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

A Guide to NURSING CARE FOR ADMINISTERING TREATMENT CENTER STAFF

Managing patients and follow-up care during and after LUTATHERA administration

Not an actual patient.

INDICATION

LUTATHERA® (lutetium Lu 177 dotatate) is indicated for the treatment of adult and pediatric patients aged 12 years and older with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors.

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, patient management procedures, Nuclear Regulatory Commission patient release guidance, and instructions to the patient for follow-up radiation protection at home.

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NOVARTIS

A Guide to NURSING CARE

FOR ADMINISTERING TREATMENT CENTER STAFF

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Coordinating care: Multidisciplinary roles and responsibilities

As an administering nurse, you help put patients at ease—and your communication with their referring staff can be crucial in helping ensure their continuity of care.

It is important to keep in mind that guidelines may vary by institution.

1: IDENTIFY

Referring Medical Oncology Practice

Identify and test appropriate patients for LUTATHERA

- The medical oncology practice identifies a patient with an SSTR+ GEP-NET in the foregut, midgut, or hindgut[1]
- LUTATHERA has evidence in both newly diagnosed patients and those who have progressed on an SSA, and can be used across grade 1, 2, and 3 well-differentiated SSTR+ GEP-NETs[1-3]

The referring oncologist examines the patient holistically, including testing for SSTR presence and tumor localization via imaging—part of each patient's staging and eligibility process for LUTATHERA[1,4]

Referring nurses may help identify appropriate patients for LUTATHERA early by[1-3]:

- Monitoring patients with newly diagnosed SSTR+ metastatic or advanced GEP-NETs
- Closely monitoring patients for disease progression on an SSA—regardless of the presence of symptoms

2: REFER

Referring Medical Oncology Practice

Refer patient to treatment site

Referring practice nurse coordinates patient care with treatment site care team, and makes sure to follow the recommendations from the treating physician such as:

- Long-acting SSAs should be discontinued ≥4 weeks prior to the administration of LUTATHERA[1]
- Patients can receive short-acting octreotide as needed; discontinue at least 24 hours prior to initiating LUTATHERA[1]
- Patient undergoes periodic laboratory testing as needed[1]
- Pregnancy status must be verified for patients of childbearing potential[1]

3: ADMINISTER

Administering Nuclear Medicine or Radiation Oncology Practice

Initiate LUTATHERA at treatment site

- Patient may undergo additional testing at the treatment site to confirm eligibility or readiness to initiate treatment[1,4]
- Recommended dosing is 4 cycles of treatment at 8-week intervals[1]

GEP-NET, gastroenteropancreatic neuroendocrine tumor; SSA, somatostatin analogue; SSTR, somatostatin receptor; SSTR+, somatostatin receptor-positive.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Myelosuppression:** In the NETTER-1 clinical trial, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide compared with patients receiving high-dose long-acting octreotide (all grades/grade 3/4): anemia (81%/0 vs 54%/1%), thrombocytopenia (53%/1% vs 17%/0), and neutropenia (26%/3% vs 11%/0).

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Coordinating care for LUTATHERA administration and follow-up

Administering nurses have responsibilities and challenges that can go beyond treatment, including communicating and aligning with the referring staff, understanding timing and the medications that must be coadministered, and managing any infusion safety concerns.

Treatment Site: Administering Nuclear Medicine or Radiation Oncology Practice

Before[1,4]

- Patient is checked in for treatment and provided assessment, expectations for the day, and orientation of the room
- Antiemetics are administered 30 minutes before the recommended amino acid solution to prevent nausea and vomiting
- An IV sterile amino acid solution containing L-lysine and L-arginine is initiated 30 minutes before administering LUTATHERA
- Patients who have had prior grade 1/2 hypersensitivity reactions to LUTATHERA are premedicated

During[1]

- Infusion is continued during and for at least 3 hours after the completion of the infusion of LUTATHERA
- The dose of the amino acid solution is not decreased if a reduced dose of LUTATHERA is administered
- Patients who experience grade 3/4 hypersensitivity reactions to LUTATHERA are not rechallenged

Treatment Site: Administering Nuclear Medicine or Radiation Oncology Practice

AFTER each dose of LUTATHERA[1]

- Long-acting octreotide 30 mg IM is administered between 4 and 24 hours after each dose of LUTATHERA
- Monitor patients for adverse reactions and laboratory abnormalities
- Patient is reminded when and where they will receive their next SSA treatment

IM, intramuscular; IV, intravenous.

