Advanced Accelerator Applications
A Novartis Company

AAA PatientCONNECT™

Enrollment Form

PHONE: 1-844-638-7222 • FAX: 1-844-638-7329

NOTE: The enrollment cannot be processed without both prescriber and patient signatures.

Expected LUTATHERA® (lutetium Lu 177 dotatate) injection Treatment Date: _____ **Indicates Required Field*

PATIENT INFORMATION

*Patient Name:		*Date of Birth (DOB):
*Address:		*Sex: ☐ M ☐ F
*City:	*State:	*Zip:
*Phone No.: ☐ Home:	☐ Cell:	
*OK to leave a message: ☐ Yes ☐ No ☐ Cell ☐ Home		
Alternate Contact Name:	Relationship:	
Patient Email:		

PATIENT AUTHORIZATION *(Required — CANNOT PROCESS FORM WITHOUT THIS COMPLETED)*

I CONFIRM THAT THE INFORMATION PROVIDED HEREIN IS TRUTHFUL AND ACCURATE TO THE BEST OF MY KNOWLEDGE

If eligible, I would like to be considered for the AAA PatientCONNECT™ program, which may provide co-pay assistance or free access to my medication. If my financial situation or health coverage changes, I will call AAA PatientCONNECT™ at 1-844-638-7222. Novartis Patient Assistance Foundation, Inc. (NPAF) provides free LUTATHERA to eligible uninsured and underinsured patients. Proof of income is required.

☐ I have read and agree to the Terms and Conditions for the AAA PatientCONNECT™ program on pages 6 and 7

☐ I have read and agree to the Telephone Consumer Protection Act (TCPA) Consent on page 6

☐ I would like to receive marketing information from Advanced Accelerator Applications, a Novartis Company

☐ **I HAVE READ AND AGREE TO THE PATIENT AUTHORIZATION ON PAGES 5 AND 6**

STOP *PATIENT/LEGAL GUARDIAN SIGNATURE:

*Print Patient/Legal Guardian Name:	*Relationship to Patient:
*Date:	

INSURANCE INFORMATION *(Required for Benefit Verification and Co-Pay Assistance)*

☐ Patient has no insurance

Carrier 1

*Carrier:	*Health Plan:	
*Carrier Phone No.:	*Policy ID No.:	
*Group No.:	*Policy Holder Name:	
*Policy Holder Sex: ☐ M ☐ F	*Policy Holder DOB:	*Policy Holder Relationship:

Carrier 2

Carrier:	Health Plan:	
Carrier Phone No.:	Policy ID No.:	
Group No.:	Policy Holder Name:	
Policy Holder Sex: ☐ M ☐ F	Policy Holder DOB:	Policy Holder Relationship:

Please see Important Safety Information on page 4, as well as full Prescribing Information.

PATIENT INFORMATION

Name:	Date of Birth:

PRESCRIBER INFORMATION

*Ordering Physician Name:		*Specialty:
*Physician Practice Name:	*Practice National Provider Identifier (NPI) No.:	
*Office Contact Name:	*Office Contact's Phone No.:	Ext:
*Physician Address:		
*City:	*State:	*Zip:
*Physician Phone No.:	*Physician Fax No.:	
Physician Email:		
*Physician NPI No.:	*State License No.:	*Tax ID No.:

SITE OF TREATMENT INFORMATION

*Administering Facility:	☐ Hospital Outpatient ☐ Freestanding / Physician Office	
*Facility Address:		
*City:	*State:	*Zip:
*Facility Phone No.:	*Facility Fax No.:	
*Facility NPI No.:	*Tax ID No.:	
*Facility Contact Person:	*Facility Contact Phone No.:	Ext:

CLINICAL INFORMATION

*Include at least 1 International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code below. Please refer to page 3 for a list of potential ICD-10-CM code options.

