Radiation Safety and LUTATHERA®

(Lutetium Lu 177 dotatate)

IN THIS SECTION

• General precautions: ALARA
• Important safety instructions
• Radiation associated with LUTATHERA
• Managing spills and other concerns

"ALARA" principle: keeping radiation exposure “As Low As Reasonably Achievable”

ALARA is the guiding principle of radiation safety. It means that even a small radiation dose should be avoided if at all possible. Radiation exposure can be limited by proper shielding,衰减, and time spent near the radiation source.

TIME:
Reducing the time spent near a radiation source

DISTANCE:
Increasing the distance between you and the radiation source

SOURCE:
Minimizing radiation exposure by using a source with a lower strength

ALARA is an important principle to follow at all times. Even a small exposure can contribute to a patient's overall radiation burden. Radiation exposure can be reduced by limiting the amount of time near the radiation source, using appropriate shielding, and using sources with lower radiation output.

IN THIS SECTION

• General precautions: ALARA
• Important safety instructions
• Radiation associated with LUTATHERA
• Managing spills and other concerns

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

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

IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.

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This brochure is intended as a guide for nurses providing care to patients receiving treatment with LUTATHERA. It DOES NOT contain all information required to administer LUTATHERA. Additional information about LUTATHERA is included in the LUTATHERA Administration Guide and in LUTATHERA full Prescribing Information. LUTATHERA should always be handled and administered in accordance with your institution’s radiation safety guidelines.

What are GEP-NETs?
GEP-NETs are malignancies (cancers) that arise in the gastrointestinal tract and pancreas from neuroendocrine cells, which are specialized cells that secrete hormones and other bioactive substances. These cancers may or may not secrete bioactive substances at levels high enough to cause symptoms. Although described as an orphan and rare disease, NETs are being diagnosed with increasing frequency. The increase is thought to reflect improved awareness and diagnosis at earlier stages of the disease, though NETs are often diagnosed at an advanced or metastatic stage.

Mechanism of action of LUTATHERA®
LUTATHERA® (lutetium Lu 177 dotatate) and Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Myelosuppression:
In NETTER-1 clinical trial, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

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. In ERASMUS, 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) and 55 months (32 to 155 months) for acute leukemia.

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.

Mechanism of action of LUTATHERA®
LUTATHERA® (lutetium Lu 177 dotatate)

• LUTATHERA® is a radiopharmaceutical created by linking a radionuclide to a peptide that binds somatostatin receptors on the surface of GEP-NET tumor cells.1

• This class of medication is referred to as Peptide Receptor Radionuclide Therapy (PRRT)
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LUTATHERA® (lutetium Lu 177 dotatate) and Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

IMPORTANT SAFETY INFORMATION
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**IMPORTANT SAFETY INFORMATION**

**DRUG INTERACTIONS**

LUTATHERA® (lutetium Lu 177 dotatate) competitively binds to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Concomitant long-acting somatostatin analogs administered at least 4 weeks prior to and after each LUTATHERA dose. Administer short- and long-acting analogs in sequence during LUTATHERA treatment as recommended.

**SPECIFIC POPULATIONS**

**Pregnancy**

Lactation:

Because of the potential 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.

**LIVER IMPAIRMENT**

LUTATHERA has not been studied in patients with severe renal impairment (CrCL < 30 mL/min).

**RENAAL IMPAIRMENT**

Monitor serum creatinine and creatinine clearance to assess changes in renal function in patients with mild or moderate impairment. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of reaction. Do not decrease the dose of amino acid solution if the dose of LUTATHERA is reduced.

**URINE**

Patients should urinate frequently during and after administration of LUTATHERA. A concomitant intravenous infusion of sodium bicarbonate is recommended to minimize the potential for renal toxicity. Advise patients to monitor their urine color and report change in urine color to their health care provider.

**NURSING**

Please see additional Important Safety Information throughout and full prescribing information in pocket.

Please see important safety information throughout and full prescribing information in pocket.

**INDICATION**

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**

**WARNINGS AND PRECAUTIONS**

Radiation Exposure: Treatment with LUTATHERA contributes to the patient’s overall long-term cumulative radiation exposure, which may be associated with an increased risk for cancer. Radiation can be detected in the urine, blood, and saliva for up to 30 days after treatment with LUTATHERA. Advise patients to take appropriate radiation precautions during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures.

