleen, and in some patients in the pituitary gland and in the thyroid. The co-administration of amino acid solution decreases the kidney uptake, enhancing the elimination of radioactivity (see section 4.4). Biodistribution studies show that lutetium (^{177}Lu) oxodotreotide is rapidly cleared from the blood.
An analysis performed with human plasma to determine the extent of plasma protein binding of non-radioactive compound (lutetium (^{175}Lu) oxodotreotide) showed that about 50% of the compound is bound to plasmatic proteins.
Transchelation of lutetium from lutetium (^{175}Lu) oxodotreotide into serum proteins has not been observed.

Biotransformation
There is evidence , from the analysis of urine samples of 20 patients included in the NETTER-1 phase III Dosimetry, pharmacokinetic and ECG substudy, that lutetium (^{177}Lu) oxodotreotide is poorly metabolized and is excreted mainly as intact compound by renal route.
The high performance liquid chromatography (HPLC) analyses performed on urine samples collected up to 48 hours post infusion showed lutetium (^{177}Lu) oxodotreotide radiochemical purity close to 100% in most of the analysed samples (with lowest radiochemical purity value being greater than 92%), indicating that the compound is eliminated in urine mainly as intact compound.
This evidence confirms what has been previously observed in the Erasmus phase I/II study, in which HPLC analysis of a urine specimen collected 1 hour post administration of lutetium (^{177}Lu) oxodotreotide from one patient receiving 1.85 MBq of lutetium (^{177}Lu) oxodotreotide indicated that the main portion (91%) was excreted unchanged.
These finding are supported by *in vitro* metabolism data in human hepatocytes, in which no metabolic degradation of lutetium (^{175}Lu) oxodotreotide was observed.

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

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

5.3 Preclinical safety data

Toxicological studies with rats have demonstrated that a single intravenous injection of up to 4,550 MBq/kg was well tolerated and no deaths were observed. When testing the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) as a single intravenous injection in rats and dogs at doses up to 20,000 µg/kg (rats) and 3,200 µg/kg (dogs), the compound was well tolerated in both species and no deaths were observed. Toxicity with four repeated administrations, once every 2 weeks, of 1,250 µg/kg of the cold compound in rats and 80 µg/kg in dogs was not observed. This medicinal product is not intended for regular or continuous administration.
Mutagenicity studies und long-term carcinogenicity studies have not been carried out.
Non-clinical data on the cold compound (non-radioactive lutetium (^{175}Lu) oxodotreotide) reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Sodium acetate

Gentisic acid
Ascorbic acid
Pentetic acid
Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

72 hours from the date and time of calibration.

6.4 Special precautions for storage

Store below 25°C.
Store in the original package to protect from ionizing radiation (lead shielding).
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Clear colourless Type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal.
Each vial contains a volume varying from 20.5 to 25.0 mL of solution corresponding to an activity of 7,400 MBq at date and time of infusion.
The vial is enclosed within a lead container for protective shielding.

6.6 Special precautions for disposal and other handling

For single use only.

General warning
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For instruction on preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this medicinal product the integrity of this container and vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.
It is necessary to wear waterproof gloves and suitable aseptic techniques when handling the medicinal product.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

The surface dose rates and the accumulated dose depend on many factors. Measurements on the location and during work are critical and should be practiced for more precise and instructive determination of overall radiation dose to the staff. Healthcare personnel are advised to limit the time of close contact with patients injected with Lutathera. The use of television monitor systems to monitor the patients is recommended. Given the half-life of ^{177}Lu it is specially recommended to avoid internal contamination. It is necessary to use protective high quality (latex/nitrile) gloves to avoid direct contact with the radiopharmaceutical (vial/syringe). For minimising radiation exposure, always use the principles of time, distance and shielding (reducing the manipulation of the vial and using the material already supplied par the manufacturer).

This preparation is likely to result in a relatively high radiation dose to most patients. The administration of 7,400 MBq may result in significant environmental hazard.
This may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered, hence radioprotection rules should be followed (section 4.4). Suitable precautions in accordance with national regulations should be taken concerning the activity eliminated by the patients in order to avoid any contaminations.