Diagnosis (ICD-10-CM Code): _____ Description: _____

Diagnosis (ICD-10-CM Code): _____ Description: _____

PHYSICIAN CERTIFICATION

I certify that the above therapy is medically necessary, and that the information provided is accurate to the best of my knowledge. I certify that I am the prescriber who has prescribed LUTATHERA® (lutetium Lu 177 dotatate) injection to the previously identified patient and that I provided the patient with a description of the LUTATHERA AAA PatientCONNECT™ program. I authorize the AAA PatientCONNECT™ program to act on my behalf for the purposes of determining patient's eligibility for participation in the AAA PatientCONNECT™ program.

I agree to receive communications, including faxes, related to my patient's enrollment or participation in the AAA PatientCONNECT™ program. I have obtained from my patient all required authorizations to disclose to AAA PatientCONNECT™ and its representatives the patient's protected health information (PHI), including the information provided on this form. I also agree that AAA may contact the patient directly in connection with the AAA PatientCONNECT™ program.

STOP *PHYSICIAN SIGNATURE:

*Physician Printed Name:	*Date:

Please see Important Safety Information on page 4, as well as full Prescribing Information.

ICD-10-CM Codes

The tables below list the ICD-10-CM potential diagnosis codes that you may consider for patient treatment with LUTATHERA® (lutetium Lu 177 dotatate) injection.

ICD-10-CM CODE	DESCRIPTION
C7A.00	Malignant carcinoid tumor of unspecified site
C7A.010	Malignant carcinoid tumor of the duodenum
C7A.011	Malignant carcinoid tumor of the jejunum
C7A.012	Malignant carcinoid tumor of the ileum
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
C7A.020	Malignant carcinoid tumor of the appendix
C7A.021	Malignant carcinoid tumor of the cecum
C7A.022	Malignant carcinoid tumor of the ascending colon
C7A.023	Malignant carcinoid tumor of the transverse colon
C7A.024	Malignant carcinoid tumor of the descending colon
C7A.025	Malignant carcinoid tumor of the sigmoid colon
C7A.026	Malignant carcinoid tumor of the rectum
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.092	Malignant carcinoid tumor of the stomach
C7A.094	Malignant carcinoid tumor of the foregut NOS
C7A.095	Malignant carcinoid tumor of the midgut NOS
C7A.096	Malignant carcinoid tumor of the hindgut NOS
C7A.098	Malignant carcinoid tumors of other site
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7B.00	Secondary carcinoid tumors, unspecified site
C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7B.02	Secondary carcinoid tumors of liver
C7B.04	Secondary carcinoid tumors of peritoneum
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified

*This information is taken from publicly available sources. It is not intended to guarantee, increase, or maximize reimbursement by any payer. It is the provider's responsibility to report the codes that accurately describe the products and services furnished to individual patients. Reimbursement is dynamic. We recommend that providers consult their payer organizations regarding local policies and rates. Laws and regulations regarding reimbursement change frequently and providers are solely responsible for all decisions related to coding and billing including determining, if and under what circumstances, it is appropriate to seek reimbursement for products and services and obtaining preauthorization, if necessary. AAA makes no representation or warranty regarding this information or its completeness or accuracy and will bear no responsibility for the results or consequences of the use of this information. You should reference the current CPT®, ICD-10-CM, and Healthcare Common Procedure Coding System (HCPCS) manuals and follow the "Documentation Guidelines for Evaluation and Management Services" for the most detailed and up-to-date information. Current Procedural Terminology (CPT©) is a copyright and trademark of the 2012 American Medical Association (AMA). All rights reserved.

Please see Important Safety Information on page 4, as well as full Prescribing Information.

What is LUTATHERA?
LUTATHERA® (lutetium Lu 177 dotatate) injection is a prescription medicine used to treat adults with a type of cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that are positive for the hormone receptor somatostatin, including GEP-NETs in the foregut, midgut, and hindgut.