Please see additional Significant Safety Information and full prescribing information in pocket.
Important safety instructions

- LUTATHERA is a radiopharmaceutical; handle with appropriate safety measures to minimize radiation exposure
- 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

Radiation associated with LUTATHERA

The $^{177}$Lu isotope in LUTATHERA decays with a half-life of 6.647 days$^1$ and emits 2 types of radiation$^{10}$:
- A low-to-medium-energy $\beta$ particle, which is predominantly absorbed within the body of the patient
- $\gamma$ radiation at a low quantity and low-to-medium energy

These characteristics help keep radiation exposure to bystanders, such as medical personnel and caregivers, within established regulatory guidance.$^1^1$

A study evaluated the typical radiation dose received by healthcare providers and caregivers or family members during and after treatment with lutetium Lu 177 dotatate.$^1^1$

Methods$^1^1$

- 76 patients with progressive, metastatic NETs received 4 cycles of 7.4 GBq lutetium Lu 177 dotatate at 8-week intervals in an outpatient setting
- 4 patients were treated in 1 room with each patient remaining until radiation exposure was below the release limit
- Radiation exposures to healthcare providers and caregivers were monitored by personal dosimeter

Results$^1^1$

- Mean whole-body exposures per therapy day ranged from 0.7 mrem (nuclear medicine technologist) to 3.3 mrem (nurse)
- Mean total exposure to 25 caregivers during the day of therapy and at home for a period of up to 5 days was 9 mrem, with a median exposure of 4 mrem and range of 1 mrem to 47 mrem
- Exposures to healthcare providers, caregivers, and family members were well within the limits recommended by the International Commission on Radiological Protection

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.
In case of a radiation spill

If a radiation spill occurs, you should always follow the guidance of your institution’s radiation safety department. The information below is only a general guide.

STOP
Stop what you are doing and don’t leave the immediate area
Don’t panic—take a moment to collect your thoughts

STAY PUT
Assume that you are contaminated, so don’t spread the contamination with unnecessary movement
Check skin, clothes, and shoes for contamination

INFORM
Tell others in the immediate area what has happened
Contact officials according to your institution’s radiation safety policies

LOCALIZE
Place absorbent materials (paper towels, drapes, wipes, etc) over the spilled radioactive material
Wear gloves and other protection

LABEL
Mark the area as contaminated and don’t allow individuals to enter or leave the area until the spill has been evaluated by your institution’s radiation authorities

Adapted from Tufts University.[12]

Nausea and vomiting are often seen during the infusion procedure.¹ Vomit from a patient who has received LUTATHERA® (lutetium Lu 177 dotatate) should be considered radioactive and cleaned up following the procedures for a radiation spill. Measures to reduce the possible risk of vomiting will be discussed in the next section.

Urine and feces from a patient who has received LUTATHERA is radioactive and should be cleaned up following the procedures for a radiation spill. Measures to reduce the risk of contamination from urine and feces are discussed on page 9 of this brochure.

IMPORTANT SAFETY INFORMATION¹

WARNINGS AND PRECAUTIONS

Hepatotoxicity: In ERASMUS, <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.
The LUTATHERA regimen

LUTATHERA is administered according to the following regimen:

- The recommended treatment regimen consists of 7.4 GBq (200 mCi) IV every 8 weeks for a total of 4 doses.
- Following each dose, the patient should receive long-acting octreotide 30 mg IM between 4 and 24 hours after each LUTATHERA dose.
- Long-acting octreotide 30 mg IM should be continued every 4 weeks after completing LUTATHERA until disease progression or for up to 18 months following LUTATHERA treatment initiation.

IN THIS SECTION

- The LUTATHERA regimen
- Concomitant medications
- Preparing for LUTATHERA administration
- Infusion set-up
- Administration timeline
- What to watch for
- Dealing with waste and medical consumables
- After LUTATHERA administration

Administration of LUTATHERA

The following is a brief overview of LUTATHERA administration. For more complete information, please consult the LUTATHERA Administration Guide, available at www.LUTATHERA.com.

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.

IM, intramuscular; IV, intravenous.
Concomitant medications—somatostatin analogs

Discontinue long-acting somatostatin analogs (eg, long-acting octreotide) for at least 4 weeks prior to initiating LUTATHERA.

Short-acting octreotide may be given for acute or urgent symptomatic management during LUTATHERA treatment, but must be withheld for at least 24 hours prior to each LUTATHERA dose.

