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

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

IN THIS SECTION

- What are gastroenteropancreatic neuroendocrine tumors (GEP-NETs)?
- Mechanism of action of LUTATHERA

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 classified 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 still often diagnosed at an advanced or metastatic stage.

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.
Mechanism of action of LUTATHERA® (lutetium Lu 177 dotatate)¹

- LUTATHERA is a radiopharmaceutical created by linking a radionuclide to a peptide that binds somatostatin receptors on the surface of GEP-NET tumor cells¹,⁵
- This class of medication is referred to as Peptide Receptor Radionuclide Therapy (PRRT)⁵

1. LUTATHERA is infused into the bloodstream.
2. LUTATHERA binds to cells expressing somatostatin receptors, including GEP-NET cells.
3. LUTATHERA is internalized into somatostatin receptor-bearing cells...
4. ...where it delivers beta radiation.
5. The radiation causes damage in somatostatin receptor-positive cells and neighboring cells.

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.
“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 there is no benefit to receiving it. It includes 3 basic protective measures:

**TIME:**
- minimize time near a radiation source
- Spend only the time needed to complete your job near the radiation source, and then leave the area

**DISTANCE:**
- maximize distance from a radiation source
- Stay as far away as you can from the radiation source

**SHIELDING:**
- use appropriate shielding between yourself and a radiation source
- Put appropriate materials between you and the radiation source. The appropriate materials will depend on what type of radiation the source emits

This brochure may help you implement the ALARA principle while preparing the patient and administering LUTATHERA.

You should follow these procedures, in addition to your institution’s radiation safety guidelines, whenever handling or administering LUTATHERA:

- Use disposable plastic, latex, or rubber gloves
- Wear a lab coat, which must be monitored before leaving the laboratory
- Wear safety glasses
- Minimize handling time
- Use tongs to handle unshielded sources and potentially contaminated vessels
- Use disposable absorbent liners on trays
- Ensure that waste and medical consumables exposed to radioactivity are disposed of in compliance with your institution’s radiation safety policies

**IMPORTANT SAFETY INFORMATION:** WARNINGS AND PRECAUTIONS

**Renal Toxicity:** Treatment with LUTATHERA will expose kidneys to radiation, which may impair renal function. In ERASMUS <1% of patients developed renal failure 3 to 36 months following LUTATHERA. Monitor serum creatinine and creatinine clearance to assess changes in renal function. Advise patients to urinate frequently during and after administration of LUTATHERA. A concomitant intravenous infusion of amino acids before, during and after LUTATHERA administration is mandatory for renal protection. Patients with baseline renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild or moderate impairment. Withhold, reduce dose, or permanently discontinue based on severity of reaction. Do not decrease the dose of amino acid solution if the dose of LUTATHERA is reduced. LUTATHERA has not been studied in patients with severe renal impairment (CrCL < 30 mL/min).
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 and emits 2 types of radiation:
- 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.

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.

Methods

- 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

- 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.

**RADIATION SPILL PROCEDURE**

<table>
<thead>
<tr>
<th>STOP</th>
<th>Stop what you are doing and don’t leave the immediate area</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Don’t panic—take a moment to collect your thoughts</td>
</tr>
<tr>
<td>STAY PUT</td>
<td>Assume that you are contaminated, so don’t spread the contamination with unnecessary movement</td>
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<tr>
<td></td>
<td>Check skin, clothes, and shoes for contamination</td>
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<tr>
<td>INFORM</td>
<td>Tell others in the immediate area what has happened</td>
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<td></td>
<td>Contact officials according to your institution’s radiation safety policies</td>
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<tr>
<td>LOCALIZE</td>
<td>Place absorbent materials (paper towels, drapes, wipes, etc) over the spilled radioactive material</td>
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<tr>
<td></td>
<td>Wear gloves and other protection</td>
</tr>
<tr>
<td>LABEL</td>
<td>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</td>
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</tbody>
</table>