Any unused medicinal product or waste material should be disposed according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Advanced Accelerator Applications
20 rue Diesel
01630 Saint Genis Pouilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1226/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The following conclusions on treatment with Lutathera were determined from radiation dosimetry evaluations performed in clinical studies:

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

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

Table 12. Absorbed dose estimates for lutetium (^{177}Lu) oxodotreotide from NETTER-1 phase III study (Olinda output)

Organ	**Organ absorbed dose (mGy/MBq) (n = 20)**	
	Mean	**SD**
Adrenals	0.04	0.02
Brain	0.03	0.02
Breasts	0.03	0.01
Gallbladder Wall	0.04	0.02
Lower Large Intestine Wall	0.03	0.02
Small Intestine	0.03	0.02
Stomach Wall	0.03	0.02
Upper Large Intestine Wall	0.03	0.02
Heart Wall	0.03	0.02
Kidneys	0.65	0.29
Liver	0.49	0.62
Lungs	0.03	0.01
Muscle	0.03	0.02
Ovaries**	0.03	0.01
Pancreas	0.04	0.02
Red Marrow	0.03	0.03
Osteogenic Cells	0.15	0.27
Skin	0.03	0.01
Spleen	0.85	0.80
Testes*	0.03	0.02
Thymus	0.03	0.02
Thyroid	0.03	0.02
Urinary Bladder Wall	0.45	0.18
Uterus**	0.03	0.01
Total Body	0.05	0.03

*n=11 (male patients only)
**n=9 (female patients only)

Radiation dose to specific organs, which may not be the target organ of therapy, can be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Quality controls
The solution should be visually inspected for damage and contamination before use, and only clear solutions free of visible particles should be used. The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes. The vial must not be opened.

If at any time in the preparation of this medicinal product the integrity of this vial is compromised, it should not be used.

The amount of radioactivity in the vial must be measured prior to infusion using a suitable radioactivity calibration system in order to confirm that the actual amount of radioactivity to be administered is equal to the planned amount at the infusion time.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 6.6).

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUTATHERA safely and effectively. See full prescribing information for LUTATHERA.

LUTATHERA® (lutetium Lu 177 dotatate) injection, for intravenous use
Initial U.S. Approval: 2018

----------RECENT MAJOR CHANGES ----------

Dosage and Administration, Preparation and Administration (2.5) 5/2020

---------- INDICATIONS AND USAGE----------

LUTATHERA is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Verify pregnancy status in females of reproductive potential prior to initiating LUTATHERA. (2.1)
- Administer 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. (2.2)
- Administer long-acting octreotide 30 mg intramuscularly 4 to 24 hours after each LUTATHERA dose and short-acting octreotide for symptomatic management. (2.3)
- 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. (2.3)
- Administer antiemetics before recommended amino acid solution. (2.3)
- Initiate recommended intravenous amino acid solution 30 minutes before LUTATHERA infusion; continue during and for 3 hours after LUTATHERA infusion. Do not reduce dose of amino acid solution if LUTATHERA dose is reduced. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------

Injection: 370 MBq/mL (10 mCi/mL) in single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk from Radiation Exposure: Minimize radiation exposure during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures (2.1, 5.1)
- Myelosuppression: Monitor blood cell counts. Withhold, reduce dose, or permanently discontinue based on severity. (2.4, 5.2)
- Secondary Myelodysplastic Syndrome (MDS) and Leukemia: Median time to development: MDS is 28 months; acute leukemia is 55 months. (5.3)
- Renal Toxicity: Advise patients to urinate frequently during and after administration of LUTATHERA. Monitor serum creatinine and calculated creatinine clearance. Withhold, reduce dose, or permanently discontinue based on severity. (2.3, 2.4, 5.4)
- Hepatotoxicity: Monitor transaminases, bilirubin and albumin. (2.4, 5.5)
- Neuroendocrine Hormonal Crisis: Monitor for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms. (5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus and to use effective contraception (5.7, 8.1, 8.3)
- Risk of Infertility: LUTATHERA may cause infertility. (5.8, 8.3)

