Advanced Accelerator Applications

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

A NEW ERA OF PRECISION TARGETING HAS ARRIVED

Consider LUTATHERA® (lutetium Lu 177 dotatate) treatment for your adult patients with somatostatin receptor-postive GEP-NETs

The first FDA-approved Peptide Receptor Radionuclide Therapy (PRRT)[1]

Indication

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

Important Safety Information

Radiation Exposure: Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures.

Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

Neuroendocrine tumors (NETs): a potentially fatal malignancy observed with increasing frequency

- NETs are malignancies that arise from neuroendocrine cells, which are specialized cells that secrete hormones and other bioactive substances.[2] NETs may or may not be secretory[2]
- Most NETs originate in the GI tract, lungs, and pancreas[2]
- The reported incidence of NETs has increased >6-fold over the last 4 decades, according to SEER data from 1973-2012[3]

Advanced NETs may be fatal, even for patients with low-grade disease

- The 5-year overall survival (OS) rate for patients with distant metastases of well-differentiated disease ranged from 29% to 69%, depending on primary tumor site[3]
- OS in advanced disease has increased recently, likely due to advances in systemic therapy[3]

PATIENTS WITH GEP-NETs MAY BENEFIT FROM NEW, NOVEL TREATMENTS

LUTATHERA® (lutetium Lu 177 dotatate) is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Important Safety Information

DRUG INTERACTIONS

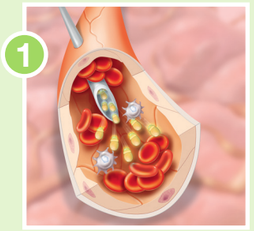
Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended.

GI, gastrointestinal; SEER, Surveillance, Epidemiology, and End Results.

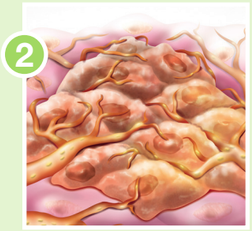
Introducing the first FDA-approved Peptide Receptor Radionuclide Therapy (PRRT)

- LUTATHERA® (lutetium Lu 177 dotatate), the first FDA-approved PRRT, is a radiopharmaceutical created by attaching a radionuclide to a peptide that binds to receptors on GEP-NET cells
- LUTATHERA delivers radiation into the tumor, causing cellular death

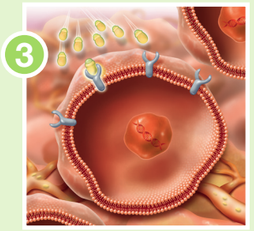
PRRT: a novel treatment strategy for GEP-NETs



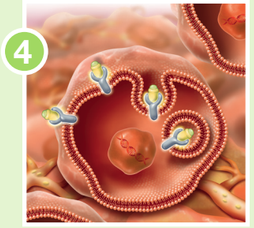
LUTATHERA is injected into the bloodstream…



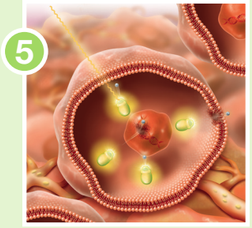
…where it concentrates in GEP-NET sites.



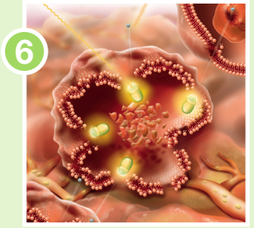
LUTATHERA binds to somatostatin receptors overexpressed by GEP-NET cells.



LUTATHERA is internalized into GEP-NET cells…



…where it delivers radiation within the cells…



…which leads to their death.

Important Safety Information

ADVERSE REACTIONS

The most common Grade 3-4 adverse reactions observed in LUTATHERA clinical trials were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), elevated AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).

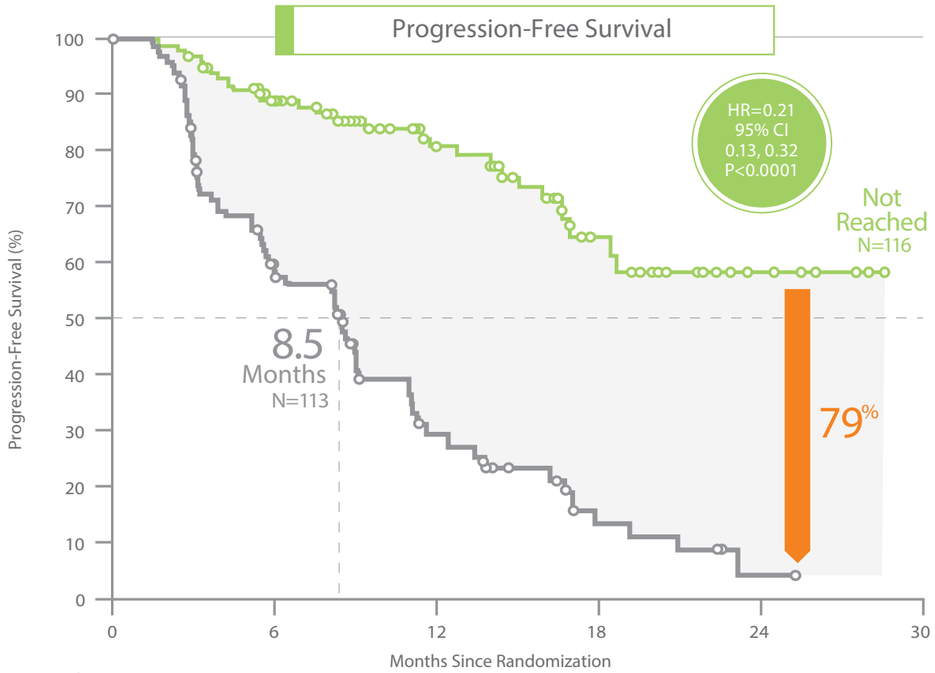
Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