Referring Medical Oncology Practice

AFTER all doses of LUTATHERA are completed[1,3]

- Long-acting octreotide 30 mg IM should continue every 4 weeks until disease progression or for 18 months following treatment initiation at the discretion of the physician
- Patients are closely monitored for disease progression on an SSA—regardless of the presence of symptoms

Have you confirmed the details with your patient's referring staff?

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Myelosuppression (continued):** In NETTER-1, platelet nadir occurred at a median of 5.1 months 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 19 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 dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of myelosuppression.

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Gathering essential patient information before treatment

Before treatment with LUTATHERA, it's important to gather the following information from patients and their referring team.

Eligibility[1]

- ✓ Confirmed SSTR+ GEP-NET in the foregut, midgut, or hindgut

Patient management

- ✓ Any medical conditions patients may have
- ✓ Urinary or fecal incontinence
- ✓ Changes in symptoms
  - Anticipate patient accommodations and potential treatment reactions

Compatibility with treatment

- ✓ Pregnancy status and breastfeeding intentions
  - Advise patients able to get pregnant to use effective contraception during treatment with LUTATHERA and for 7 months after the last dose[1]
  - Advise patients with a partner who is able to get pregnant to use effective contraception during treatment with LUTATHERA and for 4 months after the last dose[1]
  - Patients should not breastfeed during treatment with LUTATHERA and for 2.5 months after the last dose[1]
  - See the full Prescribing Information for risks associated with pregnancy and breastfeeding
- ✓ Any medications (including over-the-counter medications)
  - SSAs: See the dosing section on page 6 and the full Prescribing Information for discontinuation timing and other details
  - Repeated administration of high doses of glucocorticoids can affect LUTATHERA efficacy and are to be avoided during treatment[1]
  - Timing and administration of other concomitant medications may need to be taken under consideration

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Secondary Myelodysplastic Syndrome and Leukemia:** In NETTER-1, with a median follow-up time of 76 months in the main study, myelodysplastic syndrome (MDS) was reported in 2.3% of patients receiving LUTATHERA with long-acting octreotide compared with no patients receiving high-dose long-acting octreotide. In ERASMUS, a phase 2 clinical study, 16 patients (2.0%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to onset was 29 months (range, 9-45 months) for MDS and 55 months (range, 32-125 months) for acute leukemia.

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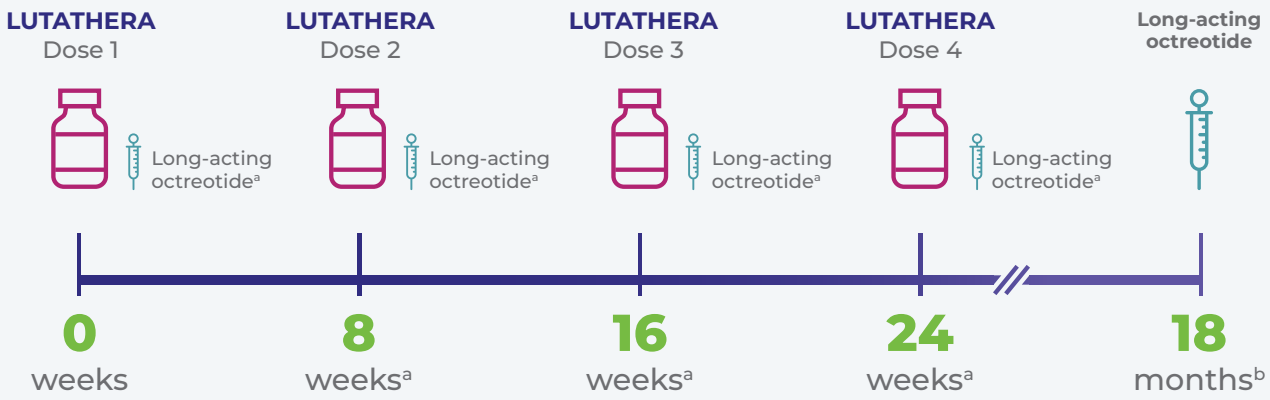
Regardless of patient type, the dosing regimen for LUTATHERA remains the same[1]

The defined 4-dose LUTATHERA regimen is available at treatment centers nationwide[1]



[a]The interval between infusions may be extended up to 16 weeks in the case of a dose modification due to an adverse reaction. Permanently discontinue LUTATHERA in patients who experience grade 3/4 hypersensitivity reactions. Please see the Prescribing Information for additional information on dose modifications.[1]

[b]Continue long-acting octreotide 30 mg IM every 4 weeks after completing LUTATHERA until disease progression or for 18 months following treatment initiation at the discretion of the physician.