---------- ADVERSE REACTIONS ----------

Most common Grade 3-4 adverse reactions (≥ 4% with a higher incidence in LUTATHERA arm) are lymphopenia, increased GGT, vomiting, nausea, increased AST, increased ALT, hyperglycemia and hypokalemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Advanced Accelerator Applications USA, Inc. at 1-844-863-1930 or *us-pharmacovigilance@adacap.com,* or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

Somatostatin Analogs: Discontinue long-acting analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. (2.3, 7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUTATHERA is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Instructions

LUTATHERA is a radiopharmaceutical; handle with appropriate safety measures to minimize radiation exposure *[see Warnings and Precautions (5.1)]*. Use waterproof gloves and effective radiation shielding when handling LUTATHERA. Radiopharmaceuticals, including LUTATHERA, should be used by or under the control of healthcare providers 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 Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage

The recommended LUTATHERA dosage is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. Administer premedications and concomitant medications as recommended *[see Dosage and Administration (2.3)]*.

2.3 Premedication and Concomitant Medications

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 (7.1)]*.
- 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.

Antiemetic

Administer antiemetics before the recommended amino acid solution.

Amino Acid Solution

Initiate an intravenous amino acid solution containing L-lysine and L-arginine (Table 1) 30 minutes before administering LUTATHERA. Use a three-way valve to administer amino acids using the same venous access as LUTATHERA or administer amino acids through a separate venous access in the patient's other arm. 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 (5.4)]*.

Table 1. Amino Acid Solution

Item	**Specification**
L-Lysine HCl content	Between 18 g and 25 g*
L-Arginine HCl content	Between 18 g and 25 g**
Volume	1 L to 2 L
Osmolarity	< 1050 mOsmol/L
*equivalent to 14.4 to 20 g lysine **equivalent to 14.9 to 20.7 g arginine	

2.4 Dosage Modifications for Adverse Reactions

Recommended dose modifications of LUTATHERA for adverse reactions are provided in Table **2**.

Table 2. Recommended Dosage Modifications of LUTATHERA for Adverse Reactions

Adverse Reaction	**Severity of Adverse Reaction***	**Dose Modification**
Thrombocytopenia *[see Warnings and Precautions (5.2)]*	Grade 2, 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 2, 3 or 4	Permanently discontinue LUTATHERA.
Anemia and Neutropenia *[see Warnings and Precautions (5.2)]*	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

Adverse Reaction	Severity of Adverse Reaction*	Dose Modification
		result in Grade 3 or 4 anemia or neutropenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue LUTATHERA.
Renal Toxicity *[see Warnings and Precautions (5.4)]*	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 or return to baseline. 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 (5.5)]*	Defined as: • Bilirubinemia greater than 3 times the upper limit of normal (Grade 3 or 4), or • Hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.	Withhold dose until complete resolution or return to baseline. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution or return to baseline. If reduced LUTATHERA dose does not result in hepatotoxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for hepatotoxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent hepatotoxicity	Permanently discontinue LUTATHERA.
Other Non-Hematologic Toxicity *[see Adverse Reactions (6.1)]*	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.

* Grading of severity is defined in the most current Common Terminology Criteria for Adverse Events (CTCAE)

2.5 Preparation and Administration

- Use aseptic technique and radiation shielding when administering the LUTATHERA solution. Use tongs when handling vial to minimize radiation exposure.
- Do not inject LUTATHERA directly into any other intravenous solution.
- Confirm the amount of radioactivity of LUTATHERA in the radiopharmaceutical vial with an appropriate dose calibrator prior to and after LUTATHERA administration.
- Inspect the product visually for particulate matter and discoloration prior to administration under a shielded screen. Discard vial if particulates or discoloration are present.
- Dispose of any unused medicinal product or waste material in accordance with local and federal laws.