IMPORTANT SAFETY INFORMATION:

What are some important things to know about the safety of LUTATHERA?
LUTATHERA® is associated with some serious safety considerations, and in some cases these may require your healthcare provider to adjust or stop your treatment. You should always follow your healthcare provider's instructions. Safety considerations include:

- **Radiation exposure:** Treatment with LUTATHERA will expose you to radiation which can contribute to your long-term radiation exposure. Overall radiation exposure is associated with an increased risk for cancer. The radiation will be detectable in your urine for up to 30 days following administration of the drug. It is important to minimize radiation exposure to household contacts consistent with good radiation safety practices as advised by your healthcare provider.
- **Bone marrow problems:** Treatment with LUTATHERA increases the risk of myelosuppression, a condition in which bone marrow activity is decreased, resulting in a drop in blood cell counts. You may experience blood-related side effects such as low red blood cells (anemia), low numbers of cells that are responsible for blood clotting (thrombocytopenia), and low numbers of white blood cells (neutropenia). Speak with your healthcare provider if you experience any signs or symptoms of infection, fever, chills, dizziness, shortness of breath or increased bleeding or bruising. Your healthcare provider may need to adjust or stop your treatment accordingly.
- **Secondary bone marrow and blood cancers:** Other serious conditions that you may develop as a direct result of treatment with LUTATHERA include blood and bone marrow disorders known as secondary myelodysplastic syndrome and cancer known as acute leukemia. Your healthcare provider will routinely check your blood cell counts and tell you if they are too low or too high.
- **Kidney problems:** Treatment with LUTATHERA will expose your kidneys to radiation and may impair their ability to work as normal. You may be at an increased risk for kidney problems after LUTATHERA treatment if you already have kidney impairment before treatment. In some cases, patients have experienced kidney failure after treatment with LUTATHERA. Your healthcare provider will provide you with an amino acid solution before, during, and after LUTATHERA to help protect your kidneys. You should stay well hydrated before, during, and after your treatment. You should urinate frequently during and after administration of LUTATHERA. Your doctor will monitor your kidney function and may withhold, reduce, or stop your LUTATHERA treatment accordingly.
- **Liver problems:** In clinical studies of LUTATHERA, less than 1% of patients were reported to have tumor bleeding (hemorrhage), swelling (edema) or tissue damage (necrosis) to the liver. If you have tumors in your liver, you may be more likely to experience these side effects. Signs that you may be experiencing liver damage include increases in blood markers called ALT, AST and GGT. Your healthcare provider will monitor your liver using blood tests and may need to withhold, reduce, or stop your LUTATHERA treatment accordingly.
- **Hormonal gland problems (carcinoid crisis):** During your treatment you may experience certain symptoms that are related to hormones released from your cancer. These symptoms may include flushing, diarrhea, difficulty breathing (bronchospasm), and low blood pressure (hypotension), and may occur during or within the 24 hours after your first LUTATHERA treatment. Your healthcare provider will monitor you closely. Speak with your healthcare provider if you experience any of these signs or symptoms.
- **Pregnancy warning:** Tell your healthcare provider if you are pregnant. LUTATHERA can harm your unborn baby. Females should use an effective method of birth control during treatment and for 7 months after the final dose of LUTATHERA. Males with female partners should use an effective method of birth control during treatment and for 4 months after the final dose of LUTATHERA.
- **Breastfeeding warning:** You should not breastfeed during treatment with LUTATHERA and for 2.5 months after your final dose of LUTATHERA.
- **Fertility problems:** Treatment with LUTATHERA may cause infertility. This is because radiation absorbed by your testis or ovaries over the treatment period falls in the range of exposure where temporary or permanent infertility may occur.

What are the most common side effects of LUTATHERA?
The most common and most serious side effects of LUTATHERA include: vomiting, nausea, decreased blood cell counts, increased liver enzymes, decreased blood potassium levels, and increased blood glucose.

Talk to your doctor if you experience any of these side effects. There are other possible side effects of LUTATHERA. For more information, and to learn more about LUTATHERA, talk to your doctor or healthcare provider.

