PRODUCT MONOGRAPH

LUTATHERA®
LUTETIUM (177LU) OXODOTREOTIDE
FORMER:
177LU-DOTA³-TYR³-OCTREOTATE,
177LU-DOTATATE

370 MBq/mL solution for infusion
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INTRODUCTION

There are limited therapeutic options for patients with advanced NETs (NeuroEndocrine Tumors) progressing on first-line somatostatin analog therapy\(^1\).

Peptide receptor radionuclide therapy (PRRT) is an innovative technique that involves the intravascular administration of a specific radiopharmaceutical to deliver cytotoxic radiation to tumor cells. The radiopharmaceutical is usually composed of a β- emitting radionuclide, chelated to a somatostatin analog allowing targeted action on NETs which usually overexpress somatostatin receptors. PRRT is thus a new therapeutic option for NETs patients\(^2\).

For a long time, radiopharmaceuticals used in PRRT were home made products, prepared in hospital nuclear medicine departments. However, very few sites were able to produce these drugs making it hardly available for most patients\(^3\).

In 2010, Advanced Accelerator Applications obtained the exclusive worldwide license on the \(^{177}\)Lu-labelled oxodotreotide* peptide developed by BioSynthema Inc, registered under the trademark LUTATHERA\(^\text{®}\). Peptide receptor radionuclide therapy (PRRT) with LUTATHERA\(^\text{®}\) is a low dose rate radiotherapy (as opposed to external beam radiation) developed for treatment of neuroendocrine tumours (NETs) that utilises the carrier peptide, oxodotreotide*. The radiolabelled peptide contains a DOTA-chelated radionuclide, Lutetium-177 \(^{177}\)Lu. It binds with high affinity to somatostatin receptors that are overexpressed on the cell surface of most neuroendocrine tumors. The targeting of radiolabelled somatostatin analogues to tumour cells is the basis of the therapeutic effect of this radiopharmaceutical\(^5,6\).

The company conducted a pivotal phase III study to apply for a Marketing Authorization in Europe and in the United States.

The pivotal phase III study NETTER-1\(^6\) compared \(^{177}\)Lu-DOTATATE and octreotide LAR 60mg (double label dose) in patients with locally advanced or metastatic inoperable, grade 1 or grade 2 neuroendocrine tumors of the small intestine, progressing under treatment with octreotide LAR 20 - 30 mg every 21 to 28 days. The study showed a statistically significant 82% reduction in the risk of progression or death (Median PFS: octreotide LAR, 8.5 months LUTATHERA\(^\text{®}\), not reached. Hazard ratio: 0.18 (95% CI : [0.11 – 0.29] p < 0.0001).

* also called:
\((^{177}\text{Lu})\) oxodotreotide;
lutetium Lu 177 dotatate
In the LUTATHERA® arm, patients also experienced an overall response rate of 18% (vs 3% in comparator arm p= 0.0008) which is rarely seen with systemic therapies in the NETs population. LUTATHERA® demonstrates a favorable safety profile, with rare clinically relevant findings. Consistent acute and subacute safety profile with manageable and preventable common side effects especially regarding G.I., hematological, renal and hepatic parameters, with mild and transient hematotoxicity, while nausea and vomiting are mainly due to the infusion of an amino acid solution intended to avoid renal toxicity. This is now improved with the amino acid solution specified in the Summary of Product Characteristics (SmPC). Long term safety studies have cleared hepatic and renal toxicity. Regarding hematotoxicity, the data published so far (Dutch Cohort) shows a persistent hematological dysfunction (PHD) in 11 of the 274 GEPNETs patients (3.7%) treated with LUTATHERA®. This is consistent with previous publications on PRRT.

The Marketing Authorization was granted on Sept 26th 2017 by the EMA.

LUTATHERA®, 370 MBq/mL, solution for infusion is a ready-to-use product, indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults.
PART 1 NEUROENDOCRINE TUMORS

Definition of neuroendocrine tumors

Neuroendocrine tumors (NETs) represent a heterogeneous group of tumors arising from neuroendocrine cells, scattered throughout the human body. Thus, NETs can develop in any organ or tissue, but approximately two thirds derive from the gastrointestinal system and constitute the group of gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs). All NETs share a common characteristic, which is their capability to synthesize, store, and secrete amines and peptides. When these substances are biologically active, they cause distinct clinical syndromes and the associated tumors are referred to as functional tumors. However, a majority of NETs are non-functioning, and can remain asymptomatic for a long time. Consequently, most NETs are diagnosed at a late stage, when they are locally advanced or metastatic. For example, small intestine NETs are discovered at the stage of regional disease in 36% of cases and distant metastases are present in 48% of cases.

Epidemiology

Although these tumors are still considered rare in general terms, their incidence is continuously increasing over time. The latest US data, so far, were published in April 2017 by Dasari A et al in JAMA Oncology, representing data from the Surveillance, Epidemiology, and End Results (SEER) on 64971 patients with NETs from 1973 to 2012. The age-adjusted incidence rate increased 6.4-fold from 1973 (1.09 per 100 000) to 2012 (6.98 per 100 000). The increase occurred across all sites, stages and grades. The highest incidence rates occurred in lung (1.49 per 100 000), gastroenteropancreatic sites (3.56 per 100 000) and 0.84 per 100 00 in NETs of unknown origin.

GEP-NETs arise more frequently from the small intestine (1.05 per 100 000 persons), rectum (1.04 per 100 000 persons), and pancreas (0.48 per 100 000 persons). It seems that the highest rise in incidence is happening in patients 65 or older, with an 8-fold increase to 25.3 per 100 000, and in those 50 to 64 years to 14.3 per 100 000 persons. Since NETs are mainly indolent tumors, life expectancy is longer than for most other malignancies and the prevalence of the disease is not negligible. Also growing substantially, the 20-year limited-duration prevalence was 0.006% in 1993 up to 0.048% in 2012. With respect to groups, the highest increase took place in G1 tumors and
regarding sites, prevalence was highest in the rectum, followed by lung and small intestine\textsuperscript{13}.

In a previous publication based on US epidemiology data, Lawrence B. et al stated that the median age at diagnosis is around 63 years, and the incidence increases with age\textsuperscript{14}.

Survival of patients with NETs has improved over time, especially in distal GEP-NETs, probably related to the new therapies. According to this group of investigators from The University of Texas MD Anderson Cancer Center (Houston TX), the trend which favours the survival of patients with metastatic NETs will continue as newer agents such as PRRT become integrated into routine clinical care\textsuperscript{13}.