Administration Instructions

The gravity method or infusion pump method may be used for administration of the recommended dosage. Use the infusion pump method when administering a reduced dose of LUTATHERA following a dosage modification for an adverse reaction; using the gravity method to administer a reduced dose of LUTATHERA may result in delivery of the incorrect volume of LUTATHERA, if the dose is not adjusted prior to administration.

Instructions for Gravity Method

- Insert a 2.5 cm, 20 gauge needle (short needle) into the LUTATHERA vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport LUTATHERA during the infusion). Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient. Do not allow sodium chloride solution to flow into the LUTATHERA vial prior to the initiation of the LUTATHERA infusion and do not inject LUTATHERA directly into the sodium chloride solution.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is prefilled with 0.9% sterile sodium chloride and that is used exclusively for the LUTATHERA infusion into the patient.
- Use a clamp or pump to regulate the flow of the sodium chloride solution via the short needle into the LUTATHERA vial at a rate of 50 mL/hour to 100 mL/hour for 5 to 10 minutes and then 200 mL/hour to 300 mL/hour for an additional 25 to 30 minutes (the sodium chloride solution entering the vial through the short needle will carry the LUTATHERA from the vial to the patient via the catheter connected to the long needle over a total duration of 30 to 40 minutes).
- During the infusion, ensure that the level of solution in the LUTATHERA vial remains constant.
- Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an intravenous flush of 25 mL of 0.9% sterile sodium chloride.

Instructions for Infusion Pump Method

- Insert a 2.5 cm, 20 gauge needle (short venting needle) into the LUTATHERA vial. Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient or the infusion pump.

- Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic infusion pump according to manufacturer's instruction.
- Purge the line by opening the 3-way stopcock valve and pumping the LUTATHERA solution through the tubing until it reaches the exit of the valve.
- Purge the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the purged intravenous catheter to the patient and set the 3-way stopcock valve such that the LUTATHERA solution is in line with the infusion pump.
- Infuse one-half the volume listed on the LUTATHERA vial over a 30 min period (approximately 25 mL/h).
- When the correct volume of LUTATHERA has been delivered, stop the infusion pump and then change the position of the 3-way stopcock valve so that the infusion pump is in line with the 0.9% sterile sodium chloride solution. Restart the infusion pump and infuse an intravenous flush of 25 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

2.6 Radiation Dosimetry

The mean and standard deviation (SD) of the estimated radiation absorbed doses for adults receiving LUTATHERA are shown in Table 3. The maximum penetration in tissue is 2.2 mm and the mean penetration is 0.67 mm.

Table 3. Estimated Radiation Absorbed Dose for LUTATHERA in NETTER-1

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

*N=18 (two patients excluded because the liver absorbed dose was biased by the uptake of the liver metastases)
**N=9 (female patients only)
***N=11 (male patients only)

3 DOSAGE FORMS AND STRENGTHS

Injection: 370 MBq/mL (10 mCi/mL) of lutetium Lu 177 dotatate as a clear and colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk from 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, patient management procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

5.2 Myelosuppression

In NETTER-1, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide compared to patients receiving high-dose long-acting octreotide (all grades/grade 3 or 4): anemia (81%/0) versus (54%/1%); thrombocytopenia (53%/1%) versus (17%/0); and neutropenia (26%/3%) versus (11%/0). In NETTER-1, platelet nadir occurred at a median of 5.1 weeks following the first dose. Of the 59 patients who developed thrombocytopenia, 68% had platelet recovery to baseline or normal levels. The median time to platelet recovery was 2 months. Fifteen of the nineteen patients in whom platelet recovery was not documented had post-nadir platelet counts. Among these 15 patients, 5 improved to Grade 1, 9 to Grade 2, and 1 to Grade 3.

Monitor blood cell counts. Withhold, reduce dose, or permanently discontinue based on severity of myelosuppression *[see Dosage and Administration (2.4)]*.

5.3 Secondary Myelodysplastic Syndrome and Leukemia

In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide. In ERASMUS, 16 patients (2.0%) developed MDS and 4 (0.5%) developed acute leukemia. 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 leukemia.

5.4 Renal Toxicity

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.