During treatment, long-acting octreotide 30 mg IM will be administered between 4 and 24 hours after each dose of LUTATHERA[1]

- LUTATHERA dosage should be modified based on hematologic, renal, hepatic, hypersensitivity, or other adverse reactions (see full Prescribing Information)[1]
- For reduced dose administration instructions, refer to section 2.5 (Preparation and Administration) of the full Prescribing Information

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **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 (eg, diabetes or hypertension) and required dialysis. Administer the recommended amino acid solution before, during, and after LUTATHERA to decrease the reabsorption of lutetium Lu 177 dotatate through the proximal tubules and decrease the radiation dose to the kidneys. Advise patients to hydrate and to urinate frequently before, on the day of, and on the day after administration of LUTATHERA. Monitor serum creatinine and calculated creatinine clearance. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of renal toxicity. Patients with baseline renal impairment may be at increased risk of toxicity due to increased radiation exposure; perform more frequent assessments of renal function in patients with baseline mild or moderate impairment. LUTATHERA has not been studied in patients with baseline severe renal impairment (creatinine clearance <30 mL/min) or those with end-stage renal disease.

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Dosing regimen (continued)

Before each dose of LUTATHERA[1]

LONG-ACTING SSAs	Must be withheld **at least 4 weeks**
SHORT-ACTING SSAs	Must be withheld **at least 24 hours**
AMINO ACID INFUSION	START 30 minutes before and CONTINUE during LUTATHERA infusion and for **at least 3 hours after**
TIMING	Time for the actual LUTATHERA infusion ranges from **30 to 40 minutes** depending on the method of administration See the LUTATHERA Prescribing Information for additional infusion protocol

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

- **Hepatotoxicity:** In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with 1 patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, serum albumin, and the international normalized ratio during treatment. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of hepatotoxicity.

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Patient tips for treatment day and follow-up

When discussing treatment day and onward, these reminders can help prepare your patients for LUTATHERA. Patients will receive additional specific details from the treatment facility.

Infusion day medications

- Any required **antinausea therapy will be given on the same day**, before both the amino acid solution and LUTATHERA[1,4]
- **Amino acid infusion will be started on the same day** 30 minutes before—and last for at least 3 hours after—the LUTATHERA infusion[1]

Staying hydrated

- **Patients should drink liquids and urinate frequently** before, on the day of, and on the day after administration of LUTATHERA[1]

Breastfeeding

- **Patients should not breastfeed during treatment** with LUTATHERA and for 2.5 months after the last infusion of LUTATHERA[1]

Using birth control

- **Patients should use effective birth control** during treatment with LUTATHERA and for[1]:
  - 7 months after the last dose if the patient is able to get pregnant
  - 4 months after the last dose if the patient has a partner who is able to get pregnant

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema, occurred in patients treated with LUTATHERA. Monitor patients closely for signs and symptoms of hypersensitivity reactions, including anaphylaxis, during and following LUTATHERA administration for a minimum of 2 hours in a setting in which cardiopulmonary resuscitation medication and equipment are available. Discontinue the infusion upon the first observation of any signs or symptoms consistent with a severe hypersensitivity reaction and initiate appropriate therapy. Premedicate patients with a history of grade 1/2 hypersensitivity reactions to LUTATHERA before subsequent doses. Permanently discontinue LUTATHERA in patients who experience grade 3/4 hypersensitivity reactions.