What other medicines may interact with LUTATHERA?
Tell your healthcare provider if you are taking any other medications. Somatostatin analogs and corticosteroids may affect how your LUTATHERA treatment works. You should stop taking your long-acting somatostatin analog at least 4 weeks before LUTATHERA treatment. You may continue taking short-acting somatostatin analogs up to 24 hours before your LUTATHERA treatment. Avoid repeated high doses of glucocorticosteroids during treatment with LUTATHERA.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Prescribing Information for LUTATHERA

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

Reference: 1. LUTATHERA® [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; May 2020.

PATIENT AUTHORIZATION

I give permission for my health care providers; pharmacies; service providers and their contractors ("Health Care Providers"); health insurer(s) and their contractors ("Insurers"); and third-party contractors to disclose my Personal Information, including information about my insurance benefits, prescriptions, my medical condition and history, adherence to my treatment, and my general health ("Personal Information") to Advanced Accelerator Applications pharmaceuticals corporation, a Novartis Company, its affiliates, business partners, and agents; the Advanced Accelerator Applications Patient Assistance Program, Novartis Pharmaceuticals Corporation, its affiliates and service providers ("Novartis"); and the Novartis Patient Assistance Foundation, Inc. ("NPAF") and its service providers (collectively, "the Companies") so that the Companies may: (i) help to verify or coordinate insurance coverage or otherwise obtain payment for my treatment with LUTATHERA® (lutetium Lu 177 dotatate) injection; (ii) coordinate my receipt of and payment for LUTATHERA; (iii) facilitate my access to LUTATHERA; (iv) provide me with information about Advanced Accelerator Applications, a Novartis Company, products, disease education and management programs, and promotional materials; (v) if I am eligible, coordinate the LUTATHERA Co-pay Program, including management, reimbursement, and communication with me about co-pay assistance; (vi) conduct quality assurance, surveys, and other internal business activities in connection with the LUTATHERA AAA PatientCONNECT™ program (the "Program") and other related programs; and (vii) if I choose to apply to programs offered by the Advanced Accelerator Applications PatientCONNECT™ program or NPAF, to administer those programs, to send me information about programs that might help me pay for medicines, and to coordinate or share my Personal Information with my Health Care Providers, other programs that might help me pay for medicines, government agencies, and insurance of providing or facilitating this assistance.

I give permission to the Companies to disclose my Personal Information to my Health Care Providers, Insurer(s), caregivers, and other third-party contractors or service providers for the purposes described above. I also give permission to the Companies to combine or aggregate any information collected from me with information Advanced Accelerator Applications, a Novartis Company and AAA PatientCONNECT™ may collect about me from other sources for the purpose of providing or administering Program services.

I understand that my Health Care Providers may receive payment from the Companies depending on my enrollment or participation in the LUTATHERA Copay Program or in other therapy assistance services. I understand that once my Personal Information is disclosed, it may no longer be protected by federal privacy law and applicable state laws. Even though HIPAA may no longer apply, the Companies will safeguard patient data through reasonable security measures and will use and share it only for the purposes specified in this authorization.

I understand that I may refuse to sign this authorization. I also may revoke (cancel) or get a copy of this authorization at any time by calling 1-844-638-7222 or by writing to AAA PatientCONNECT™, 23611 Chagrin Blvd, Suite 380, Beachwood, OH 44122.

If I cancel my consent, I will no longer qualify for the services described. I also understand that if a Health Care Provider or Insurer is disclosing my Personal Information to the Companies on an authorized, ongoing basis, my cancellation with the Companies will be effective with respect to any such Health Care Provider or Insurer as soon as they receive notice of my cancellation.

My refusal or future revocation will not affect my medical treatment or insurance benefits; however, if I revoke this authorization, I may no longer be able to participate in the LUTATHERA AAA PatientCONNECT™ program and related programs. If I revoke this authorization, the Companies will stop using or sharing my information (except as necessary to end my participation in the Program), but my revocation will not affect uses and disclosures of Personal Information previously disclosed in reliance upon this authorization. I understand that this authorization will remain valid for 5 years after the date of my signature, unless I revoke it earlier. I also understand that the LUTATHERA AAA PatientCONNECT™ program may change or end at any time without prior notification.