Administer the recommended amino acid solution before, during and after LUTATHERA *[see Dosage and Administration (2.3)]* to decrease reabsorption of lutetium Lu 177 dotatate 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.

Monitor serum creatinine and calculated creatinine clearance. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of renal toxicity*[see Dosage and Administration (2.4)]*.

Patients with baseline renal impairment 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).

5.5 Hepatotoxicity

In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure.

Monitor transaminases, bilirubin and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of hepatic impairment *[see Dosage and Administration (2.4)]*.

5.6 Neuroendocrine Hormonal Crisis

Neuroendocrine hormonal crises, manifesting with flushing, diarrhea, bronchospasm and hypotension, occurred in < 1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose. Two (<1%) patients were reported to have hypercalcemia.

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

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, LUTATHERA can cause fetal harm *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of LUTATHERA in pregnant women. No animal studies using lutetium Lu 177 dotatate 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 (2.1)]*.

Advise pregnant women 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 Use in Specific Populations (8.1, 8.3)]*.

5.8 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 Dosage and Administration (2.6), Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Myelosuppression *[see Warnings and Precautions (5.2)]*
- Secondary Myelodysplastic Syndrome and Leukemia *[see Warnings and Precautions (5.3)]*
- Renal Toxicity *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Neuroendocrine Hormonal Crisis *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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.

The data in Warnings and Precautions reflect exposure to LUTATHERA in 111 patients with advanced, progressive midgut neuroendocrine tumors (NETTER-1). Safety data in Warnings and Precautions were also obtained in an additional 22 patients in a non-randomized pharmacokinetic substudy of NETTER-1 and in a subset of patients (811 of 1214) with advanced somatostatin receptor-positive tumors enrolled in ERASMUS *[see Warnings and Precautions (5)]*.

NETTER-1

The safety data of LUTATHERA with octreotide was evaluated in NETTER-1 *[see Clinical Studies (14.1)]* Patients with progressive, somatostatin receptor-positive midgut carcinoid tumors to receive LUTATHERA 7.4 GBq (200 mCi) administered every 8 to 16 weeks concurrently with the recommended 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 Studies (14.1)]*. 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. Six percent (6%) of patients required a dose reduction and 13% of patients discontinued LUTATHERA. Five patients discontinued LUTATHERA for renal-related events and 4 discontinued for hematological 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 4 and Table 5 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, hyperglycemia and hypokalemia (4% each).

Table 4. Adverse Reactions Occurring at Higher Incidence in Patients Receiving LUTATHERA and Long-Acting Octreotide Compared to Long-Acting Octreotide (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4) [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 %
Gastrointestinal disorders				
Nausea	65	5	12	2
Vomiting	53	7	10	0
Abdominal pain	26	3	19	3
Diarrhea	26	3	18	1
Constipation	10	0	5	0
General disorders				
Fatigue	38	1	26	2
Peripheral edema	16	0	9	1
Pyrexia	8	0	3	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	11	3
Nervous system disorders				
Headache	17	0	5	0
Dizziness	17	0	8	0
Dysgeusia	8	0	2	0
Vascular disorders				
Flushing	14	1	9	0
Hypertension	12	2	7	2
Musculoskeletal and connective tissue disorders				
Back pain	13	2	10	0
Pain in extremity	11	0	5	0
Myalgia	5	0	0	0
Neck Pain	5	0	0	0
Renal and urinary disorders				
Renal failure*	13	3	4	1
Radiation-related urinary tract toxicity**	8	0	3	0
Psychiatric disorders				
Anxiety	12	1	5	0
Skin and subcutaneous tissue disorders				
Alopecia	12	0	2	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	1	6	0
Cardiac disorders				
Atrial fibrillation	5	1	0	0

[1] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays adverse reactions occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2% (grades 3-4)]

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

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

Table 5. Laboratory Abnormalities Occurring at Higher Incidence in Patients Receiving LUTATHERA and Long-Acting Octreotide Compared to Long-Acting Octreotide (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4)*[1]