During LUTATHERA treatment, administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each LUTATHERA dose.

After completing the LUTATHERA 4-dose regimen, continue long-acting octreotide 30 mg intramuscularly every 4 weeks until disease progression or for up to 18 months following treatment initiation.

Concomitant medications—antiemetics and amino acids

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 IV 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
Preparing for LUTATHERA administration

Absorbent drapes should be used to cover vulnerable areas in the patient room and bathroom. This might include certain areas of the floor and toilet.\(^9\)

Patients may arrive in street clothes but may change into hospital gowns before the LUTATHERA infusion, so that their gowns may be quarantined in the event of a radiation spill.

The patient should be provided with access to an isolated bathroom unavailable to the general public as \(^{177}\)Lu is excreted in the urine, which will therefore contain radioactive material. The patient should be encouraged to urinate as frequently as possible to help eliminate radioactive material concentrated in the urine. Patients should be instructed regarding procedures to avoid contamination of the bathroom:

- Men should sit on the toilet to urinate
- Patients should double-flush the toilet after use

Example patient bathroom preparation

IMPORTANT SAFETY INFORMATION\(^1\)

WARNINGS AND PRECAUTIONS

**Neuroendocrine hormonal crisis:** Manifesting with flushing, diarrhea, bronchospasm and hypotension, neuroendocrine hormonal crisis occurred in 1% of patients in ERASMUS 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.

**Embryo-Fetal Toxicity:** LUTATHERA can cause fetal harm. 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 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. Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA.

**Risk of Infertility:** LUTATHERA may cause infertility in males and females. 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 throughout and full Prescribing Information in pocket.
Infusion set-up

LUTATHERA is a radiopharmaceutical and should be handled with appropriate safety measures to minimize radiation exposure. 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.¹

The following is a brief overview of the administration procedure. For the full procedure, please see LUTATHERA full Prescribing Information.¹

In the LUTATHERA infusion method, a saline solution carries the LUTATHERA dose into the IV infusion catheter.¹

• A clamp or pump is used to regulate the saline flow, and thus the rate of LUTATHERA infusion¹

• The amino acid solution is administered using the same venous access as LUTATHERA or through a separate venous access in the patient’s other arm¹

• The LUTATHERA infusion is usually not administered by the nurse. The radiopharmaceutical infusion will usually be administered by a nuclear medicine technologist or nuclear medicine physician, depending upon the institution. These individuals are sometimes called the “authorized user”

• The LUTATHERA infusion should be conducted over the course of 30 to 40 minutes. LUTATHERA must not be administered as an intravenous bolus¹

  – 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 minutes¹

• The LUTATHERA infusion can be disconnected once the level of radioactivity is stable for at least 5 minutes (this is the only parameter to determine the procedure’s end¹⁹)

• Use radiation shielding and tongs whenever handling the LUTATHERA vial to minimize exposure¹

IMPORTANT SAFETY INFORMATION¹

ADVERSE REACTIONS

The most common Grade 3-4 adverse reactions (≥ 4% with a higher incidence in LUTATHERA arm) observed in NETTER-1 were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), elevated AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).

In ERASMUS, 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.
Infusion schedule

1. **Pretreatment antiemetic**
   Administer an antiemetic to help avoid treatment-related nausea and vomiting 30 minutes before the start of the amino acid solution infusion.

2. **Concomitant amino acid infusion**
   For renal protection, initiate an intravenous amino acid infusion containing L-lysine and L-arginine 30 minutes before administering LUTATHERA. Continue amino acids during and for at least 3 hours after the LUTATHERA administration. Do not decrease the dose of the amino acid solution if the LUTATHERA dose is reduced.

3. **LUTATHERA infusion**
   LUTATHERA must be administered as an intravenous infusion over 30 to 40 minutes.
   - 50 mL/hour to 100 mL/hour for 5 to 10 minutes
   - 200 mL/hour to 300 mL/hour for the following 25 to 30 minutes

4. **Long-acting octreotide 30 mg**
   Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each LUTATHERA dose.

What to watch for

The following is not a complete list of things to be aware of during treatment with LUTATHERA. Please see full Prescribing Information for additional information on Warnings, Precautions, and Adverse Reactions.

**Nausea and vomiting**
- Nausea and vomiting are often seen during the infusion procedure. Vomit from a patient who has received LUTATHERA should be considered radioactive and cleaned up following the procedures for a radiation spill.