PATIENT AUTHORIZATION

I understand that I may receive a copy of this patient authorization.

I agree to be contacted by the Companies by mail, email, telephone calls, and text messages at the numbers and addresses provided on this form for all purposes described in this patient authorization. I also agree to be contacted by the Companies and others on its behalf by telephone calls and text messages made by or using automatic telephone dialing machines or artificial or prerecorded voice, at the number(s) provided on this form, for all nonmarketing purposes, including but not limited to sending me materials and asking for my participation in surveys.

I confirm that I am the subscriber for the telephone number(s) provided and the authorized user for the email address(es) provided, and I agree to notify the Companies promptly if any of my number(s) or address(es) change in the future. I understand that my wireless service provider's message and data rates may apply.

I understand that the Companies do not permit my Personal Information to be used by their business partners for their own separate marketing purposes. I understand and agree that Personal Information transmitted by email and cell phone cannot be secured against unauthorized access.

TELEPHONE CONSUMER PROTECTION ACT (TCPA) CONSENT

I consent to receive marketing calls and texts from and on behalf of Advanced Accelerator Applications, a Novartis Company, and AAA PatientCONNECT™, made with an auto dialer or prerecorded voice, at the phone number(s) provided. I understand that my consent is not required or a condition of purchase. Number of messages will vary based on your program selections. Message and data rates may apply. Text STOP to opt out and HELP for help.

AAA PATIENTCONNECT™ CO-PAY ASSISTANCE PROGRAM (CAP) TERMS AND CONDITIONS

- Limitations apply
- The Advanced Accelerator Applications (AAA) PatientCONNECT™ LUTATHERA Co-pay Assistance Program (the "Program") is valid only for patients with commercial insurance coverage who are otherwise eligible for the Program. The Program is not valid under Medicare, Medicaid, or any other federal or state program; for cash-paying patients; where the product is not covered by the patient's commercial insurance; or where the patient's insurer reimburses the patient for the entire cost of LUTATHERA® (lutetium Lu 177 dotatate) injection
- The patient is obligated to notify AAA PatientCONNECT™ at 1-844-638-7222 promptly if the patient's insurance coverage changes or the patient otherwise becomes ineligible for coverage under the Program
- Patient must be age 18 or older
- Patient must be a permanent resident of the United States, the Commonwealth of Puerto Rico, or the US Virgin Islands
- Patient must be prescribed LUTATHERA for an US Food and Drug Administration-approved indication
- Treatment with LUTATHERA must be provided in an appropriate outpatient setting
- The Program provides that an eligible patient will be responsible for the first $25.00 and then may receive assistance for up to a maximum of $15,000.00 over the course of the treatment (ie, 4 LUTATHERA infusions) to cover eligible out-of-pocket costs for LUTATHERA. After the maximum coverage is reached, the patient will be responsible for any out-of-pocket costs incurred
- Patient must have an out-of-pocket cost for LUTATHERA and be administered LUTATHERA prior to the expiration date of the Program. The benefit available under the Program is valid for the patient's out-of-pocket cost for LUTATHERA only. It is not valid for any other out-of-pocket costs (eg, office visit charges or medication administration charges) even if such costs are associated with the administration of LUTATHERA
- If a patient's insurance benefit year expires during the course of approved Program eligibility, confirmation of ongoing treatments and updated insurance information must be received from the treatment facility or physician's office for eligibility under the Program to be continued into the new benefit period
- The patient is subject to eligibility verification prior to enrollment in the Program
- The patient's eligibility for the Program expires on the anniversary of the first year following the patient's initial approval for the Program. Thereafter, the patient may re-enroll in the Program on a yearly basis. For each re-enrollment period, the patient is subject to eligibility verification
- Reimbursement under the Program is processed after services are rendered and the appropriate documentation is submitted to the Program. Such documentation must be submitted within 365 days after the date of service and must specify a line item specifically for LUTATHERA