Advanced Accelerator Applications

LUTATHERA® (lutetium Lu 177 dotatate) injection, for intravenous use

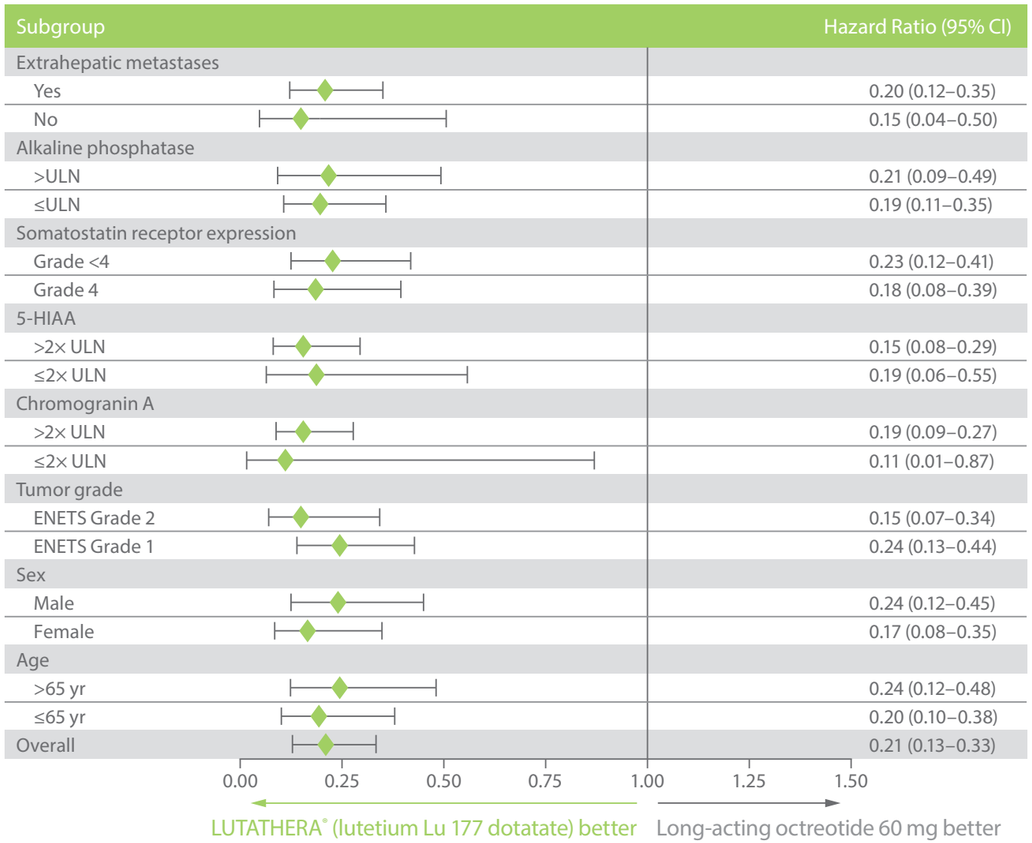
Markedly longer progression-free survival (PFS)[1,4]

- The phase 3 NETTER-1 trial was a multinational study that randomized 229 patients with inoperable, progressive, somatostatin receptor-positive, well-differentiated, midgut carcinoid tumors to[1,4]:
  - LUTATHERA® (lutetium Lu 177 dotatate) 4 doses of 7.4 GBq (200 mCi) each at planned intervals of 8 weeks (N=116)
  - Long-acting octreotide 60 mg monthly (N=113)
- Patients in the LUTATHERA treatment arm also received long-acting octreotide 30 mg after each LUTATHERA infusion and, following the 4 doses of LUTATHERA, received long-acting octreotide 30 mg monthly until disease progression or for up to 18 months after treatment initiation[1,4]



- **LUTATHERA demonstrated a 79% reduction in the risk of disease progression or death** when compared to long-acting octreotide 60 mg monthly (HR 0.21, 95% CI 0.13-0.32, *P*<0.0001)[1,4]
- Number of events (progression or death)[1]:
  - LUTATHERA: 27 (23%)
  - Long-acting octreotide 60 mg: 78 (69%)

Consistent treatment benefit on PFS across all prespecified subpopulations[4]



Reproduced with permission from New England Journal of Medicine.

5-HIAA, 5-hydroxyindoleacetic acid; ENETS, European Neuroendocrine Tumor Society; ULN, upper limit of normal.

Important Safety Information

Hepatotoxicity: In LUTATHERA clinical trials, <1% of patients were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue based on severity of reaction.

Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

Advanced Accelerator Applications
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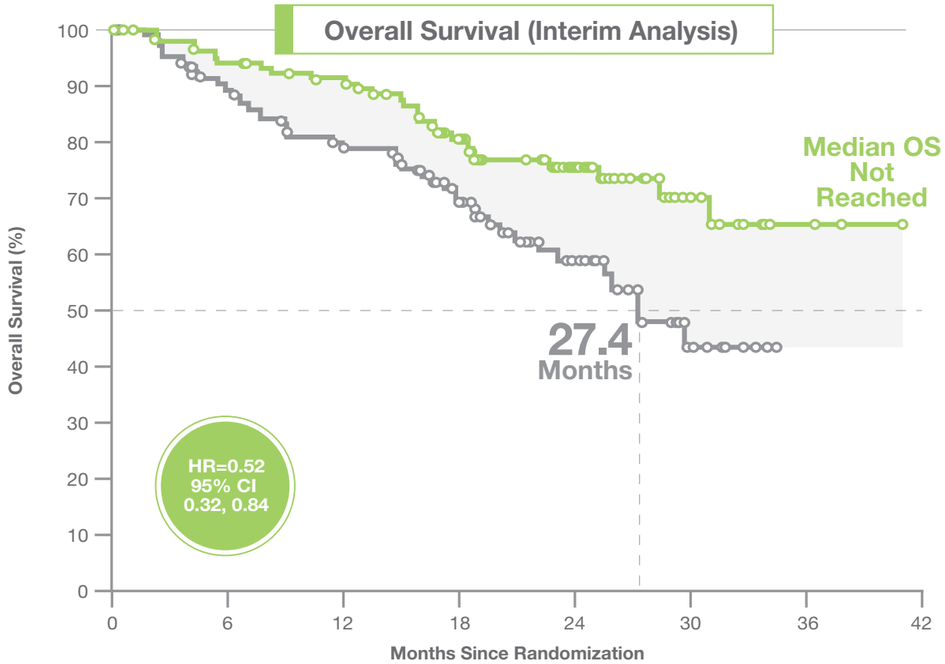
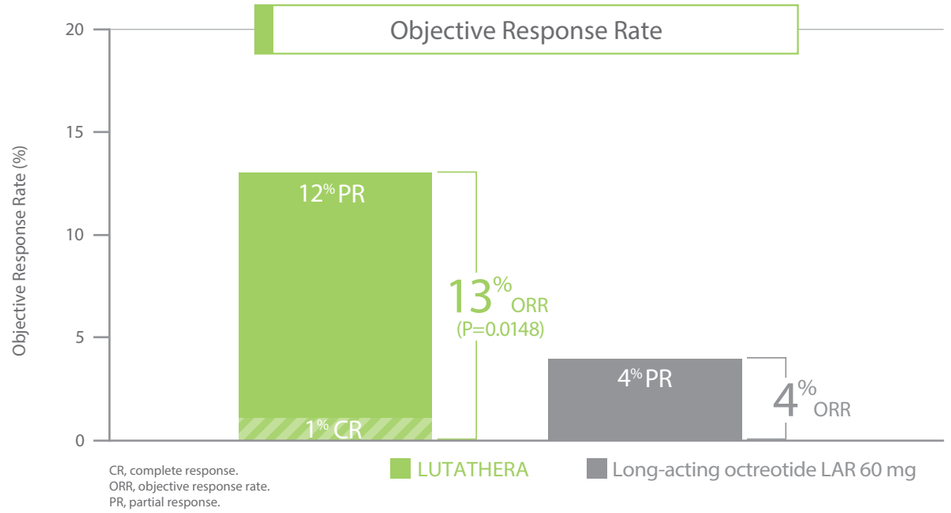
Updated 2016 interim analysis suggests longer overall survival (OS)[1]