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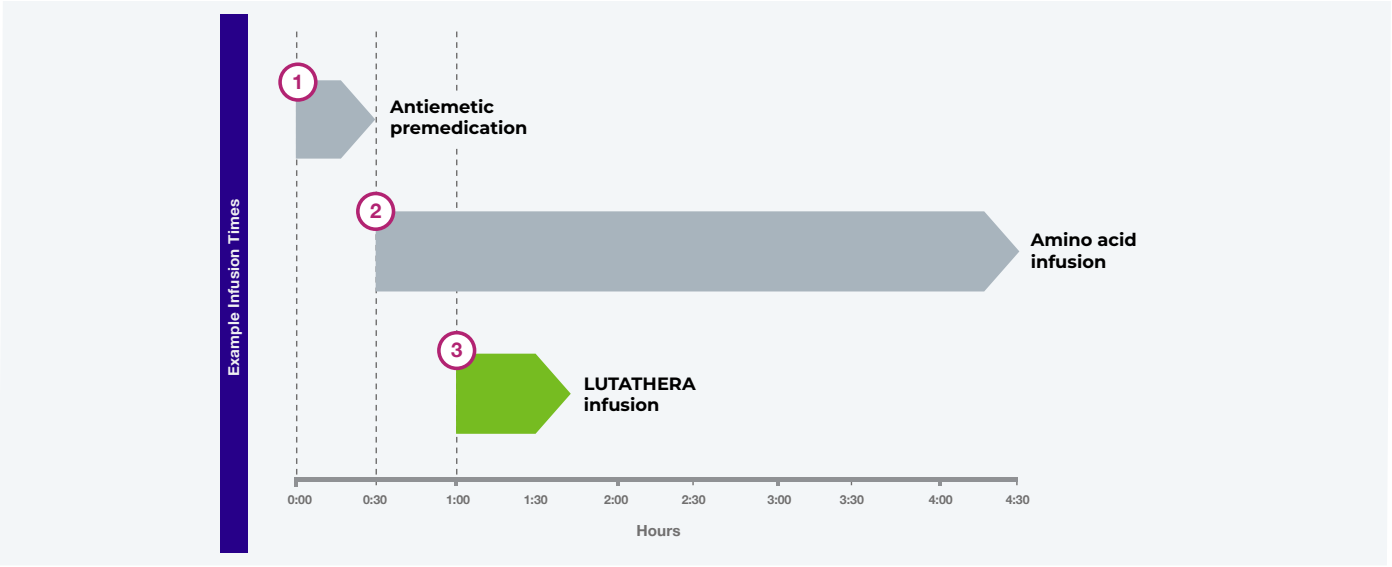
Preparing for the infusion process



1. • **Antiemetic** premedication must be given 30 minutes before both the amino acid solution and LUTATHERA[1,4]

2. • Sterile **amino acid IV solution** (containing L-lysine and L-arginine) must begin 30 minutes before the start of LUTATHERA[1,4]
   • Continue the amino acid infusion during and for at least 3 hours after the completion of the infusion of LUTATHERA[1,4]
   • Do not decrease the dose of the amino acid solution if a reduced dose of LUTATHERA is administered[1,4]
   • Use a 3-way valve to administer the amino acid solution using the same venous access as LUTATHERA, or administer in the patient's other arm (separate venous access)[1,4]

3. **LUTATHERA** infusion:
   • Premedicate patients who have had prior grade 1/2 hypersensitivity reactions[1,4]
   • Do not rechallenge patients who experience grade 3/4 hypersensitivity reactions[1,4]
   • Monitor patients closely for signs and symptoms of hypersensitivity reactions, including anaphylaxis, during and following LUTATHERA administration for a minimum of 2 hours in a setting where cardiopulmonary resuscitation medication and equipment are available[1,4]
   • Discontinue the infusion upon the first observation of any signs or symptoms consistent with a severe hypersensitivity reaction and initiate appropriate therapy[1,4]

Confirm the administration method as well as roles and responsibilities of infusion timing with the nuclear medicine professional in your treatment center

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

• **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 analogues, fluids, corticosteroids, and electrolytes as indicated.

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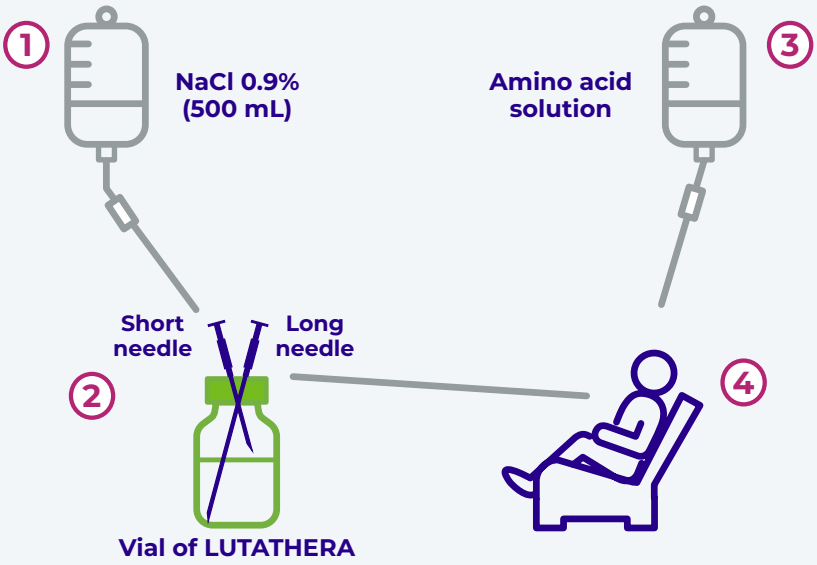
It is likely that the nuclear medicine professional will administer LUTATHERA using the gravity method*

The gravity method of administration[1,4]



1. Insert the 2.5-cm, 20-gauge needle (short needle) into the vial of LUTATHERA.
2. Connect the short needle to the 500 mL of 0.9% sterile sodium chloride solution via catheter.
3. Insert the 9-cm, 18-gauge needle (long needle) into the vial of LUTATHERA.
4. Connect the long needle to the patient by an IV catheter. Catheter should be prefilled with 0.9% sterile sodium chloride and used exclusively for LUTATHERA.