Since NETs are mainly indolent tumors, other publications already supported that life expectancy is longer than for most other malignancies and the prevalence of the disease is not negligible: for all NETs, it is estimated at 35 / 100,000 in the US\textsuperscript{15,16} and the prevalence of GEP NETs is higher than that of most gastrointestinal cancers, including pancreatic, gastric, esophageal, and hepato-biliary carcinomas, and is only exceeded by that of colorectal neoplasia\textsuperscript{14}. In Europe, the annual incidence rates incidence can be estimated from 2.36 per 100,000 inhabitants for women to 2.51 for men\textsuperscript{15}.

Classification

NETs are now classified according to grade and extent of the disease, using the European NeuroEndocrine Tumors Society (ENETS), the North American NeuroEndocrine Tumor Society (NANETS) or the WHO classifications\textsuperscript{16-18}. Grade is defined by the mitotic count and the Ki67 index.

Grading of GEP –NETs, according to ENETS and WHO classifications\textsuperscript{11-13}

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic count and Ki67 index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 2 mitoses / 10 hpf AND Ki67 &lt; 3%</td>
</tr>
<tr>
<td>2</td>
<td>2-20 mitoses / 10 hpf OR Ki67 3-30%</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 20 mitoses / hpf OR Ki67 &gt; 20%</td>
</tr>
</tbody>
</table>

Previous classifications took into account differentiation, a key factor for prognosis and therapeutic strategies. Grade 1 and 2 tumors are usually well / moderately differentiated while grade 3 tumors are usually poorly differentiated. However, the correlation between grade and differentiation is not 100% reliable. The G1 and G2 well-differentiated NETs usually display a diffuse and intense expression of chromogranin A\textsuperscript{19}.

Staging is based on the TNM (used by ENETS)\textsuperscript{18,20} or AJCC classifications\textsuperscript{21}(used
by WHO), taking into account:
- Tumor size and extent of invasion (T1 to T4)
- Lymph Node involvement (N0 or N1)
- Distant Metastases (M0 or M1)

Prognosis

According to the previously published data in the US, the overall observed 5-year survival rate of GEP-NETs was 68.1\%\textsuperscript{14}. Pancreatic NETs have the lowest rates (37.6\%), whereas rectal NETs exhibit the highest rates (88.5\%), showing that the primary location of the tumor partly determines the prognosis, regardless of other parameters\textsuperscript{14}. Midgut tumors, i.e. tumors of the small intestine, have an intermediate prognosis with a 68.1\% 5-year survival rate. However, survival is also strongly correlated with grade, differentiation and stage of the disease. Despite the fact that most GEP-NETs are slow-growing tumors, and the popular notion that they are relatively benign tumors, median overall survival in patients with metastatic liver disease is 2 to 4 years\textsuperscript{22}. Localized diseases have a better prognosis than advanced and metastatic diseases; G3 tumors are associated with poor survival rates compared to G1 and G2 tumors.

In the latest SEER update on the topic, on multivariable analysis, the median 5-year OS rate varied by stage, grade, primary site, age at diagnosis and time period of diagnosis in a significant magnitude. There was an improvement in OS rate for all NETs from the 2000-2004 period to the 2009-2012 period [HR: 0.79; 95\% CI 0.73-0.85]. Between these periods the increases in OS were even larger in distant-stage gastrointestinal NETs [HR: 0.71; 95\% CI 0.62-0.81] and distant-stage pancreatic NETs [HR:0.56; 95\% CI 0.44-0.70]\textsuperscript{13}.

Treatment

Several therapeutic options can be used for GEP-NETs. Surgery is the only curative treatment and it should always be considered. Debulking surgery can also improve prognosis, in reducing tumor burden to facilitate adjuvant therapy\textsuperscript{23}. Among other options, systemic therapies include somatostatin analogues (SSAs), chemotherapy, targeted therapies and peptide receptor radionuclide therapy (PRRT). SSAs, namely octreotide and lanreotide, were initially used as symptomatic therapies. However they have also proven antiproliferative activity in clinical trials\textsuperscript{24,25} and following the results of the CLARINET study, the indication of lanreotide was expanded to the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10\%) GEP-NETs of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease.
The PROMID study group demonstrated that Octreotide LAR prolongues significantly PFS compared to placebo in metastatic midgut NETs patients (p = .000072).
Among chemotherapies, streptozocin is the only drug that obtained a marketing authorization for the treatment of GEP-NETs. However, many other drugs are currently used with documented efficacy on tumor shrinkage. Chemotherapy is preferably used in progressive, grade 2, bulky tumors.
Two targeted therapies received a marketing authorization in the treatment of pancreatic NETs, based on the results of randomized, placebo-controlled, phase III trials, namely sunitinib\textsuperscript{26} and everolimus\textsuperscript{27}. They are indicated in unresectable or metastatic, well- or moderately-differentiated pancreatic NETs in adults with progressive disease. Later on, everolimus obtained a marketing authorization or the treatment of unresectable or metastatic, well differentiated non-functional neuroendocrine tumors of gastrointestinal or lung origin in adults with progressive disease\textsuperscript{28}.

PRRT involves the intravascular administration of a specific radiopharmaceutical to deliver cytotoxic radiation to a tumor. The radiopharmaceutical is composed of a peptide, designed to target cell surface receptors, a chelator and a radionuclide. The radiopharmaceutical binds to the surface cell receptors, is internalized in the cancer cell and delivers radiations that provoke DNA breaks and cell death. In the treatment of NETs, peptides used in radiopharmaceuticals are somatostatin analogues; their affinity for somatostatin receptors and the specificity of binding ensures a high level of specificity in the delivery of radiation to the tumor. The most widely used chelator is DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,20-tetra-acetic acid), and radionuclides are either \textsuperscript{90}Y or \textsuperscript{177}Lu\textsuperscript{29,31}.

Apart from systemic therapies, numerous loco-regional therapies can be used, mainly for the treatment of liver metastases. They include radiofrequency ablation, cryotherapy, laser ablation, embolization and chemoembolization. All these techniques can be useful for the management of progressive, symptomatic liver metastases, not amenable to surgical resection\textsuperscript{32,33}. 


Main characteristics of the product

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.

The Drug Substance, \(^{177}\text{Lu}\) oxodotreotide or \(^{177}\text{Lu}\)-dotatate, is a lutetium-177 \(^{177}\text{Lu}\) labeled somatostatin analogue conjugated with the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

LUTATHERA® is supplied as a sterile, ready-to-use solution for infusion, which will be administered intravenously in nuclear medicine settings. Each single dose vial contains suitable amount of solution that allows delivery of 7.4 GBq of \(^{177}\text{Lu}\) oxodotreotide at injection time.