P value did not meet prespecified threshold for significance for interim analysis.

- **48% reduction in the risk of death** (HR=0.52, 95% CI 0.32-0.84)[1]
- Number of deaths[1] (updated):
  - LUTATHERA: 27 (23%)
  - Long-acting octreotide 60 mg: 43 (38%)
- The final OS analysis will be conducted after 158 deaths have occurred or 5 years after last patient randomization[4]

3X greater objective response rate with LUTATHERA® (lutetium Lu 177 dotatate)[1]



Important Safety Information

Renal Toxicity: Treatment with LUTATHERA will expose kidneys to radiation, which may impair renal function. In a Phase I/II clinical trial <1% of patients developed renal failure 3 to 36 months following LUTATHERA. Monitor serum creatinine and creatinine clearance to assess changes in renal function. Advise patients to urinate frequently during and after administration of LUTATHERA. A concomitant intravenous infusion of amino acids during LUTATHERA administration is mandatory for renal protection. Patients with baseline renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild or moderate impairment. Withhold, reduce dose, or permanently discontinue based on severity of reaction.

Embryo-Fetal Toxicity: LUTATHERA can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and after. Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA.

Risk of Infertility: Radiation absorbed by testis and ovaries from the recommended cumulative LUTATHERA dose falls within the range in which temporary or permanent infertility can be expected following external beam radiotherapy.

Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

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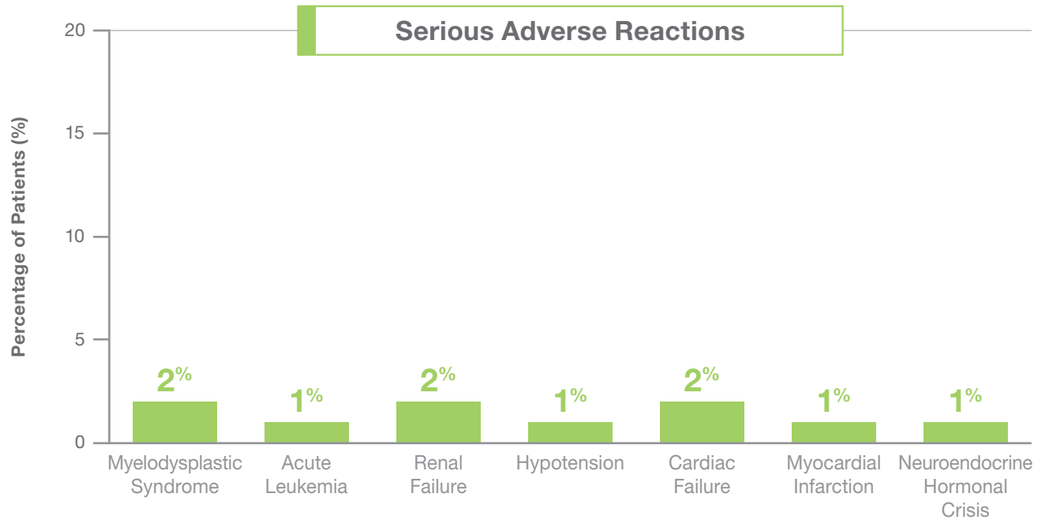
Adverse reactions[1]

Adverse Reactions Occurring in ≥5% (All Grades) of Patients Receiving LUTATHERA® (lutetium Lu 177 dotatate) With Octreotide in NETTER-1*				
	LUTATHERA and Long-Acting Octreotide (30 mg) (N=111)		Long-Acting Octreotide (60 mg) (N=112)	
Adverse Reaction*	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Cardiac disorders				
Atrial fibrillation	5	1	0	0
Gastrointestinal disorders				
Nausea	65	5	12	2
Vomiting	53	7	9	0
Abdominal pain	26	3	19	3
Diarrhea	26	3	18	1
Constipation	10	0	5	0
General disorders				
Fatigue	38	1	26	2
Peripheral edema	16	0	9	1
Pyrexia	8	0	3	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	11	3
Musculoskeletal and connective tissue disorders				
Back pain	13	2	10	0
Pain in extremity	11	0	5	0
Myalgia	5	0	0	0
Neck pain	5	0	0	0
Nervous system disorders				
Headache	17	0	5	0
Dizziness	17	0	8	0
Dysgeusia	8	0	2	0
Psychiatric disorders				
Anxiety	12	1	5	0
Renal and urinary disorders				
Renal failure†	12	3	3	1
Radiation-related urinary tract toxicity‡	8	0	3	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	1	6	0
Skin and subcutaneous tissue disorders				
Alopecia	12	0	2	0
Vascular disorders				
Flushing	14	1	9	0
Hypertension	12	2	7	2

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays adverse reactions occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2% (grades 3-4)].
† Includes the terms: Glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, renal impairment.
‡ Includes the terms: Dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain, and urinary incontinence.