- The short needle must not touch the solution of LUTATHERA inside the vial
- Do not allow sterile sodium chloride to flow into the vial prior to the start of the infusion
- Do not connect the short needle directly to the patient
- Do not inject LUTATHERA directly into the sodium chloride solution
- The long needle must touch and be secured to the bottom of the vial during the entire infusion of LUTATHERA

These are not inclusive of every administrative step. Please refer to the full Prescribing Information (section 2.5) for detailed instructions.

*The gravity method, peristaltic pump method, or the syringe pump method may be used for LUTATHERA administration. The peristaltic pump or syringe pump methods are used when administering a reduced dose of LUTATHERA following a dosage modification for an adverse reaction. When using the gravity method for a reduced dose, adjust the LUTATHERA dose before the administration to avoid the delivery of an incorrect volume of LUTATHERA.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Embryo-Fetal Toxicity:** LUTATHERA can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating LUTATHERA. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with LUTATHERA and for 4 months after the last dose.

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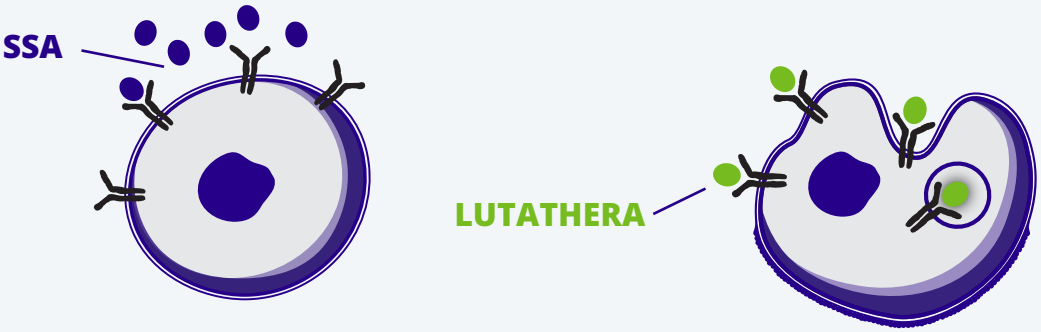
How LUTATHERA works

LUTATHERA is a targeted treatment that uses radiation to damage SSTR+ cancer cells and neighboring cells[1]

- ✓ LUTATHERA contains a **targeting component that helps find cells with SSTRs**, including GEP-NET cancer cells.
- ✓ Once it finds these target cells, **LUTATHERA binds to the SSTRs** located on the outside of the cells and enters into the cell.
- ✓ LUTATHERA then **delivers radiation that causes damage to the SSTR+ cells** and nearby cells.

Almost 90% of GEP-NETs overexpress SSTRs[5]



SSA targets SSTR+ GEP-NET cells[6,7]

LUTATHERA also acts against and destroys SSTR+ cells, including GEP-NET cells[1]

Based on preclinical models. LUTATHERA delivers radiation that causes damage to the SSTR+ cells as well as neighboring, healthy cells.

LUTATHERA delivers tumor-destroying radiation to SSTR+ GEP-NET cells and neighboring cells[1]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Risk of Infertility:** LUTATHERA may cause infertility in males and females. Radiation absorbed by testes 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.

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Radiation guidelines for patients

Posttreatment patient safety guidelines (NANETS/SNMMI consensus and Mayo Clinic recommendations)

Your treatment center may provide more specific guidance, but here are some frequently discussed topics regarding posttreatment LUTATHERA radiation precautions.