LUTATHERA® exhibits a high affinity for somatostatin subtype 2 (sst2) receptors. The compound binds to malignant cells that overexpress sst2 receptors, which is the characteristic of a majority of GEP-NETs. \(^{177}\text{Lu}\) is a \(\beta\)-emitting radionuclide. The mean path length of the \(\beta\)-emission is about 2 mm, which is sufficient to effectively kill targeted tumor cells, with only limited effect on neighboring non-target cells.

The treatment regimen consists of four intravenous (i.v.) administrations of 7.4 GBq of \(^{177}\text{Lu}\) oxodotreotide, every 8 weeks. This time interval can be extended up to 16 weeks in case of dose modifying toxicity (DMT). The product must be administered as a slow i.v. infusion, with concomitant administration of an amino acid solution containing arginine and lysine. LUTATHERA® must not be injected as a bolus.

Composition, presentation and pharmacological properties

Presentation

LUTATHERA® is supplied as a clear, colorless to slightly yellow solution for infusion.

Composition

1 mL of solution contains 370 MBq of \(^{177}\text{Lu}\) oxodotreotide at the date and
time of calibration. The total amount of radioactivity by single dose vial is 7 400 MBq (± 10 %) at the date and time of infusion. Given the fixed volumetric activity of 370 MBq/mL at the date and time of calibration, the 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 6.71 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. Also low gamma energy is emitted, for instance at 113 keV (6.2 %) and 208 keV (11 %)\(^{11}\).

Pharmacological properties

LUTATHERA\(^{8}\) belongs to the pharmacotherapeutic group of therapeutic radiopharmaceuticals.

LUTATHERA\(^{8}\) has a high affinity for subtype 2 somatostatin receptors (sst2), thus binds to malignant cells, which overexpress sst2 receptors. \(^{177}\)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 tumor cells with a limited effect on neighboring normal cells\(^{6}\).

At the concentration used (about 10 μg/ml in total, for both free and radiolabeled forms), the peptide DOTA\(^{0}\)-Tyr\(^{3}\)-Octreotate does not exert any clinically relevant pharmacodynamic effect\(^{6}\).

Pharmacokinetics\(^{6,11}\)

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. 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.

**Pharmacodynamics**

**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.

**Indications, posology and administration**

**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.

**Posology and method of administration**

LUTATHERA® should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings 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**

The recommended treatment regimen of LUTATHERA® (only 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 “Instructions for dose modification”

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 the table below.

### Composition of the standard amino acid solution

<table>
<thead>
<tr>
<th>Compound</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysine</td>
<td>25 g</td>
</tr>
<tr>
<td>Arginine</td>
<td>25 g</td>
</tr>
<tr>
<td>Sodium chloride 9 mg/mL (0.9%) solution for injection</td>
<td>1 L</td>
</tr>
</tbody>
</table>

Alternatively, some commercially available amino acid solutions can be used if compliant with the specification described in the table in the following page.
Specification of commercially available amino acid solutions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysine content</td>
<td>Between 18 and 24 g</td>
</tr>
<tr>
<td>Arginine content</td>
<td>Between 18 and 24 g</td>
</tr>
<tr>
<td>Volume</td>
<td>1.5 L to 2.2 L</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>&lt; 1,050 mOsmol</td>
</tr>
</tbody>
</table>

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 reassess 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. 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.
Scheme of instructions for dose modifications

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 instructions for dose modification.)

Criteria for temporary discontinuation treatment with LUTATHERA®

Temporarily discontinue treatment with LUTATHERA® in the following conditions:

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of an intercurrent disease (e.g. urinary tract infection), which according to the physician could increase the risks associated to LUTATHERA® administration.</td>
<td>Temporarily discontinue the treatment until resolution or stabilisation. Treatment can be resumed after resolution or stabilisation.</td>
</tr>
<tr>
<td>Major surgery.</td>
<td>Wait 12 weeks after the date of surgery to administer LUTATHERA®.</td>
</tr>
<tr>
<td>Major or some specific adverse reactions to LUTATHERA®.</td>
<td>See table Page 16</td>
</tr>
</tbody>
</table>
Instructions for dose modifications

Adjust LUTATHERA® dosing for the following severe adverse reactions:

<table>
<thead>
<tr>
<th>Severe adverse reactions Dose modifying toxicity (DMT) criteria</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia of grade 2 or superior (CTCAE)**.</td>
<td>1. Temporarily discontinue the treatment.</td>
</tr>
<tr>
<td>Any haematological toxicity of grade 3 or superior (CTCAE)**, except lymphopenia.</td>
<td>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.</td>
</tr>
<tr>
<td>Renal toxicity defined as an estimated creatinine clearance &lt; 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.</td>
<td>a. If the observed toxicity continues beyond 16 weeks after the last infusion, treatment with LUTATHERA® must be definitively stopped.</td>
</tr>
<tr>
<td>Liver toxicity defined as either: • Bilirubinemia &gt; 3 times the upper limit of normal, • Or hypoalbuminemia &lt; 30 g/L with a decreased prothrombin ratio &lt; 70%.</td>
<td>b. If the observed toxicity resolves within 16 weeks after the last infusion, it is possible to continue the treatment with LUTATHERA® by infusing a half dose (3,700 MBq)*.</td>
</tr>
<tr>
<td>Any other CTCAE grade 3 or grade 4 toxicity** possibly related to LUTATHERA®.</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

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. 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.

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.

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 taken.

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 below):

- 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.
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 intravial 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>
<thead>
<tr>
<th>Administered agents</th>
<th>Onset (h)</th>
<th>Infusion rate (mL/h)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetic</td>
<td>$T_0$</td>
<td>-</td>
<td>Bolus (few seconds)</td>
</tr>
<tr>
<td>Amino acid solution, either extemporaneously compounded (1 L) or commercial (1.5-2.2 L)</td>
<td>$T_0 + 30$ minutes</td>
<td>250 – 550 (&gt;$320$ mL/h for commercial solutions)</td>
<td>4 hours</td>
</tr>
<tr>
<td>LUTATHERA® with sodium chloride solution (9 mg/mL NaCl, 250 mL)</td>
<td>$T_0 + 60$ minutes</td>
<td>400</td>
<td>20-30 minutes</td>
</tr>
</tbody>
</table>
Contraindications

LUTATHERA® is contraindicated in patients with:
- hypersensitivity to the active substance
- hypersensitivity to any of the following excipients (Acetic acid, Sodium acetate, Gentisic acid, Ascorbic acid, Pentetic acid, Sodium chloride, Sodium hydroxide, Water for injections)
- established or suspected pregnancy or when pregnancy has not been excluded
- kidney failure with creatinine clearance < 30 mL/min

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 read the information above 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 131I 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®, 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 (75x10³/mm³), or leucocytes < 2 G/L (2,000/mm³) (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 (¹⁷⁷Lu) oxodotreotide is almost exclusively eliminated through the renal system, it is mandatory to concomitantly administer an amino acid solution containing the amino acids L-Lysine and L-arginine. The amino acids solution will help to decrease reabsorption of (¹⁷⁷Lu) oxodotreotide through the proximal tubules, resulting in a significant reduction in the kidney radiation dose. When the recommended concomitant amino acids infusion is delivered 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.