- 6% of patients required a dose reduction, and 13% of patients discontinued LUTATHERA
- 5 patients discontinued LUTATHERA for renal-related events, and 4 discontinued for hematological toxicities

Long-term (median >4 years) follow-up after LUTATHERA® (lutetium Lu 177 dotatate) treatment[1]



Important Safety Information

Myelosuppression: In LUTATHERA clinical trials, hematological adverse reactions occurred at the following rates (all grades/grade 3 or 4): anemia (81%/0), thrombocytopenia (53%/1%), and neutropenia (26%/3%). Blood cell counts must be monitored prior to, during, and after treatment. Dose modification or cessation of treatment may be necessary.

Secondary Myelodysplastic Syndrome and Leukemia: With a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide. In a Phase I/II clinical study, 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

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Discussing treatment with patients

Although information for your patient will be provided immediately prior to treatment by the health care professionals administering therapy, the following is provided for your information.

Because LUTATHERA® (lutetium Lu 177 dotatate) contains a radionuclide, patients must be informed of all specific measures they should adopt to minimize radiation exposure to others. Specific instructions will be provided by the radiation safety team at the administration site.

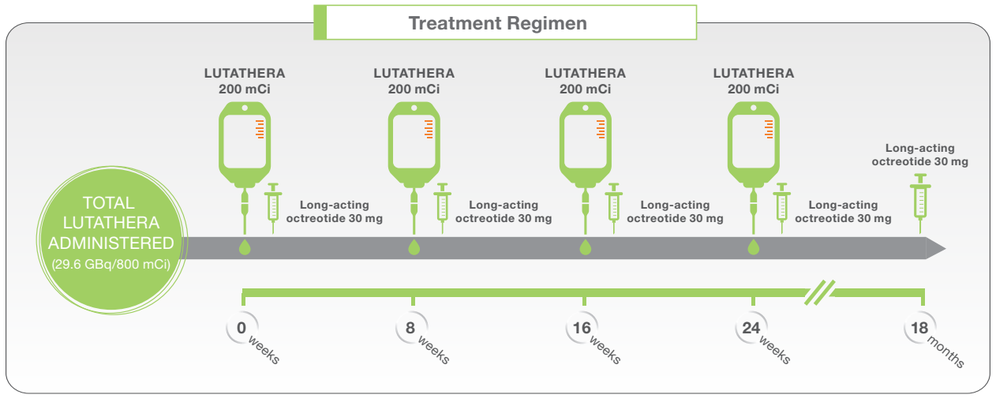
Advise patients:

- Of the potential risk to a fetus. Females of reproductive potential should use effective contraception during treatment with LUTATHERA and for 7 months after the final dose and should inform their health care provider of a known or suspected pregnancy. Males with female partners of reproductive potential should use effective contraception during treatment with LUTATHERA and for 4 months after the final dose
- To discontinue nursing during and after treatment with LUTATHERA and for 2.5 months after the last dose
- To drink a sufficient amount of water to urinate every hour on the day of LUTATHERA infusion and the day after. The patient should also be encouraged to defecate every day and to use a laxative if needed
- To avoid spending too much time in close contact (less than 1 meter) with the people they live with throughout the week following an administration of LUTATHERA, particularly young children and pregnant women
- Of the potential for secondary cancers, including myelodysplastic syndrome and acute leukemia
- Of the need for periodic tests to monitor for hepatotoxicity
- To report to a health care professional any signs of a potential adverse reaction even if not listed

This is not an exhaustive list of all information that should be provided to the patient. For further information, please refer to the accompanying full Prescribing Information for LUTATHERA.

The LUTATHERA® (lutetium Lu 177 dotatate) treatment regimen

- **Treatment course:** The recommended treatment regimen consists of 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. Following each dose, the patient should receive long-acting octreotide 30 mg. Long-acting octreotide 30 mg should be continued every 4 weeks after completing LUTATHERA until the patient's cancer spreads, grows, or gets worse or for up to 18 months following LUTATHERA treatment initiation



- **In case of toxicity,** interval between doses can be extended up to 16 weeks

Coadministered products

The following products are administered with LUTATHERA during a treatment session:

- An **antiemetic** should be administered 30 minutes before the start of the amino acid solution infusion to avoid treatment-related nausea and vomiting
- An **intravenous infusion of an amino acid solution** is started 30 minutes before LUTATHERA administration and continued during and for at least 3 hours after
  - Always administer the full amino acid solution treatment, even if administering a reduced dose of LUTATHERA

Important Safety Information

Neuroendocrine hormonal crisis: Manifesting with flushing, diarrhea, bronchospasm and hypotension, neuroendocrine hormonal crisis occurred in 1% of patients and typically occurred during or within 24 hours following the initial LUTATHERA dose. Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release. Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.

Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

Advanced Accelerator Applications
LUTATHERA® (lutetium Lu 177 dotatate) injection, for intravenous use

Patient support through AAA **Patient**CONNECT™

AAA **Patient**CONNECT™ provides services to support your patient's access to LUTATHERA® (lutetium Lu 177 dotatate) treatment.

This includes:

Reimbursement support services

- Insurance benefits verification
- Prior authorization support
- Claims appeal support
- Billing and coding support
- Payer policy support

Patient financial assistance

- Uninsured patient assistance
- Copay assistance for patients with commercial insurance

AAA PatientCONNECT™

Patient navigators may be reached by calling

1-844-NETS-AAA (638-7222)

Monday-Friday from 8 AM-8 PM

www.aaapatientconnect.com

Eligibility restrictions apply. For full terms and conditions, please call AAA **Patient**CONNECT™ at 1-844-NETS-AAA (638-7222).

Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the copayment support provided under this program, eg, copay refunds, participating patients and pharmacies are obligated to inform insurance companies and third-party payers of any benefits they receive and the value of this program, as required by contract or otherwise. Void where prohibited by law or restricted.

Important Safety Information[1]

INDICATION

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

WARNINGS AND PRECAUTIONS

- **Radiation Exposure:** Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures.
- **Myelosuppression:** In LUTATHERA clinical trials, hematological adverse reactions occurred at the following rates (all grades/grade 3 or 4): anemia (81%/0), thrombocytopenia (53%/1%), and neutropenia (26%/3%). Blood cell counts must be monitored prior to, during, and after treatment. Dose modification or cessation of treatment may be necessary.
- **Secondary Myelodysplastic Syndrome and Leukemia:** With a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide. In a Phase I/II clinical study, 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.
- **Renal Toxicity:** Treatment with LUTATHERA will expose kidneys to radiation, which may impair renal function. In a Phase I/II clinical trial <1% of patients developed renal failure 3 to 36 months following LUTATHERA. Monitor serum creatinine and creatinine clearance to assess changes in renal function. Advise patients to urinate frequently during and after administration of LUTATHERA. A concomitant intravenous infusion of amino acids during LUTATHERA administration is mandatory for renal protection. Patients with baseline renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild or moderate impairment. Withhold, reduce dose, or permanently discontinue based on severity of reaction.
- **Hepatotoxicity:** In LUTATHERA clinical trials, <1% of patients were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue based on severity of reaction.