AAA PATIENTCONNECT™ CO-PAY ASSISTANCE PROGRAM (CAP) TERMS AND CONDITIONS (CONT)

- The benefit conferred by the Program is exclusively for the patient
- The Program is not valid where prohibited by law
- The patient and the patient's HCP must not seek reimbursement for the benefit conferred by the Program from any other party, including without limitation, any health insurance program or plan, flexible spending account, or health care savings account. Providers submitting a claim for assistance on behalf of an eligible patient agree not to charge such patient for any amounts covered by the Program
- The Program is not health insurance
- The Program may not be combined with any third-party rebate, coupon, or offer
- Data related to the patient's receipt of benefits under the Program may be collected, analyzed, and shared with AAA, in an aggregated and patient deidentified form, for purposes that include assessing the Program and potentially making adjustments to such Program
- Advanced Accelerator Applications, a Novartis Company, reserves the right to rescind, revoke, or amend the Program and/or discontinue assistance at any time without notice
- No other purchase is necessary
- Program is limited to 1 per person during this offering period and is not transferable

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

None. (4)

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

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

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

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

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

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

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

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2020

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 healthcare providers who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

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

2.2 Recommended Dosage

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

2.3 Premedication and Concomitant Medications

Somatostatin Analogs

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

Antiemetic

Administer antiemetics before the recommended amino acid solution.

Amino Acid Solution

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

Table 1. Amino Acid Solution

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

2.4 Dosage Modifications for Adverse Reactions

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

Table 2. Recommended Dosage Modifications of LUTATHERA for Adverse Reactions

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

Adverse Reaction	Severity of Adverse Reaction*	Dose Modification
	• 40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.	Permanently discontinue LUTATHERA for renal toxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent renal toxicity	Permanently discontinue LUTATHERA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Defined as: • Bilirubinemia greater than 3 times the upper limit of normal (Grade 3 or 4), or • Hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.	Withhold dose until complete resolution or return to baseline. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution or return to baseline. If reduced LUTATHERA dose does not result in hepatotoxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for hepatotoxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent hepatotoxicity	Permanently discontinue LUTATHERA.
Other Non-Hematologic Toxicity *[see Adverse Reactions (6.1)]*	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue LUTATHERA.

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

2.5 Preparation and Administration

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

Administration Instructions

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

Instructions for Gravity Method

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

Instructions for Infusion Pump Method

- Insert a 2.5 cm, 20 gauge needle (short venting needle) into the LUTATHERA vial. Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient or the infusion pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic infusion pump according to manufacturer's instruction.
- Purge the line by opening the 3-way stopcock valve and pumping the LUTATHERA solution through the tubing until it reaches the exit of the valve.
- Purge the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the purged intravenous catheter to the patient and set the 3-way stopcock valve such that the LUTATHERA solution is in line with the infusion pump.
- Infuse one-half the volume listed on the LUTATHERA vial over a 30 min period (approximately 25 mL/h).
- When the correct volume of LUTATHERA has been delivered, stop the infusion pump and then change the position of the 3-way stopcock valve so that the infusion pump is in line with the 0.9% sterile sodium chloride solution. Restart the infusion pump and infuse an intravenous flush of 25 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

2.6 Radiation Dosimetry

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk from Radiation Exposure

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

Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices, patient management procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

5.2 Myelosuppression

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

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

5.3 Secondary Myelodysplastic Syndrome and Leukemia

In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide. In ERASMUS, 16 patients (2.0%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

5.4 Renal Toxicity

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

Administer the recommended amino acid solution before, during and after LUTATHERA *[see Dosage and Administration (2.3)]* to decrease reabsorption of lutetium Lu 177 dotatate through the proximal tubules and decrease the radiation dose to the kidneys. Do not decrease the dose of the amino acid solution if the dose of LUTATHERA is reduced. Advise patients to urinate frequently during and after administration of LUTATHERA.