Using the toilet

For at least 3 days, patients should use the toilet in a seated position (even for men) and flush the toilet twice after use.[4]

Showering and personal hygiene

For at least 7 days, patients should shower daily. Patients should use separate towels and washcloths.[4,8]

Sleeping

For at least 3 days, patients should sleep in a separate bed and avoid intimate contact.[4]

Interacting with others

For at least 3 days, patients should use a general distance guideline of no closer than 3 feet for no more than 1 hour per day. They should try to maintain a distance of 6 feet from others and minimize public transportation and use of public facilities.[4]

NANETS, North American Neuroendocrine Tumor Society; SNMMI, Society of Nuclear Medicine and Molecular Imaging.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common grade 3/4 adverse reactions (≥4% with a higher incidence in the LUTATHERA arm) observed in NETTER-1 were lymphopenia (44%), increased gamma-glutamyl transferase (20%), vomiting (7%), nausea (5%), increased aspartate aminotransferase (5%), increased alanine aminotransferase (4%), hyperglycemia (4%), and hypokalemia (4%).

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Radiation guidelines for HCPs and caregivers

HCP and caregiver radiation exposure was tested in a 4-patient, 4-bed outpatient center[9]

Radiation exposure in HCPs and caregivers following outpatient treatment with Lutetium 177 on the LUTATHERA dosing regimen was tested in an outpatient study with 4 sequentially treated patients in a 4-bed room.

Exposures to HCPs and caregivers were within ICRP limits (ICRP radiation exposure limit is 20 mSv per year)[9,10]

Exposure to nurses was similar to that of a flight crew on regular round-trip flights from Los Angeles to Honolulu[9,11]

Mean whole-body radiation exposures per therapy treatment day with 4 patients when administering Lutetium 177 ranged from 6.8 µSv (nuclear medicine technologist) to 33.2 µSv (nurse).[9]

Exposure is 14.5 µSv on a 5.2-hour flight from Los Angeles to Honolulu[11]

Exposure to caregivers

For caregivers, mean total exposure during the day of therapy and at home for a period of up to 5 days was 90 µSv, with a median exposure of 40 µSv and range of 10 µSv to 470 µSv.[9]

Patients are discharged from the treatment center only when radiation exposure to third parties does not exceed regulatory thresholds[9]

Seventy-six patients with progressive, metastatic NETs received 4 cycles of 7.8 GBq of Lutetium 177 at 8-week intervals in an outpatient setting at 1 treatment center. Four patients were treated sequentially on each therapy day in a 4-bed room in the hospital's day procedure unit, with each patient remaining until radiation exposure was below the release limit. Radiation exposures to HCPs and caregivers were monitored by personal dosimeter. Twenty-five carers were provided with electronic dosimeters. In the nearby staff office with a 50% staff occupancy factor, the mean (range) exposure rate measured on 10 different therapy administration days was 1.6 µSv/h (1.3–2.0 µSv/h), and at the nursing station with 100% staff occupancy it was 3.5 µSv/h (2.9–4.0 µSv/h).[9]

GBq, gigabecquerel; HCPs, health care professionals; ICRP, International Commission on Radiological Protection; µSv, microsievert; mSV, millisievert; NETs, neuroendocrine tumors.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS (continued)

In ERASMUS, the following serious adverse reactions have been observed with a median follow-up time of >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.

Adverse reactions observed in pediatric patients were similar to those observed in adults treated with LUTATHERA.

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Most of the adverse reactions seen in the LUTATHERA arm in NETTER-1 were grade 1/2[1]

Adverse Reactions Occurring at a Higher Incidence in the LUTATHERA Arm (Between-Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3/4])[1]

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

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays adverse reactions occurring at a higher incidence in LUTATHERA-treated patients (between-arm difference of ≥5% [all grades] or ≥2% [grade 3/4]).[1]
[b]Includes the terms glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, and renal impairment.[1]
[c]Includes the terms dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain, and urinary incontinence.[1]

The most common grade 3/4 adverse reactions with a higher incidence in the LUTATHERA arm were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), increased AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).[1]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LAR, long-acting release.

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NETTER-2 and long-term safety

Safety data from NETTER-2 are consistent with the established profile of LUTATHERA

- The most common adverse events (≥20% in either arm) were nausea (27% vs 18%), diarrhea (26% vs 34%), and abdominal pain (18% vs 27%) for LUTATHERA + 30 mg octreotide LAR vs 60 mg octreotide LAR, respectively[13]
- The most common grade 3/4 adverse events (>3% in either arm) were lymphocyte count decreased (5% vs 0%), GGT increased (5% vs 3%), small intestinal obstruction (3% vs 0%), and abdominal pain (3% vs 4%) for LUTATHERA + 30 mg octreotide LAR vs 60 mg octreotide LAR, respectively[13]

No new safety signals were reported in the 5-year, long-term follow-up for NETTER-1[1,12,*]