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.
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.

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.

Myelodisplastic syndrome and acute leukaemia
Late-onset myelodisplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with LUTATHERA® in 1-2% of the patients, 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. Brabander et al. (2017) reported AL in 0.7% and MDS in 1.5% of the patients in their long term toxicity Erasmus MC cohort.

Hormonal crises
Crises due to excessive release of hormones or bioactive substances may occur infrequently following treatment with LUTATHERA®, in 1% of patients. Generally, LUTATHERA® is well tolerated. Patients treated for VIPoma or bronchial carcinoids are most at risk. 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.

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® administration. Patients should be instructed to drink substantial quantities of water (1 glass every hour) on the day of infusion and the day after to facilitate elimination. The patient should also be encouraged to defecate every day and to use laxative if needed. Urine and 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 reaction6.

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 ionizing 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.

For precautions with respect to environmental hazard see later in “Excipients, storage, precautions for disposal and handling” section.
Interactions 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.

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 (177Lu)
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.

**Breast feeding**

It is unknown whether (¹⁷⁷Lu) oxodotretide 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 (¹⁷⁷Lu) oxodotretide on the fertility of either gender. Ionizing radiations of (¹⁷⁷Lu) oxodotretide 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.

**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%).

**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 (1.5%) and acute myeloid leukemia, (0.7%) have been reported following LUTATHERA® treatment.

Nephrotoxicity

(177Lu) octreotate 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.

In the Dutch cohort (long term safety) the authors concluded that no therapy related long-term renal or hepatic failure occurred. For them 177Lu- octreotate is safe with few side-effects.

An individual benefit risk assessment is recommended prior to treatment with LUTATHERA® in patients with mild and moderate renal impairment. The use of LUTATHERA® is contraindicated in patients with severe kidney failure.

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. Crises due to excessive release of hormones or bioactive substances may occur following treatment with LUTATHERA®, in 1% of patients. Generally, LUTATHERA® is well tolerated. Patients treated for VIPoma or bronchial carcinoids are most at risk.

Excipients, storage, precautions for disposal and handling

List of excipients

Acetic acid
Sodium acetate
Gentisic acid
Ascorbic acid
Pentetic acid
Sodium chloride
Sodium hydroxide
Water for injections
Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in the information about posology and method of administration.

Shelf life
72 hours from the date and time of calibration.

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.

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.

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.

Instruction on preparation of the medicinal product before administration is described in a previous section.

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 $^{177}{\text{Lu}}$ 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. 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.
PART 3 SCIENTIFIC INFORMATION

3.1 Detailed pharmaceutical information

The chemical name of lutetium (\(^{177}\text{Lu}\)) oxodotreotide is lutetium\(^{177}\text{Lu}\)-N-[(4,7,10-tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threonyl-L-cysteinyl-L-threonic-cyclic(2-7)disulfide (synonyms: DOTATATE or DOTA\(^0\)-Tyr\(^3\)-Octreotate) corresponding to the molecular formula \(\text{C}_{65}\text{H}_{87}\text{N}_{14}\text{O}_{19}\text{S}_{2}\text{Lu}\). It has a relative molecular mass of 1609.6 g/mol and the following structure:

![Structure of lutetium (\(^{177}\text{Lu}\)) oxodotreotide](image)

Description of the product

The finished product is a sterile ready-to-use solution for infusion with a volumetric activity of 370 MBq/ml at reference date and time (calibration time (Tc)).

Calibration time (Tc) corresponds to the End of Production (EOP = t0).

The finished product is presented as a single dose vial, containing suitable amount of solution that allows delivery of 7.4 GBq of radioactivity at injection time.

Considering the variable injection time and constant decay of the radionuclide, the filling volume needed for an activity of 7.4 GBq at injection time is calculated and can range from 20.5 and 25.0 ml.
The active substance is lutetium (\(^{177}\)Lu) oxodotreotide also known as lutetium Lu 177 dotatate. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances\(^1\).

The other ingredients are: acetic acid, sodium acetate, gentisic acid, ascorbic acid, pentetic acid, sodium chloride, sodium hydroxide, water for injections\(^6\).

Natural decay of the radionuclide is a property of any radiopharmaceutical, whether it is produced industrially or in-house. Consequently, specific activity, total radioactivity, and radio concentration (volumetric activity) of the finished product change over time.

AAA developed the finished product as a ready to use radiopharmaceutical solution for infusion. Overall manufacturing of the finished product involves an automated continuous process, where the synthesis of the active substance is also part of this process.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or in-house specifications. There are no novel excipients used in the finished product formulation\(^1\). The list of excipients is included in section 6.1 of the SmPC\(^6\).

The primary packaging is clear colourless type I glass vial, closed with a rubber stopper and aluminium seal. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product\(^1\).

**Manufacture of the product and process controls**

The radioactive active substance is produced as a sterile, aqueous concentrated solution. The active substance process consists of combining the carrier ligand and the radiolabelled precursor followed by sterile filtration. The active substance is produced in a shielded closed-system; manufacturing, purification and formulation process of the active substance are part of a continuous process. The decay of the radionuclide does not allow enough time for any interruption. At the end of synthesis, the active substance is collected in a sterile recovery type I vial in the dispensing isolator.

**Dosage form**

LUTATHERA\(^®\) is a sterile ready-to-use solution for infusion containing (\(^{177}\)Lu) oxodotreotide as Drug Substance with a volumetric activity of 370 MBq/mL at reference date and time (calibration time (tc)).
Calibration time (tc) corresponds to the End of Production (EOP = t0), which is the time of measurement of the activity of the first QC vial. The shelf life of Drug Product is defined as 72 hours after calibration time. LUTATHERA® is delivered as a single dose vial, containing suitable amount of solution that allows delivery of 7.4 GBq of radioactivity at injection time.

Manufacturing site prepares single doses calibrated within the range of 7.4 GBq ± 10 % (200 mCi) between t0+6h and t0+52h after the end of production. Certificates of release report both the exact activity provided and the time when this activity is reached. This value is declared as “Injection time: {DD MM YYYY} {hh:mm} UTC”.