Please see accompanying full Prescribing Information.

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(lutetium Lu 177 dotatate)
injection, for intravenous use

- **Neuroendocrine hormonal crisis:** Manifesting with flushing, diarrhea, bronchospasm and hypotension, neuroendocrine hormonal crisis occurred in 1% of patients and typically occurred during or within 24 hours following the initial LUTATHERA® (lutetium Lu 177 dotatate) dose. Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release. Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.
- **Embryo-Fetal Toxicity:** LUTATHERA can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and after. Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA.
- **Risk of Infertility:** Radiation absorbed by testis and ovaries from the recommended cumulative LUTATHERA dose falls within the range in which temporary or permanent infertility can be expected following external beam radiotherapy.

ADVERSE REACTIONS

The most common Grade 3-4 adverse reactions observed in LUTATHERA clinical trials were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), elevated AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).

The following serious adverse reactions have been observed with a median follow-up time of more than 4 years after treatment with LUTATHERA: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%). Patients should be counseled and monitored in accordance with the LUTATHERA Prescribing Information.

DRUG INTERACTIONS

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended.

Please see full Prescribing Information.

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

Distributed by: Advanced Accelerator Applications USA, Inc., NJ 07041

References

1. LUTATHERA [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; January 2018.
2. Jensen RT, Doherty GM. Carcinoid tumors and the carcinoid syndrome. In: DeVita VT, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 7th ed. Lippincott Williams and Wilkins. 2005; New York, NY.
3. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3(10):1335-1342.
4. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125-135.

Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

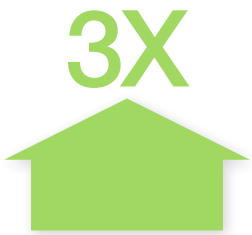
Advanced Accelerator Applications LUTATHERA® (lutetium Lu 177 dotatate) injection, for intravenous use

A NEW ERA OF PRECISION TARGETING FOR GEP-NETs HAS ARRIVED

Markedly longer progression-free survival and greater response rate[1,4]

In a clinical trial of patients with progressive, advanced, midgut neuroendocrine tumors, LUTATHERA® (lutetium Lu 177 dotatate) in combination with long-acting octreotide 30 mg vs long-acting octreotide 60 mg demonstrated:

- 79% reduction in the risk of disease progression or death (HR 0.21 [95% CI, 0.13, 0.32], *P*<0.0001)[1,4]



- 3X greater objective response rate: 13% for LUTATHERA vs 4% for long-acting octreotide 60 mg (*P*=0.0148)[1]

Important Safety Information

ADVERSE REACTIONS

The most common Grade 3-4 adverse reactions observed in LUTATHERA clinical trials were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), elevated AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).[1]

Consider LUTATHERA treatment for your adult patients with somatostatin receptor-postive GEP-NETs

Institution with radiopharmaceutical capabilities

- Speak with an AAA Account Manager by visiting www.lutathera.com and submitting a “contact-us” request
- AAA Account Managers are available to assist with the institution onboarding process

Institution without radiopharmaceutical capabilities

- Speak with an AAA Account Manager to learn about institutions in your area where you may refer your patients

OR

- Visit www.lutathera.com to learn more about how to establish a LUTATHERA treatment center

Visit www.lutathera.com to learn more

Please see additional Important Safety Information on pages 13-14 and accompanying full Prescribing Information.

AAA-Lu177-US-0048 | 03/18

Advanced Accelerator Applications

LUTATHERA® (lutetium Lu 177 dotatate) injection, for intravenous use

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

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

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

- Verify pregnancy status in females of reproductive potential prior to initiating LUTATHERA. (2.1)
- Administer 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. (2.2)
- Administer long-acting octreotide 30 mg intramuscularly 4 to 24 hours after each LUTATHERA dose and short-acting octreotide for symptomatic management. (2.3)
- Continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing LUTATHERA until disease progression or for up to 18 months following treatment initiation. (2.3)
- Premedicate with antiemetics 30 minutes before recommended amino acid solution. (2.3)
- Initiate recommended intravenous amino acid solution 30 minutes before LUTATHERA infusion; continue during and for 3 hours after LUTATHERA infusion. Do not reduce dose of amino acid solution if LUTATHERA dose is reduced. (2.3)
- Modify LUTATHERA dose based on adverse reactions. (2.4)
- Prepare and administer as recommended. (2.5)

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

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

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

None.

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

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

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

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

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

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

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

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Instructions

LUTATHERA is a radiopharmaceutical; handle with appropriate safety measures to minimize radiation exposure *[see Warnings and Precautions (5.1)]*. Use waterproof gloves and effective radiation shielding when handling LUTATHERA. Radiopharmaceuticals, including LUTATHERA, should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA *[see Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage

The recommended LUTATHERA dose is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. Administer pre- and concomitant medications and administer LUTATHERA as recommended *[see Dosage and Administration (2.3, 2.5)]*.

2.3 Premedication and Concomitant Medications

Somatostatin Analogs

- Before initiating LUTATHERA: Discontinue long-acting somatostatin analogs (e.g., long-acting octreotide) for at least 4 weeks prior to initiating LUTATHERA. Administer short-acting octreotide as needed; discontinue at least 24 hours prior to initiating LUTATHERA *[see Drug Interactions (7.1)]*.
- During LUTATHERA treatment: Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each LUTATHERA dose. Do not administer long-acting octreotide within 4 weeks of each subsequent LUTATHERA dose. Short-acting octreotide may be given for symptomatic management during LUTATHERA treatment, but must be withheld for at least 24 hours before each LUTATHERA dose.
- Following LUTATHERA treatment: Continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing LUTATHERA until disease progression or for up to 18 months following treatment initiation.

Antiemetic

Administer antiemetics 30 minutes before the recommended amino acid solution.