**Hormonal crisis (carcinoid crisis)**
- Neuroendocrine hormonal crises due to excessive release of hormones or bioactive substances occurred in 1% of patients in clinical trials and typically occurred during or within 24 hours following the initial LUTATHERA dose.
- Hormonal crises could be treated with IV high-dose somatostatin analogs, IV fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhea and/or vomiting.

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.
Dealing with waste and medical consumables

- Your institution’s policy for disposing of medical waste should be adhered to. The following is provided only for general information.

- LUTATHERA should be disposed of only by authorized persons in designated clinical settings. LUTATHERA is a beta emitter that decays with a half-life of 6.647 days. The receipt, storage, use, transfer, and disposal of LUTATHERA is subject to the regulations and/or appropriate licenses of the competent official organizations.

- A waste management service is available, at cost, through AAA Customer Service to ship and store waste resulting from LUTATHERA treatment. To learn more about this waste management service and the associated cost, please contact AAA Customer Service at customerservice-us@adacap.com.

After LUTATHERA administration

- Patients should be advised to avoid close contact with others during travel home from treatment. For example, if driving home, the patient should sit in the back seat of the car, away from the driver (or the caregiver should do this if the patient is driving).

- Patients should avoid contact from children and the elderly for several days after treatment. Further information may be found in the LUTATHERA patient brochure.

- Before being released, the patient should be provided with a completed patient release card, pictured below.
ALARA® principle: Keeping radiation exposure “As Low As Reasonably Achievable”

ALARA® is the guiding principle of radiation safety. It means that even a small radiation dose should be avoided if possible. It is part of the ALARA philosophy. It is achieved through application of ALARA® concepts, such as ALARA® in routine patient management procedures.

Roles and responsibilities

The following is a general list of potential roles and responsibilities of different healthcare team members for the infusion of LUTATHERA. Your institution’s policies may vary.

<table>
<thead>
<tr>
<th>Task Text</th>
<th>Responsible Party</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time/Task</td>
<td>Patient care/interactions</td>
</tr>
<tr>
<td>8:00 AM</td>
<td>Patient care/interactions</td>
</tr>
<tr>
<td>9:00 AM</td>
<td>Assessments and documentation of the day, completion of tumor, y's planned/expected treatments given, and LUTATHERA and evaluation of results</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>Assessments and documentation of the day, completion of tumor, y's planned/expected treatments given, and LUTATHERA and evaluation of results</td>
</tr>
<tr>
<td>11:00 AM</td>
<td>Assessments and documentation of the day, completion of tumor, y's planned/expected treatments given, and LUTATHERA and evaluation of results</td>
</tr>
<tr>
<td>12:00 PM</td>
<td>Assessments and documentation of the day, completion of tumor, y's planned/expected treatments given, and LUTATHERA and evaluation of results</td>
</tr>
</tbody>
</table>

Prepare for LUTATHERA (void, positioning, time out, and monitoring)

Assessment, expectations of the day, orientation to room, and medication prep (IV placement, posttreatment instructions given, and LUTATHERA and evaluation of results)

TIME: MIN-SEC

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IMPORTANT SAFETY INFORMATION

DIAGNOSTIC IMAGING

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the results of diagnostic imaging. Be aware that, for example, the binding can result in false negative scans.
**ALARA** principle: keeping radiation exposure “As Low As Reasonably Achievable”

ALARA is the guiding principle of radiation safety, meaning that even a small radiation dose should be avoided if at all possible. While ALARA is a good principle to follow, there are certain exceptions that must be considered when handling the radioactive materials used in nuclear medicine.

### Radiation Safety and LUTATHERA®

#### LUTATHERA® (lutetium Lu 177 dotatate)

LUTATHERA® (lutetium Lu 177 dotatate) is a radiolabeled somatostatin analog indicated for the treatment of adults with advanced, progressing, well-differentiated neuroendocrine tumors (NETs) that are positive for the radionuclide somatostatin receptor scintigraphy (SRS) imaging.

#### Radiation Safety

Radiation safety is critical to the safe and effective use of LUTATHERA®. Radiation safety protocols must be followed to minimize exposure to healthcare providers and patients. This includes proper handling and disposal of radioactive materials, wear of protective clothing, and proper decontamination procedures.

### Radiation Safety and LUTATHERA®

#### Administration of LUTATHERA®

The recommended radiation dose of LUTATHERA® is 111 MBq per 177Lu atom, which is approximately 7.4 GBq. The dose is administered intravenously over 2 minutes.