Laboratory Abnormality[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 %
Hematology				
Lymphopenia	90	44	39	5
Anemia	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
Hyperglycemia	82	4	67	2
Hyperuricemia	34	6	30	6
Hypocalcemia	32	0	14	0
Hypokalemia	26	4	21	2
Hyperkalemia	19	0	11	0
Hypernatremia	17	0	7	0
Hypoglycemia	15	0	8	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. Only displays laboratory abnormalities occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2%(grades 3-4)]

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 tumors (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). With a median follow-up time of more than 4 years, the following rates of serious adverse reactions were reported: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

7 DRUG INTERACTIONS

7.1 Somatostatin Analogs

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 (2.3)]*.

7.2 Corticosteroids

Corticosteroids can induce down-regulation of subtype 2 somatostatin receptors (SST2). Avoid repeated administration of high-doses of glucocorticosteroids during treatment with LUTATHERA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LUTATHERA can cause fetal harm *[see Clinical Pharmacology (12.1)]*. There are no available data on LUTATHERA use in pregnant women. No animal studies using lutetium Lu 177 dotatate 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 U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of lutetium Lu 177 dotatate 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.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA *[see Use in Specific Populations (8.1)]*.

Contraception

Females

LUTATHERA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. 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 Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)]*.

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 Dosage and Administration (2.6)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 1325 patients treated with LUTATHERA in clinical trials, 438 patients (33%) were 65 years and older. The response rate and number of patients with a serious adverse event were similar to that of younger subjects.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. 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 *[see Warnings and Precautions (5.4)]*.

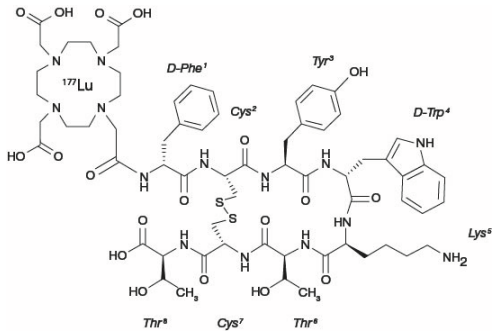
8.7 Hepatic Impairment

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.

11 DESCRIPTION

Lutetium Lu 177 dotatate is a radiolabeled somatostatin analog. The drug substance lutetium Lu 177 dotatate is a cyclic peptide linked with the covalently bound chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to a radionuclide.

Lutetium Lu 177 dotatate is described as 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. The molecular weight is 1609.6 Daltons and the structural formula is as follows:



LUTATHERA (lutetium Lu 177 dotatate) 370 MBq/mL (10 mCi/mL) Injection is a sterile, clear, colorless to slightly yellow solution for intravenous use. Each single-dose vial contains acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), sodium hydroxide (0.65 mg/mL), ascorbic acid (2.8 mg/mL), diethylene triamine pentaacetic acid (0.05 mg/mL), sodium chloride (6.85 mg/mL), and Water for Injection (ad 1 mL). The pH range of the solution is 4.5 to 6.

11.1 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 6.

Table 6. Lu 177 Main Radiations

Radiation	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

11.2 External Radiation

Table 7 summarizes the radioactive decay properties of Lu 177.

Table 7. 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)	0.901	1080 (45 days)	0.009

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lutetium Lu 177 dotatate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSRT2). Upon binding to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors, 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.

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

The ability of LUTATHERA to prolong the QTc interval at the therapeutic dose was assessed in an open label study in 20 patients with somatostatin receptor-positive midgut carcinoid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of lutetium Lu 177 dotatate have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors. The mean blood exposure (AUC) of lutetium Lu 177 dotatate at the recommended dose is 41 ng.h/mL [coefficient of variation (CV) 36 %]. The mean maximum blood concentration (C_{max}) for lutetium Lu 177 dotatate is 10 ng/mL (CV 50%), which generally occurred at the end of the LUTATHERA infusion.

Distribution

The mean volume of distribution for lutetium Lu 177 dotatate is 460 L (CV 54%).

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

The non-radioactive form of lutetium dotatate is 43% bound to human plasma proteins.