Amino Acid Solution

Initiate an intravenous amino acid solution containing L-lysine and L-arginine (Table 1) 30 minutes before administering LUTATHERA. Use a three-way valve to administer amino acids using the same venous access as LUTATHERA or administer amino acids through a separate venous access in the patient's other arm. Continue the infusion during, and for at least 3 hours after LUTATHERA infusion. Do not decrease the dose of the amino acid solution if the dose of LUTATHERA is reduced *[see Warnings and Precautions (5.4)]*.

Table 1. Amino Acid Solution

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

2.4 Dose Modifications for Adverse Reactions

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

Table 2. Recommended Dose Modifications of LUTATHERA for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction[1]	Dose Modification
Thrombocytopenia *[see Warnings and Precautions (5.2)]*	Grade 2, 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 2, 3 or 4	Permanently discontinue LUTATHERA.
Anemia and Neutropenia *[see Warnings and Precautions (5.2)]*	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 anemia or neutropenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue LUTATHERA.
Renal Toxicity *[see Warnings and Precautions (5.4)]*	Defined as: • Creatinine clearance less than 40 mL/min; calculate using Cockcroft Gault with actual body weight, or • 40% increase in baseline serum creatinine, or • 40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.	Withhold dose until complete resolution. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution. If reduced dose does not result in renal toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for renal toxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent renal toxicity	Permanently discontinue LUTATHERA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Defined as: • Bilirubinemia greater than 3 times the upper limit of normal (Grade 3 or 4), or • Hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.	Withhold dose until complete resolution. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution. If reduced LUTATHERA dose does not result in hepatotoxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for hepatotoxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent hepatotoxicity	Permanently discontinue LUTATHERA.
Other Non-Hematologic Toxicity	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue LUTATHERA.

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

2.5 Preparation and Administration

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

Administration Instructions

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

2.6 Radiation Dosimetry

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk from Radiation Exposure

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

Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures *[see Dosage and Administration (2.1)]*.

5.2 Myelosuppression

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

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

5.3 Secondary Myelodysplastic Syndrome and Leukemia

In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide. In ERASMUS, 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

5.4 Renal Toxicity

In ERASMUS, 8 patients (<1%) developed renal failure 3 to 36 months following LUTATHERA. Two of these patients had underlying renal impairment or risk factors for renal failure (e.g., diabetes or hypertension) and required dialysis.

Administer the recommended amino acid solution before, during and after LUTATHERA *[see Dosage and Administration (2.3)]* to decrease reabsorption of lutetium Lu 177 dotatate through the proximal tubules and decrease the radiation dose to the kidneys. Do not decrease the dose of the amino acid solution if the dose of LUTATHERA is reduced. Advise patients to urinate frequently during and after administration of LUTATHERA. Monitor serum creatinine and calculated creatinine clearance. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of reaction *[see Dosage and Administration (2.4)]*.

Patients with baseline renal impairment may be at greater risk of toxicity; perform more frequent assessments of renal function in patients with mild or moderate impairment. LUTATHERA has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min).

5.5 Hepatotoxicity

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

Monitor transaminases, bilirubin and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of reaction *[see Dosage and Administration (2.2)]*.

5.6 Neuroendocrine Hormonal Crisis

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

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

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, LUTATHERA can cause fetal harm *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of LUTATHERA in pregnant women. No animal studies using lutetium Lu 177 dotatate have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm.

Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA *[see Dosage and Administration (2.1)]*.

Advise females and males of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.8 Risk of Infertility

LUTATHERA may cause infertility in males and females. The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy *[see Dosage and Administration (2.6) and Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

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

6.1 Clinical Trials Experience

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

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

NETTER-1

The safety data described below are from NETTER-1, which randomized (1:1) patients with progressive, somatostatin receptor-positive midgut carcinoid tumors to receive LUTATHERA 7.4 GBq (200 mCi) administered every 8 to 16 weeks concurrently with the recommended amino acid solution and with long-acting octreotide (30 mg administered by intramuscular injection within 24 hours of each LUTATHERA dose) (n = 111), or high-dose octreotide (defined as long-acting octreotide 60 mg by intramuscular injection every 4 weeks) (n = 112) *[see Clinical Studies (14.1)]*. Among patients receiving LUTATHERA with octreotide, 79% received a cumulative dose > 22.2 GBq (> 600 mCi) and 76% of patients received all four planned doses. Six percent (6%) of patients required a dose reduction and 13% of patients discontinued LUTATHERA. Five patients discontinued LUTATHERA for renal-related events and 4 discontinued for hematological toxicities. The median duration of follow-up was 24 months for patients receiving LUTATHERA with octreotide and 20 months for patients receiving high-dose octreotide.

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

Table 4. Adverse Reactions Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-1[1]

Adverse Reaction[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Cardiac disorders				
Atrial fibrillation	5	1	0	0
Gastrointestinal disorders				
Nausea	65	5	12	2
Vomiting	53	7	9	0
Abdominal pain	26	3	19	3
Diarrhea	26	3	18	1
Constipation	10	0	5	0
General disorders				
Fatigue	38	1	26	2
Peripheral edema	16	0	9	1
Pyrexia	8	0	3	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	11	3
Musculoskeletal and connective tissue disorders				
Back pain	13	2	10	0
Pain in extremity	11	0	5	0
Myalgia	5	0	0	0
Neck Pain	5	0	0	0
Nervous system disorders				
Headache	17	0	5	0
Dizziness	17	0	8	0
Dysgeusia	8	0	2	0
Psychiatric disorders				
Anxiety	12	1	5	0
Renal and urinary disorders				
Renal failure*	12	3	3	1
Radiation-related urinary tract toxicity**	8	0	3	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	1	6	0
Skin and subcutaneous tissue disorders				
Alopecia	12	0	2	0
Vascular disorders				
Flushing	14	1	9	0
Hypertension	12	2	7	2

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

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

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

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

Laboratory Abnormality[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All grades %	Grade 3-4 %	All grades %	Grade 3-4 %
Hematology				
Lymphopenia	90	44	39	4
Anemia	81	0	54	1
Leukopenia	55	2	20	0
Thrombocytopenia	53	1	17	0
Neutropenia	26	3	11	0
Renal/Metabolic				
Creatinine increased	85	1	73	0
Hyperglycemia	82	4	67	2
Hyperuricemia	34	6	29	6
Hypocalcemia	32	0	14	0
Hypokalemia	26	4	21	2
Hyperkalemia	19	0	11	0
Hypernatremia	17	0	7	0
Hypoglycemia	15	0	8	0
Hepatic				
GGT increased	66	20	67	16
Alkaline phosphatase increased	65	5	54	9
AST increased	50	5	35	0
ALT increased	43	4	34	0
Blood bilirubin increased	30	2	28	0