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 INFORMATION**

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

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

The LUTATHERA regimen

LUTATHERA is administered according to the following regimen¹:

- 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

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<table>
<thead>
<tr>
<th>Weeks</th>
<th>LUTATHERA 200 mCi</th>
<th>Infusion Set-up</th>
<th>Administration Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>8</td>
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<td>16</td>
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<td>24</td>
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<tr>
<td>18</td>
<td></td>
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</tr>
</tbody>
</table>
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*Continue long-acting octreotide 30 mg IM every 4 weeks after completing LUTATHERA until disease progression or for up to 18 months following treatment initiation.

- Administer premedication and concomitant medications
- In case of toxicity: Interval between doses can be extended up to 16 weeks as needed. Information is provided in section 2.4 of the LUTATHERA full Prescribing Information as to when treatment with LUTATHERA should be suspended, the dose adjusted, or treatment permanently discontinued due to adverse reactions, including thrombocytopenia, anemia and neutropenia, renal toxicity, hepatotoxicity, and other non-hematologic toxicity¹

IM, intramuscular; IV, intravenous.

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.
Concomitant medications—somatostatin analogs

MONTH

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

24 HOURS

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.

4-24 HOURS

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

MONTH

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 177Lu 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 INFORMATION¹

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 end¹,⁹)**
- 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\textsuperscript{1}

<table>
<thead>
<tr>
<th>Pretreatment antiemetic\textsuperscript{1}</th>
<th>Concomitant amino acid infusion\textsuperscript{1}</th>
<th>LUTATHERA infusion\textsuperscript{1}</th>
<th>Long-acting octreotide 30 mg\textsuperscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer an antiemetic to help avoid treatment-related nausea and vomiting 30 minutes before the start of the amino acid solution infusion</td>
<td>For renal protection, initiate an intravenous amino acids 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</td>
<td>LUTATHERA must be administered as an intravenous infusion over 30 to 40 minutes • 50 mL/hour to 100 mL/hour for 5 to 10 mins • 200 mL/hour to 300 mL/hour for the following 25 to 30 mins</td>
<td>Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each LUTATHERA dose</td>
</tr>
</tbody>
</table>

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\textsuperscript{1}

- 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)\textsuperscript{1}

- 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 organization.
- 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:

![Patient Release Card Image]
Roles and responsibilities\(^9\)

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

<table>
<thead>
<tr>
<th>Time</th>
<th>Task</th>
<th>Responsible Party</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM</td>
<td>Patient check in for treatment</td>
<td>Nursing Staff</td>
</tr>
<tr>
<td>8:15-9:00 AM</td>
<td>Assessment, expectations of the day, orientation to room, IV placement, posttreatment instructions given, and LUTATHERA and medication prep</td>
<td>Nursing Staff</td>
</tr>
<tr>
<td>9:00-9:45 AM</td>
<td>Antiemetic administration and start of amino acids infusion</td>
<td>Nursing Staff</td>
</tr>
<tr>
<td>10:15 AM</td>
<td>Prep for LUTATHERA (void, positioning, time out, and monitoring)</td>
<td>Nuclear Medicine/Radiation Oncology</td>
</tr>
<tr>
<td>11:00-11:15 AM</td>
<td>Completion of LUTATHERA infusion</td>
<td>Nuclear Medicine/Radiation Oncology</td>
</tr>
<tr>
<td>11:15-16:00 PM</td>
<td>Symptom monitoring and management, amino acid titration, antiemetics as needed, and completion of amino acids infusion</td>
<td>Nursing Staff</td>
</tr>
<tr>
<td>16:00-17:00 PM</td>
<td>Discharge instruction review and IV removal</td>
<td>Discharge Staff</td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION\(^1\)**

**DRUG INTERACTIONS**

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

**SPECIFIC POPULATIONS**

**Lactation:** 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.

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.
References