Adverse Events	During the long-term follow-up, only serious adverse events (SAEs) deemed related to treatment with LUTATHERA and AEs of special interest (hematotoxicity, cardiovascular events, and nephrotoxicity, regardless of causality) in the LUTATHERA arm were reported[12]
Grade ≥3 Treatment-Related SAEs During the Entire Study	7 (6%) of 111 patients treated in the LUTATHERA arm[12]
Incidence of Treatment-Related SAEs During the Long-Term Follow-Up Period	**3 (3%) of 111 patients treated with LUTATHERA**[12] — 2 (1.8%) patients experienced at least 1 grade ≥3 SAE (1 grade 5 MDS event)[12] — 1 (0.9%) patient experienced an SAE leading to study discontinuation[12]
MDS or Acute Leukemia	**No new cases were reported during long-term follow-up**[12] — MDS incidence from the Prescribing Information for LUTATHERA: In NETTER-1, with a median follow-up time of 76 months in the main study, MDS was reported in 2.3% of patients receiving LUTATHERA with long-acting octreotide compared with no patients receiving high-dose, long-acting octreotide[1,12] — In ERASMUS, 16 patients (2.0%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to onset was 29 months (range, 9-45 months) for MDS and 55 months (range, 32-125 months) for acute leukemia[1,a]
Diffuse Large B-Cell Lymphoma	One patient developed diffuse large B-cell lymphoma during long-term follow-up that was deemed unrelated to treatment with LUTATHERA[12]
Nephrotoxicity of Grade ≥3, Regardless of Causality	Reported in 6 (5%) of 111 patients in the LUTATHERA arm and 4 (4%) of 112 patients in the control arm during the study[12]

*Cutoff date for final analysis was January 18, 2021.[12]

[a] ERASMUS study design: Retrospective safety data are available from 1214 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with SSTR+ tumors (neuroendocrine and other primaries). The median duration of follow-up was >4 years.[1]

AEs, adverse events; MDS, myelodysplastic syndrome.

ERASMUS: The retrospective, long-term safety study for LUTATHERA[1]

ERASMUS was a retrospective study analyzing safety in a long-term (median, >4 years) follow-up after LUTATHERA treatment

Study Design	Retrospective safety data are available from 1214 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with SSTR+ tumors (neuroendocrine and other primaries). The median duration of follow-up was >4 years
Administration	LUTATHERA 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses with or without octreotide. Retrospective medical record review was conducted on a subset of 811 patients to document serious adverse reactions — 81% of patients in the subset received a cumulative dose ≥22.2 GBq (≥600 mCi)
Safety Data	**The following rates of serious adverse reactions were reported in ERASMUS:** myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%)

Please see Warnings and Precautions in the full Prescribing Information for myelosuppression, MDS, and leukemia. Monitor blood cell counts[1]

mCi, millicurie.

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

Discontinue long-acting somatostatin analogues at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose.

SPECIFIC POPULATIONS

Lactation: Advise patients not to breastfeed during LUTATHERA treatment.

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

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Dosing modifications

LUTATHERA dosing may require modification for patients who experience adverse reactions

See more details regarding adverse reactions in the LUTATHERA full Prescribing Information.

Adverse Reaction[1]	Severity of Adverse Reaction[1,a]	Dose Modification[1]
Thrombocytopenia	Grade 2, 3, or 4	Withhold dose until complete or partial resolution (grade 0 to 1). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in grade 2, 3, or 4 thrombocytopenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.
	Recurrent grade 2, 3, or 4	Permanently discontinue LUTATHERA.
Anemia and Neutropenia	First occurrence of grade 3 or 4	Withhold dose until complete or partial resolution (grade 0, 1, or 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in grade 3 or 4 anemia or neutropenia, administer LUTATHERA at 7.4 GBq (200 mCi) as next dose. Permanently discontinue LUTATHERA for grade 3 or higher anemia or neutropenia requiring a dosing interval beyond 16 weeks.
	Recurrent grade 3 or 4	Permanently discontinue LUTATHERA.
Renal Toxicity	First occurrence of: • Creatinine clearance less than 40 mL/min; calculated using Cockcroft-Gault formula with actual body weight, or • 40% increase from baseline serum creatinine, or • 40% decrease from baseline creatinine clearance; calculated using Cockcroft-Gault formula with actual body weight	Withhold dose until resolution or return to baseline. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with resolution or return to baseline. If reduced dose does not result in renal toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) as next dose. Permanently discontinue LUTATHERA for renal toxicity requiring a dosing interval beyond 16 weeks.
	Recurrent renal toxicity	Permanently discontinue LUTATHERA.