*Values are worst grade observed after randomization

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

ERASMUS

Safety data are available from 1214 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with somatostatin receptor-positive tumors (neuroendocrine and other primaries). Patients received LUTATHERA 7.4 GBq (200 mCi) administered every 6 to 13 weeks with or without octreotide. Retrospective medical record review was conducted on a subset of 811 patients to document serious adverse reactions. Eighty-one (81%) percent of patients in the subset received a cumulative dose ≥ 22.2 GBq (≥ 600 mCi). With a median follow-up time of more than 4 years, the following rates of serious adverse reactions were reported: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

7 DRUG INTERACTIONS

7.1 Somatostatin Analogs

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LUTATHERA can cause fetal harm *[see Clinical Pharmacology (12.1)]*. There are no available data on LUTATHERA use in pregnant women. No animal studies using lutetium Lu 177 dotatate have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm. Advise pregnant women of the risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary
There are no data on the presence of lutetium Lu 177 dotatate in human milk, or its effects on the breastfed infant or milk production. No lactation studies in animals were conducted. Because of the potential risk for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose.

8.3 Females and Males of Reproductive Potential

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

Contraception
Females
LUTATHERA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the final dose of LUTATHERA.

Males
Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of LUTATHERA *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*.

Infertility
The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy *[see Dosage and Administration (2.6)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild to moderate impairment. The safety of LUTATHERA in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied.

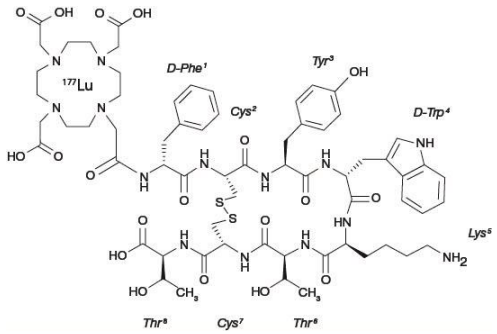
8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The safety of LUTATHERA in patients with severe hepatic impairment (total bilirubin > 3 times upper limit of normal and any AST) has not been studied.

11 DESCRIPTION

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

Lutetium Lu 177 dotatate is described as lutetium (Lu 177)-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl) acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic (2-7) disulfide. The molecular weight is 1609.6 Daltons and the structural formula is as follows:



LUTATHERA (lutetium Lu 177 dotatate) 370 MBq/mL (10 mCi/mL) Injection is a sterile, clear, colorless to slightly yellow solution for intravenous use. Each single-dose vial contains acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), sodium hydroxide (0.65

mg/mL), ascorbic acid (2.8 mg/mL), diethylene triamine pentaacetic acid (0.05 mg/mL), sodium chloride (6.85 mg/mL), and Water for Injection (ad 1 mL). The pH range of the solution is 4.5 to 6.

11.1 Physical Characteristics

Lutetium (Lu 177) decays to stable hafnium (Hf 177) with a half-life of 6.647 days, by emitting beta radiation with a maximum energy of 0.498 MeV and photonic radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (6.4%). The main radiations are detailed in Table 6.

Table 6. Lu 177 Main Radiations

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

11.2 External Radiation

Table 7 summarizes the radioactive decay properties of Lu 177.

Table 7. Physical Decay Chart: Lutetium Lu 177 Half-life = 6.647 days

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1.000	48 (2 days)	0.812
1	0.996	72 (3 days)	0.731
2	0.991	168 (7 days)	0.482
5	0.979	336 (14 days)	0.232
10	0.958	720 (30 days)	0.044
24 (1 day)	0.901	1080 (45 days)	0.009

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

12.3 Pharmacokinetics

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

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

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

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

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

Metabolism
Lutetium Lu 177 dotatate does not undergo hepatic metabolism.

Excretion
Lutetium Lu 177 dotatate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following LUTATHERA administration. Prolonged elimination of lutetium Lu 177 dotatate in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium Lu 177 dotatate, greater than 99% will be eliminated within 14 days after administration of LUTATHERA *[see Warnings and Precautions (5.1)]*.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

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

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

Two hundred twenty-nine (229) patients were randomized (1:1) to receive either LUTATHERA 7.4 GBq (200 mCi) every 8 weeks for up to 4 administrations (maximum cumulative dose of 29.6 GBq) or high-dose long-acting octreotide (defined as 60 mg by intramuscular injection every 4 weeks). Patients in the LUTATHERA arm also received long-acting octreotide 30 mg as an intramuscular injection 4 to 24 hours after each LUTATHERA dose and every 4 weeks after completion of LUTATHERA treatment until disease progression or until week 76 of the study. Patients in both arms could receive short-acting octreotide for symptom management; however, short-acting octreotide was withheld for at least 24 hours before each LUTATHERA dose. Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤ 6 or > 6 months). The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee (IRC) per RECIST v1.1. Additional efficacy outcome measures were overall response rate (ORR) by IRC, duration of response, and overall survival (OS).