#### References


### Radiation Safety and LUTATHERA®

#### 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 after treatment. The long-term effects of radiation exposure are not yet known.

#### Lactation:

Lactation is not recommended for women who are or will be breast-feeding during or after treatment with LUTATHERA®.

### Resources

- Los Angeles Carcinoid Neuroendocrine Tumor Society. www.lacnets.org
- Neuroendocrine Cancer Awareness Network. www.neuroendocrinecancer.org
- Northern California CarciNET Community. https://norcalcarcinet.org
- Carcinoid Cancer Foundation. www.carcinoid.org
- Carcinoid Cancer Foundation. www.carcinoid.org

### IMPORTANT SAFETY INFORMATION

#### Drugs Interactions

LUTATHERA® is a somatostatin receptor antagonist (SRTA). It is not recommended to use LUTATHERA® in combination with other somatostatin receptor antagonists.

#### Contraindications

LUTATHERA® is contraindicated in patients with known hypersensitivity to any component of the formulation. LUTATHERA® should not be administered to patients with severe renal impairment (CrCL < 30 mL/min).

#### 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 after treatment. The long-term effects of radiation exposure are not yet known.

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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)

DOSEAGE 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)

DOSE 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)

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. (7.1, 7.3, 7.4)

USE IN SPECIFIC POPULATIONS
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Safety Instructions
2.2 Recommended Dosage
2.3 Premedication and Concomitant Medications
2.4 Dose Modifications for Adverse Reactions
2.5 Preparation and Administration
2.6 Radiation Dosimetry
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Risk from Radiation Exposure
5.2 Myelosuppression
5.3 Secondary Myelodysplastic Syndrome and Leukemia
5.4 Renal Toxicity
5.5 Hepatotoxicity
5.6 Neuroendocrine Hormonal Crisis
5.7 Embryo-Fetal Toxicity
5.8 Risk of Infertility
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Somatostatin Analogs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
11 DESCRIPTION
11.1 Physical Characteristics
11.2 External Radiation
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Progressive, Well-differentiated Advanced or Metastatic Somatostatin Receptor-Positive Midgut Carcinoid Tumors
14.2 Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*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 Analog

- 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

<table>
<thead>
<tr>
<th>Item</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysine HCl content</td>
<td>Between 18 g and 24 g</td>
</tr>
<tr>
<td>Arginine HCl content</td>
<td>Between 18 g and 24 g</td>
</tr>
<tr>
<td>Volume</td>
<td>1.5 L to 2.2 L</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>&lt; 1050 mOsmol</td>
</tr>
</tbody>
</table>

2.4  Dose Modifications for Adverse Reactions

Recommended dose modifications of LUTATHERA for adverse reactions are provided in Table 2.
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity of Adverse Reaction¹</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia [see Warnings and Precautions (5.2)]</td>
<td>Grade 2, 3 or 4</td>
<td>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.</td>
</tr>
<tr>
<td>Anemia and Neutropenia [see Warnings and Precautions (5.2)]</td>
<td>Grade 3 or 4</td>
<td>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.</td>
</tr>
<tr>
<td>Renal Toxicity [see Warnings and Precautions (5.4)]</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Hepatotoxicity [see Warnings and Precautions (5.5)]</td>
<td>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%.</td>
<td>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.</td>
</tr>
<tr>
<td>Other Non-Hematologic Toxicity</td>
<td>Grade 3 or 4</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

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

* 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 dotate 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 dotate 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)].
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 $\geq 5\%$ (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-1

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

$^1$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 $\geq 5\%$ (all grades) or $\geq 2\%$ (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

<table>
<thead>
<tr>
<th>Laboratory Abnormality^1</th>
<th>LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)</th>
<th>Long-Acting Octreotide (60 mg) (N = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>Anemia</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>85</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>82</td>
<td>4</td>
</tr>
<tr>
<td>Hypuricemia</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>66</td>
<td>20</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>AST increased</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>ALT increased</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>30</td>
<td>2</td>
</tr>
</tbody>
</table>

^1Values are worst grade observed after randomization

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 dotate 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 treatment 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)-[4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl] acetyl]-D-phenylalananyl-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:

![Structural formula of LUTATHERA](image)

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>
<thead>
<tr>
<th>Radiation</th>
<th>Energy (keV)</th>
<th>Iβ%</th>
<th>Iγ%</th>
</tr>
</thead>
<tbody>
<tr>
<td>β</td>
<td>176.5</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>248.1</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>384.9</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>497.8</td>
<td>78.6</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>71.6</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>112.9</td>
<td>6.40</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>136.7</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>208.4</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>249.7</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>321.3</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

11.2 External Radiation

Table 7 summarizes the radioactive decay properties of Lu 177.