Elimination

The mean clearance (CL) is 4.5 L/h (CV 31%) for lutetium Lu 177 dotatate. 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 Lu 177 dotatate does not undergo hepatic metabolism.

Excretion

Lutetium Lu 177 dotatate 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 Lu 177 dotatate in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium Lu 177 dotatate, greater than 99% will be eliminated within 14 days after administration of LUTATHERA *[see Warnings and Precautions (5.1)]*.

Drug Interaction Studies

The non-radioactive form of lutetium is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 in vitro. It is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or OCT1 in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with Lutetium Lu 177 dotatate; however, radiation is a carcinogen and mutagen.

No animal studies were conducted to determine the effects of lutetium Lu 177 dotatate on fertility.

13.2 Animal Toxicology and/or Pharmacology

The primary target organ in animal studies using a non-radioactive form of lutetium Lu 177 dotatate (lutetium Lu 175 dotatate) was the pancreas, a high SSTR2 expressing organ. Pancreatic acinar apoptosis occurred at lutetium Lu 175 dotatate doses ≥ 5 mg/kg in repeat dose toxicology studies in rats. Pancreatic acinar cell atrophy also occurred in repeat dose toxicology studies in dogs at doses ≥ 500 mg/kg. These findings were consistent with high uptake of the radiolabeled peptide in the pancreas in animal biodistribution studies.

14 CLINICAL STUDIES

14.1 Progressive, Well-differentiated Advanced or Metastatic Somatostatin Receptor-Positive Midgut Carcinoid Tumors

The efficacy of LUTATHERA in patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumors 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 in both arms could receive short-acting octreotide for symptom management; however, short-acting octreotide was withheld for at least 24 hours before each LUTATHERA dose. Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization ($\leq$ 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).

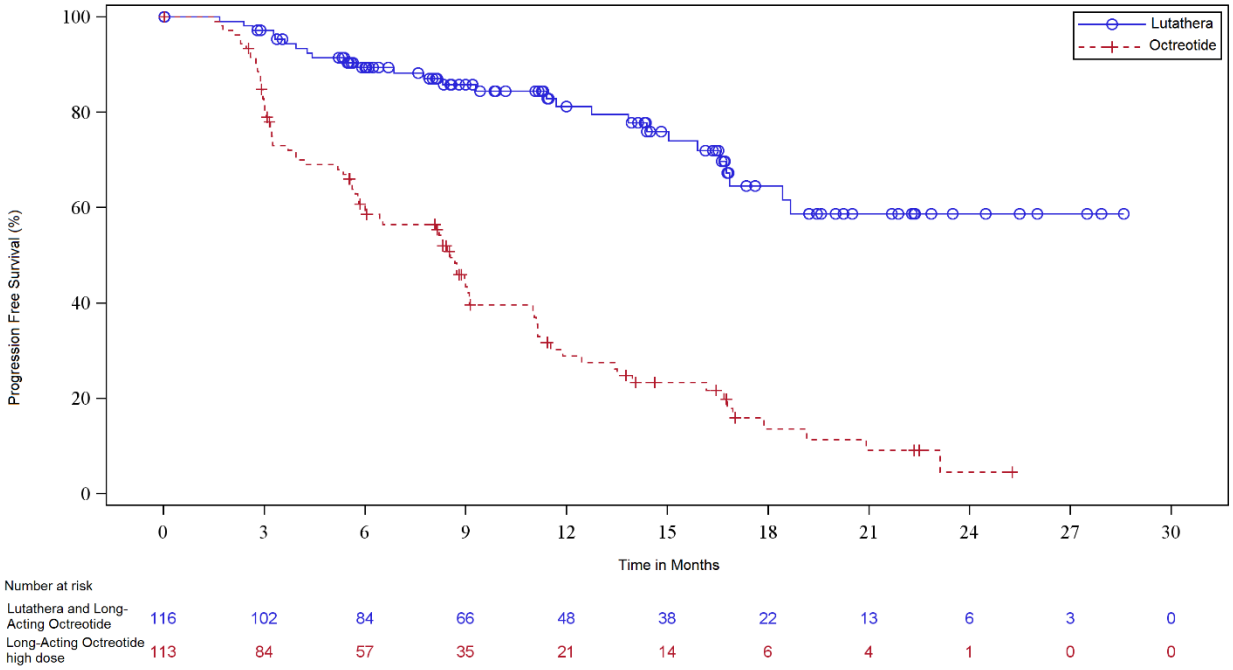
Demographic and baseline disease characteristics were balanced between the treatment arms. Of the 208 patients, whose race/ethnicity was reported, 90% were White, 5% were Black, and 4% were Hispanic or Latino. The median age was 64 years (28 to 87 years); 51% were male, 74% had an illial primary, and 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 $\leq$ 2% of tumor cells, 77% had CgA > 2 times the upper limit of normal (ULN), 65% had 5-HIAA > 2 x ULN, and 65% had alkaline phosphatase $\leq$ ULN. Efficacy results for NETTER-1 are presented in Table 8 and Figure 1.