Stability of the product

Based on available stability data, the proposed shelf-life of 72 hours from the date and time of calibration stored below 25 °C in the original package to protect from ionizing radiation (lead shielding) as stated in the SmPC (section 6.3) is acceptable.

3.2 Clinical trials

Investigator-driven phase I/II studies

177Lu-based PRRT has been available for investigational use for more than 10 years. Many investigator-initiated studies have been carried out in clinical centers in Europe, Asia and Australia, having treated more than 3,000 patients with somatostatin receptor positive NETs. The results of these studies have demonstrated meaningful evidence of tumor regression and safety. Furthermore, if kidney-protective agents are used, side effects of this therapy are usually few and mild.

Erasmus phase I/II study was a monocentric single arm open label study (protocol MEC 127.545/1993/84) conducted by the Erasmus Medical Center (Rotterdam, The Netherlands) to evaluate the efficacy of LUTATHERA® (7,400 MBq administered for 4 times every 8 weeks) in patients with various somatostatin receptor positive NETs. 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 (full analysis set) Dutch population with gastroenteropancreatic and bronchial NETs are presented in the table of the following page. Best response, ORR and DoR observed in the Erasmus phase I/II study in Dutch patients with GEP and bronchial NETs – (FAS, N=360).
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 the following Table.

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

<table>
<thead>
<tr>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>All*</td>
<td>360</td>
<td>11</td>
<td>3%</td>
</tr>
<tr>
<td>Bronchial</td>
<td>19</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>133</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Foregut**</td>
<td>12</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>Midgut</td>
<td>183</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Hindgut</td>
<td>13</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORR</th>
<th>DoR (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>All*</td>
<td>162</td>
</tr>
<tr>
<td>Bronchial</td>
<td>7</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>81</td>
</tr>
<tr>
<td>Foregut**</td>
<td>7</td>
</tr>
<tr>
<td>Midgut</td>
<td>61</td>
</tr>
<tr>
<td>Hindgut</td>
<td>6</td>
</tr>
</tbody>
</table>

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
Given the promising results of the Erasmus Phase I/II study, and as mentioned in the Introduction section, Advanced Accelerator Applications, decided to pursue the development of \(^{177}\text{Lu}\) oxodotreotide for the treatment of NETs patients and the company conducted a pivotal phase III study (The NETTER-1 Study)\(^6\) to apply for a Marketing Authorization in Europe and in the United States.

Both the European Commission\(^5\) and the FDA granted orphan drug designation to \(^{177}\text{Lu}\) oxodotreotide for the treatment of GEP-NETs (EU/3/07/523; US 08-2710/12-Jan-2009).

**Phase III NETTER-1 Study\(^7,11\)**

NETTER-1\(^7\) [Clinical Trials .gov number NCT01578239; EudraCT number 2011-005049-11] published in the New England Journal of Medicine on 12 Jan 2017 was a multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with \(^{177}\text{Lu}\)-DOTATATE (now \(^{177}\text{Lu}\) oxodotreotide) to octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors. The study was positive with highly significant results\(^7,11\).

The primary objective of the study\(^7\) was to compare Progression Free Survival (PFS) after treatment with LUTATHERA\(^8\) plus 30 mg octreotide LAR (symptoms control) to treatment with high dose (60 mg – double label dose) octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, well-differentiated midgut neuroendocrine tumors.

The primary efficacy endpoint\(^7\) was PFS, defined as the time from randomization to documented, centrally assessed disease progression, as evaluated by the Independent Reading Centre (IRC), and death due to any cause.

Secondary objectives were\(^7\)
- To compare the Objective Response Rate (ORR) between the two study arms.
- To compare the Overall Survival (OS) between the two study arms.
- To compare the Time to Tumour Progression (TTP) between the two study arms.
- To evaluate the safety and tolerability of \(^{177}\text{Lu}\) oxodotreotide.
- To evaluate the health-related quality of life (QoL) as measured by the EORTC QLQ-30 and G.I.NET21 questionnaires.
The secondary efficacy variables were
- Objective Response Rate (ORR)
- Overall Survival (OS)
- Time to Tumor Progression (TTP)
- Duration of Response (DoR)

Design of NETTER-1:

Main inclusion criteria were:
- Patients ≥18 years of age
- Presence of metastasized or locally advanced, inoperable (with curative intent) at enrollment time, histologically proven, midgut carcinoid tumor
- Ki67 index ≤ 20%
- Treatment with octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to randomization in the study
- Progressive disease based on RECIST Criteria, Version 1.1 while receiving octreotide LAR (20-30 mg/3-4 weeks).
- Confirmed presence of somatostatin receptors on all target lesions, based on positive OctreoScan® imaging within 24 weeks prior to randomization in the study
- Karnofsky Performance Score (KPS) ≥ 60

Main exclusion criteria were:
- Either serum creatinine >150 μmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min.
- Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x109/L (2000/mm3); platelets <75x109/L (75x103/mm3).
- Total bilirubin >3 x ULN
- Serum albumin <3.0 g/dL unless prothrombin time is within the normal range
- Pregnancy or lactation
• Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization in the study
• Any surgery, radioembolization, chemoembolization, chemotherapy and radiofrequency ablation within 12 weeks prior to randomization in the study
• Interferons, everolimus or other systemic therapies within 4 weeks prior to randomization in the study
• Known brain metastases, unless treated and stabilized
• Uncontrolled congestive heart failure and uncontrolled diabetes mellitus
• Prior external beam radiation therapy to more than 25% of the bone marrow

Measurement of outcomes
An objective CT/MRI tumor assessment was performed in both arms every 12 ± 1 weeks from the randomization date (central assessment). Date of death was recorded at any time during the treatment/assessment phase and the long-term follow-up assessment phase, when known.
Safety was assessed on the basis of adverse events (AEs), adverse events of special interest (AESIs), laboratory results for hematology, blood chemistry and urinalysis, physical examinations, vital signs, electrocardiogram (ECG), and KPS.

Randomization
Eligible patients were randomly assigned in an equal ratio (1:1) to one of the two study arms. Randomization was stratified according to OctreoScan® tumor uptake score (Grade 2, 3 and 4); and the length of time that patients have been on the most recent constant dose of octreotide prior to randomization (≤6 and >6 months), according to a stratified permuted block scheme with a block size of 4.