<table>
<thead>
<tr>
<th>Hours</th>
<th>Fraction Remaining</th>
<th>Hours</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.000</td>
<td>48 (2 days)</td>
<td>0.812</td>
</tr>
<tr>
<td>1</td>
<td>0.996</td>
<td>72 (3 days)</td>
<td>0.731</td>
</tr>
<tr>
<td>2</td>
<td>0.991</td>
<td>168 (7 days)</td>
<td>0.482</td>
</tr>
<tr>
<td>5</td>
<td>0.979</td>
<td>336 (14 days)</td>
<td>0.252</td>
</tr>
<tr>
<td>10</td>
<td>0.958</td>
<td>720 (30 days)</td>
<td>0.044</td>
</tr>
<tr>
<td>24 (1 day)</td>
<td>0.901</td>
<td>1080 (45 days)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

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 (Cmax) 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 dotate. 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 dotate does not undergo hepatic metabolism.

**Excretion**
Lutetium Lu 177 dotate 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 dotate in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium Lu 177 dotate, 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.

**NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
Carcinogenicity and mutagenicity studies have not been conducted with Lutetium Lu 177 dotate; however, radiation is a carcinogen and mutagen.

No animal studies were conducted to determine the effects of lutetium Lu 177 dotate 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 dotate (lutetium Lu 175 dotate) was the pancreas, a high SSTR2 expressing organ. Pancreatic acinar apoptosis occurred at lutetium Lu 175 dotate doses ≥ 5 mg/kg in repeat dose toxicity studies in rats. Pancreatic acinar cell atrophy also occurred in repeat dose toxicity 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.

**CLINICAL STUDIES**

**14.1 Progressive, Well-differentiated 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 ill or primary, and 96% had metastatic disease in the liver. The median Karnofsky performance score was 95 (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

<table>
<thead>
<tr>
<th></th>
<th>LUTATHERA and Long-Acting Octreotide (30 mg) N=116</th>
<th>Long-Acting Octreotide (60 mg) N=113</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS by IRC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events (%)</td>
<td>27 (23%)</td>
<td>78 (69%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>15 (13%)</td>
<td>61 (54%)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>12 (10%)</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>NR (NE, NE)</td>
<td>8.5 (5.8, 9.1)</td>
</tr>
<tr>
<td>Hazard ratio† (95% CI)</td>
<td>0.21 (0.13, 0.32)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>OS (Updated)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>27 (23%)</td>
<td>43 (38%)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>NR (31.0, NE)</td>
<td>27.4 (22.2, NE)</td>
</tr>
<tr>
<td>Hazard ratio†† (95% CI)</td>
<td>0.52 (0.32, 0.84)</td>
<td></td>
</tr>
<tr>
<td><strong>ORR by IRC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>13% (7%, 19%)</td>
<td>4% (0.1%, 7%)</td>
</tr>
<tr>
<td>Complete response rate, n (%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response rate, n (%)</td>
<td>14 (12%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>P-Value‡</td>
<td>0.0148</td>
<td></td>
</tr>
<tr>
<td>Duration of response, median in months (95% CI)</td>
<td>NR (2.8, NE)</td>
<td>1.9 (1.9, NE)</td>
</tr>
</tbody>
</table>

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

![Kaplan-Meier Curves](image-url)
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 55 months (95% CI: 17, 38).

16 HOW SUPPLIED/STORAGE AND HANDLING

LUTATHERA Injection containing 370 MBq/mL (10 mCi/mL) of lutetium Lu 177 dotate 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 dotate 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
Advertise 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
Advertise 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
Advertise patients of the potential for secondary cancers, including myelodysplastic syndrome and acute leukemia [see Warnings and Precautions (5.3)].

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

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

Neuroendocrine Hormonal Crises
Advertise 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
Advertise 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)].

Advertise 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)].

Advertise 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
Advertise 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
Advertise 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

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

Or

Advanced Accelerator Applications USA, Inc.
57 East Willow Street, Millburn, NJ 07041, USA

Distributed by:
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