Table 8. 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] (18.4, 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] (95% CI)	0.52 (0.32, 0.84)	
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 1. Kaplan-Meier Curves for Progression-Free Survival in NETTER-1



14.2 Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

The efficacy of LUTATHERA in patients with foregut, midgut, and hindgut gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was assessed in 360 patients in the ERASMUS study. In ERASMUS, LUTATHERA was initially provided as expanded access 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 whom 578 patients had baseline tumor assessments. Of the 578 patients, 360 (62%) had gastroentero-pancreatic neuroendocrine tumors (GEP-NETs) and long term follow-up. Of these 360 patients, 145 (40%) had their tumors prospectively evaluated according to RECIST criteria. 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 60 years (30 to 85 years), 51% were male, 71% had a baseline Karnofsky performance status ≥ 90, 51% had progressed within 12 months of treatment, and 7%% had received prior chemotherapy. Fifty two percent (52%) of patients received a concomitant somatostatin analog. The median dose of LUTATHERA was 29.6 GBq (800 mCi). The investigator assessed ORR was 17% (95% CI 13, 21) based on an analysis that required responders to have had prospective response assessments according to RECIST criteria. Three complete responses were observed (< 1%). Median DoR in the 60 responding patients was 35 months (95% CI: 17, 38).

16 HOW SUPPLIED/STORAGE AND HANDLING

LUTATHERA Injection containing 370 MBq/mL (10 mCi/ml) of lutetium Lu 177 dotatate 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 Lu 177 dotatate at the time of injection (**NDC# 69488-003-01**). 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 (**NDC# 69488-003-01**). The product is shipped in a Type A package (**NDC# 69488-003-70**).

Store below 25 °C (77 °F). Do not freeze LUTATHERA. Store in the original package to protect from ionizing radiation.

The shelf life is 72 hours. Discard appropriately at 72 hours.

17 PATIENT COUNSELING INFORMATION

Radiation Risks

Advise patients to minimize radiation exposure to household contacts consistent with institutional good radiation safety practices and patient management procedures *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.

Myelosuppression

Advise patients to contact their healthcare provider for any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, or increased bleeding or bruising *[see Warnings and Precautions (5.2)]*.

Secondary Myelodysplastic Syndrome and Acute Leukemia

Advise patients of the potential for secondary cancers, including myelodysplastic syndrome and acute leukemia *[see Warnings and Precautions (5.3)]*.

Renal Toxicity

Advise patients to hydrate and urinate frequently during and after administration of LUTATHERA *[see Warnings and Precautions (5.4)]*.

Hepatotoxicity

Advise patients of the need for periodic laboratory tests to monitor for hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Neuroendocrine Hormonal Crises

Advise patients to contact their health care provider for signs or symptoms that may occur following tumor-hormone release, including severe flushing, diarrhea, bronchospasm, and hypotension *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women and males and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LUTATHERA and for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise females not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise female and male patients that LUTATHERA may impair fertility *[see Warnings and Precautions (5.8), Use in Specific Populations (8.3)]*.

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