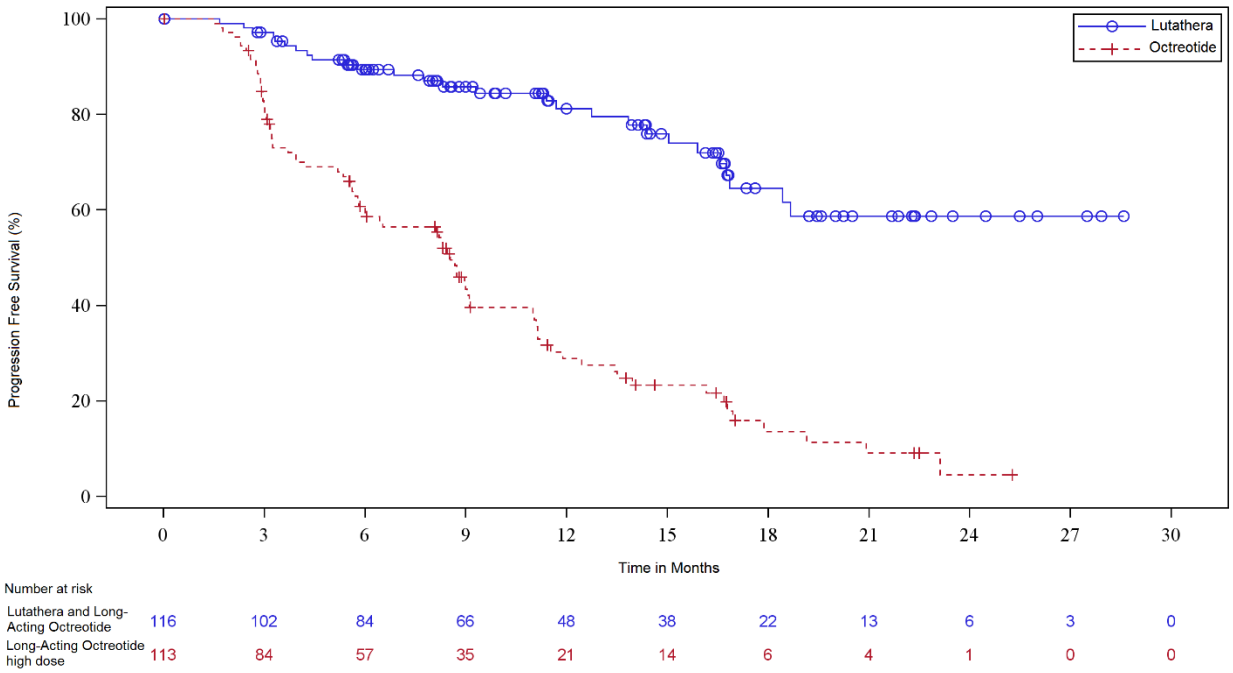
Demographic and baseline disease characteristics were balanced between the treatment arms. Of the 208 patients, whose race/ethnicity was reported, 90% were White, 5% were Black, and 4% were Hispanic or Latino. The median age was 64 years (28 to 87 years); 51% were male, 74% had an illial primary, and 96% had metastatic disease in the liver. The median Karnofsky performance score was 90 (60 to 100), 74% received a constant dose of octreotide for > 6 months and 12% received prior treatment with everolimus. Sixty-nine percent of patients had Ki67 expression in ≤ 2% of tumor cells, 77% had CgA > 2 times the upper limit of normal (ULN), 65% had 5-HIAA > 2 x ULN, and 65% had alkaline phosphatase ≤ ULN. Efficacy results for NETTER-1 are presented in Table 8 and Figure 1.

Table 8. Efficacy Results in NETTER-1

	LUTATHERA and Long-Acting Octreotide (30 mg) N=116	Long-Acting Octreotide (60 mg) N=113
PFS by IRC		
Events (%)	27 (23%)	78 (69%)
Progressive disease, n (%)	15 (13%)	61 (54%)
Death, n (%)	12 (10%)	17 (15%)
Median in months (95% CI)	NR[c] (NE, NE)	8.5 (5.8, 9.1)
Hazard ratio[a] (95% CI)	0.21 (0.13, 0.32)	
P-Value[b]	< 0.0001	
OS (Updated)		
Deaths (%)	27 (23%)	43 (38%)
Median in months (95% CI)	NR (31.0, NE)	27.4 (22.2, NE)
Hazard ratio[a,d] (95% CI)	0.52 (0.32, 0.84)	
ORR by IRC		
ORR, % (95% CI)	13% (7%,19%)	4% (0.1%, 7%)
Complete response rate, n (%)	1 (1%)	0
Partial response rate, n (%)	14 (12%)	4 (4%)
P-Value[e]	0.0148	
Duration of response, median in months (95% CI)	NR (2.8, NE)	1.9 (1.9, NE)

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

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



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

The efficacy of LUTATHERA in patients with foregut, midgut, and hindgut gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was assessed in 360 patients in the ERASMUS study. In ERASMUS, LUTATHERA was initially provided as expanded access under a general peptide receptor radionuclide therapy protocol at a single site in the Netherlands. A subsequent LUTATHERA-specific protocol written eight years after study initiation did not describe a specific sample size or hypothesis testing plan but allowed for retrospective data collection. A total of 1214 patients received LUTATHERA in ERASMUS, of which 601 (50%) were assessed per RECIST criteria. Of the 601 patients evaluated by investigators using RECIST criteria, 360 (60%) had gastroentero-pancreatic neuroendocrine tumors (GEP-NETs). LUTATHERA 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. The major efficacy outcome was investigator-assessed ORR. The median age in the efficacy subset was 61 years (25 to 88 years), 52% were male, 61% had a baseline Karnofsky performance status ≥ 90 (60 to 100), 60% had progressed within 12 months of treatment, and 15% had received prior chemotherapy. Fifty five percent (55%) of patients received a concomitant somatostatin analog. The median dose of LUTATHERA was 29.6 GBq (800 mCi). Baseline tumor assessments were obtained in 39% of patients. The investigator assessed ORR was 16% (95% CI 13, 20) in the 360 patients with GEP-NETs. Three complete responses were observed (< 1%). Median DoR in the 58 responding patients was 35 months (95% CI: 17, 38).

16 HOW SUPPLIED/STORAGE AND HANDLING

LUTATHERA Injection containing 370 MBq/mL (10 mCi/ml) of lutetium Lu 177 dotatate is a sterile, preservative-free and clear, colorless to slightly yellow solution for intravenous use supplied in a colorless Type I glass 30 mL single-dose vial containing 7.4 GBq (200 mCi) ± 10% of lutetium Lu 177 dotatate at the time of injection (**NDC# 69488-003-01**). The solution volume in the vial is adjusted from 20.5 mL to 25 mL to provide a total of 7.4 GBq (200 mCi) of radioactivity.

The product vial is in a lead shielded container placed in a plastic sealed container (**NDC# 69488-003-01**). The product is shipped in a Type A package (**NDC# 69488-003-70**).

Store below 25 °C (77 °F).

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

Manufactured by:
Advanced Accelerator Applications, S.r.l.
Via Ribes 5, 10010 Colleretto Giacosa (TO), Italy

Or

Advanced Accelerator Applications, S.r.l.
Via Piero Maroncelli 40/1, 47014 Meldola (FC), Italy

Distributed by:
Advanced Accelerator Applications USA, Inc., NJ 07041

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