[a]Grading of severity is defined in the most current National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

Dosing modifications (continued)

Adverse Reaction[1]	Severity of Adverse Reaction[1,a]	Dose Modification[1]
Hepatotoxicity	First occurrence of: • Bilirubinemia greater than 3 times the upper limit of normal (grade 3 or 4), or • Serum albumin less than 30 g/L with international normalized ratio (INR) >1.5	Withhold dose until resolution or return to baseline. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with resolution or return to baseline. If reduced LUTATHERA dose does not result in hepatotoxicity, administer LUTATHERA at 7.4 GBq (200 mCi) as next dose. Permanently discontinue LUTATHERA for hepatotoxicity requiring a dosing interval beyond 16 weeks.
	Recurrent hepatotoxicity	Permanently discontinue LUTATHERA.
Hypersensitivity Reactions[b]	First occurrence of grade 3 or 4	Permanently discontinue LUTATHERA.
Any Other Adverse Reactions[c]	First occurrence of grade 3 or 4	Withhold dose until complete or partial resolution (grade 0 to 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in grade 3 or 4 toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) as next dose. Permanently discontinue LUTATHERA for grade 3 or higher adverse reactions requiring a dosing interval beyond 16 weeks.
	Recurrent grade 3 or 4	Permanently discontinue LUTATHERA.

[a]Grading of severity is defined in the most current National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).
[b]Including allergic reaction and anaphylaxis.
[c]No dose modification required for hematological toxicities of grade 3 or grade 4 solely due to lymphopenia.

Novartis Patient Support™

Support to help your patients start and stay on therapy

Designed to provide support in the following areas:

- **Access & Reimbursement**
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We help make treatment more affordable for your patients through co-pay savings.

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*Limitations apply. Valid only for those with commercial insurance. Not valid under Medicare or any other federal or state program. Offer subject to a maximum benefit per course of treatment. See complete Terms and Conditions in the Enrollment Forms for details.

Here's How to Enroll

Simply download the Start Form at www.novartis-patientsupport.com/RLT, fill it out, and fax it to **1-844-638-7329** OR you can also access support by registering for our portal. Registration is required.

Have questions about the enrollment process? Call us at **1-844-638-7222.**

Additional Educational Support Is Available for Your Patients

After the decision to start LUTATHERA is made, our dedicated team of Patient Navigators can help answer some of the most common treatment questions. To put your patients in contact with one of our Patient Navigators, call **1-844-638-7222.**

Patients must be enrolled in Novartis Patient Support to be considered for financial support.

Visit our website at www.novartis-patientsupport.com/RLT for more information

Visit www.LUTATHERA-hcp.com

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GEP-NET advocacy organizations

Are your patients ready to explore more about GEP-NETs on their own?

The following support networks may help patients with general information and social support.

The Carcinoid Cancer Foundation (CCF)

www.carcinoid.org

The Healing NET Foundation

415 Spence Lane
Nashville, TN 37210
1-615-369-6463

info@thehealingnet.org
www.thehealingnet.org

Learn • Advocate • Connect A Neuroendocrine Tumor Society (LACNETS)

PO Box 370466
Denver, CO 80237

info@lacnets.org
www.lacnets.org

The Neuroendocrine Cancer Awareness Network (NCAN)

3074 Brookchase Boulevard
Fort Mill, SC 29707
1-866-850-9555

info@netcancerawareness.org
www.netcancerawareness.org

Neuroendocrine Tumor Research Foundation (NETRF)

31 St. James Avenue, Suite 365
Boston, MA 02116
1-617-946-1780

info@netrf.org
www.netrf.org

Northern California CarciNET Community (NorCal CarciNET)

info@norcalcarcinet.org
www.norcalcarcinet.org

These are provided for informational purposes only. This is not intended to be a recommendation or endorsement of any organization.

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For patients coming to you for LUTATHERA treatment, enable them to

START STRONG WITH LUTATHERA

Having a greater understanding of LUTATHERA can help strengthen ongoing care for your patients with GEP-NETs

Help coordinate a smooth patient journey through communication and alignment with the referring nurse and greater care team

You play an essential role in providing clarity concerning the LUTATHERA treatment process—including safety and patient management—to help prepare patients for what to expect from treatment

Treatment with LUTATHERA consists of a 4-dose treatment regimen, given every 8 weeks at a LUTATHERA treatment center.[1] See inside for more administration details

To learn more about LUTATHERA and find useful resources, visit www.LUTATHERA-hcp.com

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, patient management procedures, Nuclear Regulatory Commission patient release guidance, and instructions to the patient for follow-up radiation protection at home.

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