Study treatments
LUTATHERA® was available as a ready-to-use radioactive liquid solution for intravenous infusion.
Patients in the experimental group received in total 29.6 GBq (800 mCi) of LUTATHERA® administered in four equally divided doses, i.e. four administrations of 7.4 GBq (200 mCi) of LUTATHERA®, each dose to be infused over 30 minutes, at 8±1-week intervals, which could be extended to 16 weeks for resolving acute toxicity.
Patients were scheduled to continue to receive study treatment until unacceptable toxicity, progressive disease, inability or unwillingness of the patient to comply with study procedures or patient withdrawing consent to participate.
Predefined rules were established for the management of patients who experienced dose-modifying toxicities in the LUTATHERA® arm.
Patients in the octreotide group (octreotide acetate powder for suspension for intramuscular (i.m.) injection) received 60 mg octreotide acetate (Sandostatin® LAR) treatment every 4 weeks (i.m. injections) ± 3 days until the final overall analysis of PFS, unless the patient progressed or died.

**Patients’ and tumors characteristics**

The characteristics of patients and tumors were well balanced between the 2 arms.

**Main patients characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LUTATHERA®, n=116</th>
<th>octreotide LAR, n=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median ± SD</td>
<td>63.5 ± 9.4</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>63.3 ± 9.4</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Female</td>
<td>53 (45.7)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>63 (54.3)</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>Mean ± SD</td>
<td>25.4 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>26.2 ± 4.7</td>
<td></td>
</tr>
<tr>
<td>Median time (in months) between the oldest pre-baseline and baseline scans*</td>
<td>Median</td>
<td>11.4</td>
</tr>
<tr>
<td>Karnofsky PS</td>
<td>100</td>
<td>29 (25.0)</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>53 (45.7)</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>26 (22.4)</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>88.6 ± 9.3</td>
</tr>
</tbody>
</table>

* Median time (in months, per e-CRF data) between oldest pre-baseline and baseline scan, used to determine the progression at enrolment**.
Main tumors characteristics, FAS$^{11,44}$

<table>
<thead>
<tr>
<th></th>
<th>LUTATHERA®, n=116</th>
<th>octreotide LAR, n=113</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor site, n (%)</strong></td>
<td>Jejunum</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td></td>
<td>Ileum</td>
<td>86 (74.1)</td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Right colon</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>20 (17.2)</td>
</tr>
<tr>
<td><strong>Disease stage, n (%)</strong></td>
<td>Not assessed</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>II A</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>III A</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>III B</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>105 (90.5)</td>
</tr>
<tr>
<td><strong>Ki67</strong></td>
<td>G1 (≤ 2%)</td>
<td>76 (65.5)</td>
</tr>
<tr>
<td></td>
<td>G2 (3-20%)</td>
<td>40 (34.5)</td>
</tr>
<tr>
<td><strong>Metastases, n (%)</strong></td>
<td>Yes</td>
<td>116 (100)</td>
</tr>
<tr>
<td><strong>Site of metastases, n (%)</strong></td>
<td>Bone</td>
<td>13 (11.2)</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>97 (83.6)</td>
</tr>
<tr>
<td></td>
<td>Lungs</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>77 (66.4)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>40 (34.5)</td>
</tr>
</tbody>
</table>

**Statistics**

The primary analysis of PFS was conducted after 74 PFS events (evaluable and centrally confirmed progressions or deaths) which provide 90% power to confirm primary endpoint (PFS). The sample size of 230 patients was calculated to also allow for analysis of OS. The final OS analysis will occur when 158 deaths have occurred or 5 years after the last subject is randomized. An interim analysis for OS was done at the time of the final analysis of PFS using a conservative O’Brien-Fleming plan ($\alpha = 0.0085\%$). A hierarchical method was used to control family-wise type I error for ORR and OS secondary endpoints. This required an analysis of ORR at $p = 0.05$ prior to OS analysis. Both PFS and OS were analyzed by the unstratified log-rank test with medians estimated by Kaplan-Meier methodology.

**Results**

two hundred twenty-nine (229) patients have been randomized to receive either LUTATHERA® ($n=116$) or octreotide LAR ($n=113$). 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$^6$. 


Results of efficacy

At the time of final per-protocol PFS statistical analysis (cut-off date 24 July 2015, SmPC), the number of centrally confirmed disease progressions or deaths was 21 events in the LUTATHERA® arm and 70 events in the octreotide LAR arm. PFS differed highly 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.

PFS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - cut-off date 24 July 2015 (NETTER-1 phase III study; FAS, \( N=229 \))
Progression Free Survival at the 24 July 2015 cut-off date is the final analysis for the primary endpoint according to the protocol and the Statistical Analysis Plan (SAP)\textsuperscript{6,11}.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LUTATHERA\textsuperscript{®}</th>
<th>Octreotide LAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>116</td>
<td>113</td>
</tr>
<tr>
<td>Patients with events</td>
<td>21</td>
<td>70</td>
</tr>
<tr>
<td>Censored patients</td>
<td>95</td>
<td>43</td>
</tr>
<tr>
<td>Median months (95%-CI)</td>
<td>NR</td>
<td>8.5</td>
</tr>
<tr>
<td>p value of Log rank test</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95%-CI)</td>
<td>0.18 (95% CI : 0.11 ; 0.29)</td>
<td></td>
</tr>
</tbody>
</table>

During the regulatory review process, a request was made to submit an update of the NETTER-1 PFS most recent data. The cut-off date for this analysis was 30 June 2016\textsuperscript{6,11}.

This analysis was unplanned and holds no statistical penalty. The results were in line with the PFS per protocol final analysis. (PFS Events: 30 LUTATHERA\textsuperscript{®} vs 78 octreotide LAR; Censored: 87 LUTATHERA\textsuperscript{®} vs 36 octreotide LAR; mPFS: 28.4 vs 8.5m; p<0.0001; HR: 0.21 (95% CI: 0.14 - 0.33); 79% risk reduction PD or death for the patients who were treated in the LUTATHERA\textsuperscript{®} arm)\textsuperscript{6,11}.

With respect to overall survival (OS), in the NETTER-1 protocol OS multiple testing, according to protocol and SAP, foresaw one interim analysis to be tested at a P value of 0.000085 to be performed at the time of the PFS final analysis, and one final analysis to be tested at a P value of 0.05 to be conducted after 158 deaths or 5 years after randomization of the last patient\textsuperscript{7}.