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

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

5.5 Hepatotoxicity

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

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

5.6 Neuroendocrine Hormonal Crisis

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

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

5.7 Embryo-Fetal Toxicity

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

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

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

5.8 Risk of Infertility

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

NETTER-1

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

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

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

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

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

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

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

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

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

*Values are worst grade observed after randomization

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

ERASMUS

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

7 DRUG INTERACTIONS

7.1 Somatostatin Analogs

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

7.2 Corticosteroids

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild to moderate impairment. The safety of LUTATHERA in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied *[see Warnings and Precautions (5.4)]*.

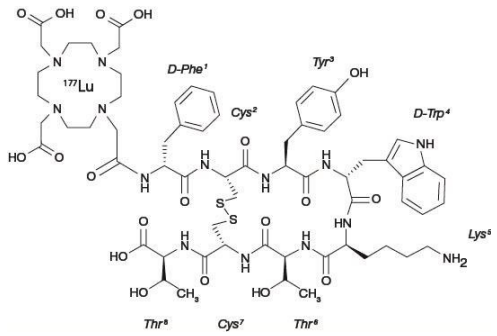
8.7 Hepatic Impairment

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

11 DESCRIPTION

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

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



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

11.1 Physical Characteristics

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

Table 6. Lu 177 Main Radiations

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

11.2 External Radiation

Table 7 summarizes the radioactive decay properties of Lu 177.

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

Distribution

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

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

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

Elimination

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

Metabolism

Lutetium Lu 177 dotatate does not undergo hepatic metabolism.

Excretion

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

Drug Interaction Studies

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

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

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

Two hundred twenty-nine (229) patients were randomized (1:1) to receive either LUTATHERA 7.4 GBq (200 mCi) every 8 weeks for up to 4 administrations (maximum cumulative dose of 29.6 GBq) or high-dose long-acting octreotide (defined as 60 mg by intramuscular injection every 4 weeks). Patients in the LUTATHERA arm also received long-acting octreotide 30 mg as an intramuscular injection 4 to 24 hours after each LUTATHERA dose and every 4 weeks after completion of LUTATHERA treatment until disease progression or until week 76 of the study. Patients in both arms could receive short-acting octreotide for symptom management; however, short-acting octreotide was withheld for at least 24 hours before each LUTATHERA dose. Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤ 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).