At the time of the planned per protocol and SAP OS interim analysis (24 July 2015, SmPC), there were 17 deaths in the LUTATHERA\textsuperscript{®} arm and 31 in octreotide LAR 60 mg. Median OS was 27.4 months in octreotide LAR arm and was not reached in LUTATHERA\textsuperscript{®} arm. Hazard ratio was 0.459 in favour of LUTATHERA\textsuperscript{®}, with a p= 0.009 which did not reach the level of significance for interim analysis mentioned in the plan (α = 0.0085\%)\textsuperscript{6,11}. 
During the regulatory review process, a request was made to submit an update of the NETTER-1 OS most recent data. The cut-off date for this analysis was 30 June 2016. This analysis was unplanned and holds no statistical penalty. The analysis showed similar trend with 28 deaths in the LUTATHERA® arm and 43 in octreotide LAR 60 mg arm, an HR of 0.536. According to these latest data, the median OS was reached in the octreotide LAR arm after 27.4 months and was still not reached in LUTATHERA® arm after 42 months. The final OS analysis is foreseen after 158 cumulative deaths have occurred or five years after the last patient was randomized, whichever occurs first.
Dose-modifying toxicities (DMT) in the LUTATHERA® group, n=111

**LUTATHERA® Exposure**

<table>
<thead>
<tr>
<th>Number of administration</th>
<th>Patients who completed treatment phase (N=103†)</th>
<th>no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>79 (77)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>6 (6)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>12 (12)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>5 (5)</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>1 (77)</td>
</tr>
</tbody>
</table>

All treated patients (N=111)

<table>
<thead>
<tr>
<th>No DMT</th>
<th>103 (93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMT</td>
<td>8 (7)</td>
</tr>
</tbody>
</table>

* DMT denotes dose-modifying toxicity.
† Excluding patients still under treatment (n=8) or no treatment (n = 5).

The benefits of LUTATHERA® were observed irrespective of baseline stratification and prognostic factors.

### Prespecified Subgroup Analysis of Progression-Free Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrahepatic metastases</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.20 (0.12–0.35)</td>
</tr>
<tr>
<td>No</td>
<td>0.15 (0.04–0.50)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>0.21 (0.09–0.49)</td>
</tr>
<tr>
<td>≤ULN</td>
<td>0.19 (0.11–0.35)</td>
</tr>
<tr>
<td>Somatostatin receptor expression</td>
<td></td>
</tr>
<tr>
<td>Grade &lt;4</td>
<td>0.23 (0.12–0.41)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0.18 (0.08–0.39)</td>
</tr>
<tr>
<td>5-HIAA</td>
<td></td>
</tr>
<tr>
<td>&gt;2x ULN</td>
<td>0.15 (0.08–0.29)</td>
</tr>
<tr>
<td>≤2x ULN</td>
<td>0.19 (0.06–0.55)</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td></td>
</tr>
<tr>
<td>&gt;2x ULN</td>
<td>0.19 (0.09–0.27)</td>
</tr>
<tr>
<td>≤2x ULN</td>
<td>0.11 (0.01–0.67)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
</tr>
<tr>
<td>ENETS Grade 2</td>
<td>0.15 (0.07–0.34)</td>
</tr>
<tr>
<td>ENETS Grade 1</td>
<td>0.24 (0.13–0.44)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.24 (0.12–0.45)</td>
</tr>
<tr>
<td>Female</td>
<td>0.17 (0.08–0.35)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>0.24 (0.12–0.48)</td>
</tr>
<tr>
<td>≤65 yr</td>
<td>0.20 (0.10–0.38)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.21 (0.13–0.33)</td>
</tr>
</tbody>
</table>

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**Safety**

In the SAF population, the majority of patients (73.8%) in the LUTATHERA® arm was exposed to >22.2 GBq (>600 mCi), only few patients (2.7%) received 0 to 7.4 GBq (0 - 200 mCi), however the study was still ongoing at the time of the primary end-point analysis.

Please review again the Summary of the Safety Analysis in Page 27 of this Monograph.

**Summary of adverse events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LUTATHERA®, n=111</th>
<th>Octreotide LAR 60 mg (N = 110)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Any</em></td>
<td>106 (95)</td>
<td>95 (86)</td>
<td>0.02</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>95 (86)</td>
<td>34 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Serious adverse event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Any</em></td>
<td>29 (26)</td>
<td>26 (24)</td>
<td>0.76</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>10 (9)</td>
<td>1 (1)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Withdrawal from the trial because of adverse event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Because of any adverse event</td>
<td>7 (6)</td>
<td>10 (9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Because of adverse event related to treatment</td>
<td>5 (5)</td>
<td>0 (0)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* The safety population included all patients who underwent randomization and received at least one dose of trial treatment.
† P values were calculated with the use of Fisher’s exact text.

**Treatment emergent AEs and grade, SAF n=221**

For NETTER-1, the safety population comprised of patients with mid-gut GEP-NETs who had received at least one dose of LUTATHERA®. For the Erasmus MC study, the safety analysis was not limited to GEP-NETs and includes all tumour types enrolled in the Erasmus MC study.

For SOC “blood and lymphatic system disorders”, the frequency of AEs in the LUTATHERA® arm was higher than in the octreotide LAR arm. Suggesting an effect of LUTATHERA® on hematology, although transient and consistent with previous findings as already reported.
The identified treatment emergent AESIs in the Dutch population were: thrombocytopenia (129 cases, 15.9%), leukopenia (40 cases, 4.9%), anaemia (33 cases, 4.1%), cardiac disorders (62 cases, 7.6%), renal and urinary disorders (49 cases, 6.0%), secondary haematological malignancies (20, 2.5%).

All AESI belonging to the neoplasms SOC were of haematological origin. More specifically, there were 16 Dutch patients (2.0%) who developed myelodysplastic syndrome (MDS). The other AESI with a frequency greater/equal to 1% were hypotension (10 patients, 1.2%), cardiac failure (12 patients, 1.5%), myocardial infarction (9 patients 1.1%), renal failure (8 patients, 1.0%), and renal impairment (10 patients, 1.2%). The incidence of other blood neoplasms was, 0.1% for acute leukaemia and 0.4% for acute myeloid leukaemia, 0.1% for chronic myeloid leukaemia and 0.1% for chronic myelomonocytic leukaemia.

99% of the patients in the LUTATHERA® arm and 95% in the Octreotide LAR arm experienced at least one AE during the study. 98% of the patients in the LUTATHERA® arm and 93% in the Octreotide LAR arm experienced at least one treatment emergent AE (TEAE).

TEAEs leading to premature withdrawal occurred in 14 patients (12.5%) in the LUTATHERA® arm and in 12 patients (10.8%) in the Octreotide LAR arm; the difference observed in the two arms was not statistically significant. Eight patients (7.1%) in the LUTATHERA® arm and one patient (0.9%) in the Octreotide LAR arm reported TEAEs leading to premature withdrawal which were considered by the investigator to be related to study treatment.

In the Lutathera arm, the most frequent possible cause of treatment emergent adverse events based on the number of episodes was:

- treatment for 701 (38.3%) AEs,
- pre-existing/ underlying disease for 425 (23.2%)
- AEs,
- unknown for 271 (14.8%) AEs,
- other causes for 144 (7.9%) AEs,
- other treatment for 44 (2.4%) AEs
- protocol related procedure for 23 (1.3%) AEs.