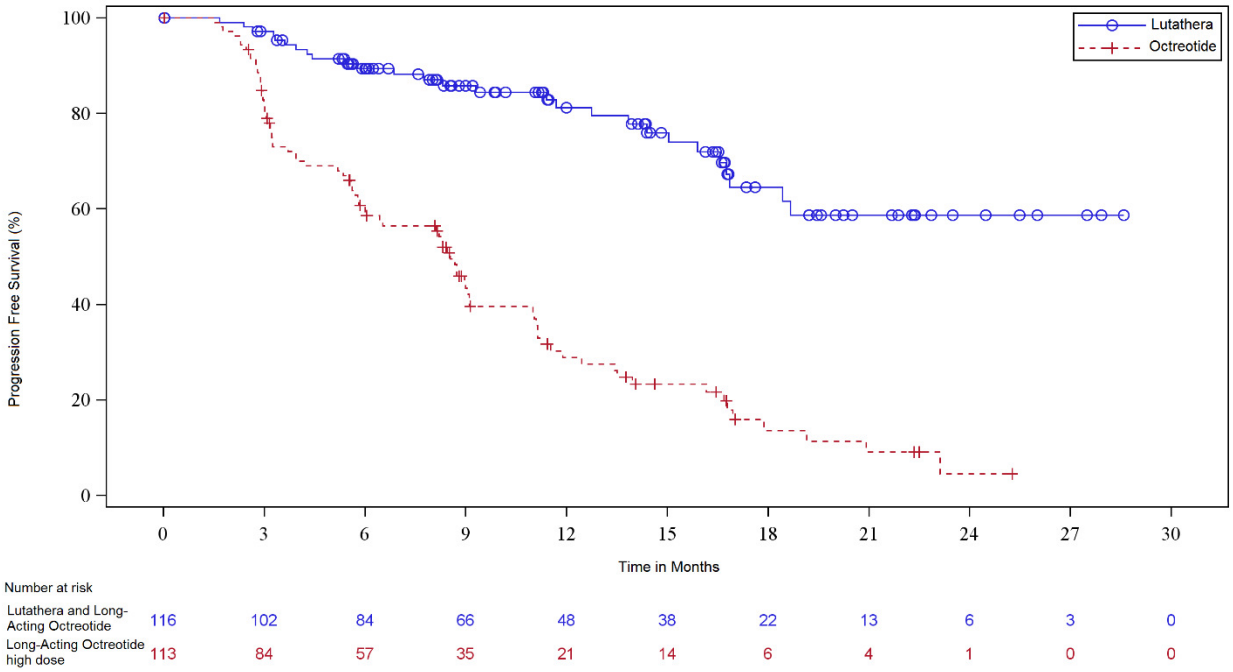
Demographic and baseline disease characteristics were balanced between the treatment arms. Of the 208 patients, whose race/ethnicity was reported, 90% were White, 5% were Black, and 4% were Hispanic or Latino. The median age was 64 years (28 to 87 years); 51% were male, 74% had an illial primary, and 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] (18.4, NE)	8.5 (6.0, 9.1)
Hazard ratio[a] (95% CI)	0.21 (0.13, 0.32)	
P-Value[b]	< 0.0001	
OS (Updated)		
Deaths (%)	27 (23%)	43 (38%)
Median in months (95% CI)	NR (31.0, NE)	27.4 (22.2, NE)
Hazard ratio[a,d] (95% CI)	0.52 (0.32, 0.84)	
ORR by IRC		
ORR, % (95% CI)	13% (7%,19%)	4% (0.1%, 7%)
Complete response rate, n (%)	1 (1%)	0
Partial response rate, n (%)	14 (12%)	4 (4%)
P-Value[e]	0.0148	
Duration of response, median in months (95% CI)	NR (2.8, NE)	1.9 (1.9, NE)

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

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



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

The efficacy of LUTATHERA in patients with foregut, midgut, and hindgut gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was assessed in 360 patients in the ERASMUS study. In ERASMUS, LUTATHERA was initially provided as expanded access under a general peptide receptor radionuclide therapy protocol at a single site in the Netherlands. A subsequent LUTATHERA-specific protocol written eight years after study initiation did not describe a specific sample size or hypothesis testing plan but allowed for retrospective data collection. A total of 1214 patients received LUTATHERA in ERASMUS, of whom 578 patients had baseline tumor assessments. Of the 578 patients, 360 (62%) had gastroentero-pancreatic neuroendocrine tumors (GEP-NETs) and long term follow-up. Of these 360 patients, 145 (40%) had their tumors prospectively evaluated according to RECIST criteria. LUTATHERA 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. The major efficacy outcome was investigator-assessed ORR. The median age in the efficacy subset was 60 years (30 to 85 years), 51% were male, 71% had a baseline Karnofsky performance status ≥ 90, 51% had progressed within 12 months of treatment, and 7%% had received prior chemotherapy. Fifty two percent (52%) of patients received a concomitant somatostatin analog. The median dose of LUTATHERA was 29.6 GBq (800 mCi). The investigator assessed ORR was 17% (95% CI 13, 21) based on an analysis that required responders to have had prospective response assessments according to RECIST criteria. Three complete responses were observed (< 1%). Median DoR in the 60 responding patients was 35 months (95% CI: 17, 38).

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

17 PATIENT COUNSELING INFORMATION

Radiation Risks

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

Myelosuppression

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

Secondary Myelodysplastic Syndrome and Acute Leukemia

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

Renal Toxicity

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

Hepatotoxicity

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

Neuroendocrine Hormonal Crises

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

Embryo-Fetal Toxicity

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

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

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

Lactation

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

Infertility

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

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