In the Octreotide LAR arm, the most frequent possible cause of treatment emergent adverse event based on the number of episodes was:

- pre-existing /underlying disease for 332 (35.5%) AEs,
- unknown for 231 (24.7%) AEs,
- other causes for 134 (14.36%) AEs,
- study treatment for 97 (10.7%) AEs,
- other treatment for 12 (1.3%) AEs and protocol related procedure for 5 (0.5%) AEs11.
For serum chemistry, in general, despite the high number of out of normal range values, the changes did not show a clear trend towards worsening of the laboratory parameters under study treatment. There was no grade 3 to 5 increase in liver toxicity relevant parameters. Only at week 12 it was observed a statistically significant change (p= 0.002) from baseline in creatinine clearance between the 2 arms in favor of LUTATHERA® (+2.2 ml/min in LUTATHERA® arm and -1.7 ml/min in the octreotide LAR). Overall, creatinine clearance remained stable during the 2-year follow-up period.44,11,45
Creatinine increase and creatinine clearance in the two study arms\textsuperscript{45}

<table>
<thead>
<tr>
<th></th>
<th>(^{177}\text{Lu-Dotatate} (n=111))</th>
<th>Octreotide LAR (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

In the LUTATHERA\textsuperscript{®} arm, 49 patients (43.8%) had a lymphopenia (Grade 3 or 4) and 22 patients (19.6%) had an increased GGT (Grade 3 or 4) diagnosed post randomization. In each of the following categories, between 4 and 7 patients (3.6 to 6.3%) showed post randomization Grade 3 or 4 hyperglycemia, hyperuricemia, hypokalemia, alkaline phosphatase increased, ASAT increased and ALAT increased\textsuperscript{44}.

In the comparator arm, the following toxicities were notable: lymphopenia (5 (5%) patients), hyperuricemia (7 (6.3%) patients), GGT increased (19 (17.1%) patients), and alkaline phosphatase increased (10 (9%) patients).

As expected, considering the mechanism of action of LUTATHERA\textsuperscript{®}, only relevant differences were observed for the haematological parameters. Regarding the Grade 3 or 4 laboratory toxicities, no relevant differences were observed between the 2 arms, except for lymphopenia, however lymphopenia was not associated with an increased number of infections in the LUTATHERA\textsuperscript{®} arm compared to the control arm\textsuperscript{44}.

**Platelets mean relative change**\textsuperscript{45}
Leukocytes count relative changes

Lymphocytes count relative changes

Neutrophil count relative changes
Health related QoL data, a pre-specified secondary objective in the NETTER-1 trial, demonstrate not only a maintenance but an improvement in those patients in the LUTATHERA® arm. Khan et al published Health related QoL data for the Erasmus cohort 47 concluding that the Global Health Status/QoL and the patients’ symptoms improved significantly after LUTATHERA® therapy and there was no significant decrease in QoL in patients who had no symptoms before therapy46,47.

Conclusions
In this randomized phase III study comparing LUTATHERA® and octreotide LAR 60mg in patients with G1 or G2, unresectable NETs of the small intestine, progressing under octreotide 20-30mg, the characteristics were well balanced in terms of demography. For the majority of patients in the FAS the ileum was diagnosed as primary tumor site (73.4%); for almost all patients (99.1%) the presence of metastases was confirmed (liver (83.4%) and/or lymph node metastases (62.0%))7.

The primary efficacy end-point was PFS as measured by objective tumor response, determined by RECIST Criteria. At the time of final per-protocol PFS statistical analysis (cut–off date 24 July 2015, SmPC), the number of centrally confirmed disease progressions or deaths was 21 events in the LUTATHERA® arm and 70 events in the octreotide LAR arm. PFS differed highly 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 LAR6.

At 20 months 65% of the patients on the LUTATHERA® arm were alive and free from progression vs only 11% in the control arm7. With respect to overall survival (OS), in the NETTER-1 protocol OS multiple testing, according to protocol and SAP, foresaw one interim analysis to be tested at a P value of 0.000085 to be performed at the time of the PFS final analysis, and one final analysis to be tested at a P value of 0.05 to be conducted after 158 deaths or 5 years after randomization of the last patient6.

At the time of the planned per protocol and SAP OS interim analysis (24 July 2015, SmPC), there were 17 deaths in the LUTATHERA® arm and 31 in octreotide LAR 60 mg. Median OS was 27.4 months in octreotide LAR arm and was not reached in LUTATHERA® arm. Hazard ratio was 0.459 in favour of LUTATHERA®, with a very good p= 0.009 which did not reach the level of significance for interim analysis mentioned in the plan (α = 0.0085%).
During the regulatory review process, a request was made to submit an update of the NETTER-1 OS most recent data. The cut-off date for this analysis was 30 June 2016. This analysis was unplanned and holds no statistical penalty. According to these latest data, median OS of 27.4 months is in octreotide LAR arm and is still not reached in LUTATHERA® arm after 42 months.

Patients in the LUTATHERA® arm had a significantly higher ORR, compared to patients of the control arm. The ORR was 18% in the LUTATHERA® arm compared to 3% in the Octreotide LAR arm (p<0.001). The objective response rate was defined as the percentage of patients who had a response according to Response Evaluation Criteria in Solid Tumors (RECIST) (sum of partial responses and complete responses). The P value was calculated with the use of Fisher’s exact test.

Treatment with LUTATHERA® was relatively safe and well tolerated. The incidence of SAEs, laboratory abnormalities and other physical examination findings did not indicate a worsening of the safety variables relative to the baseline or any issues with tolerability.

As expected, considering the mechanism of action of LUTATHERA®, only relevant differences were observed for the hematological parameters. Regarding the Grade 3 or 4 laboratory toxicities, no relevant differences were observed between the 2 arms, except for lymphopenia, however lymphopenia was not associated with an increased number of infections in the LUTATHERA® arm compared to the control arm.

3.3 Place of PRRT in the therapeutic strategy
LUTATHERA®, 370 MBq/mL, solution for infusion is a ready-to-use product, indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults.

PRRT is already a reality in the clinical practice and it is endorsed by the relevant scientific societies.

The latest Consensus Guidelines issued by the European NeuroEndocrine Tumor Society (ENETS) were published in Neuroendocrinology April 2017 (ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues). They consider that PRRT appears to be a highly effective therapy, although long term data and more insights on safety, combinations, and practical experience are warranted.
PART 4 REFERENCES


11. LUTATHERA® EPAR  www.ema.europa.eu


44. Clinical Study Report (CSR)V.02.05072017