HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

Dosage and Administration (2.1, 2.3, 2.4, 2.5, 2.6)	6/2022
Warnings and Precautions (5.3, 5.5, 5.6, 5.8)	6/2022

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

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

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

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

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

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

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

None. (4)

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

- Risk From Radiation Exposure: Minimize radiation exposure during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures. (2.1, 5.1)
- Myelosuppression: Monitor blood cell counts. Withhold, reduce dose, or permanently discontinue based on severity. (2.4, 5.2)
- Secondary Myelodysplastic Syndrome (MDS) and Leukemia: Median time to onset: MDS is 29 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 serum albumin. (2.4, 5.5)
- Hypersensitivity Reactions: Monitor patients closely for signs and symptoms of hypersensitivity reactions, including anaphylaxis. Permanently discontinue LUTATHERA based on severity. (2.3, 2.4, 5.6)
- Neuroendocrine Hormonal Crisis: Monitor for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.8, 8.1, 8.3)
- Risk of Infertility: LUTATHERA may cause infertility. (5.9, 8.3)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceutical Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Instructions

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

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

Monitor patients closely for signs and symptoms of hypersensitivity reactions during and following the LUTATHERA administration for a minimum of 2 hours in a setting where cardiopulmonary resuscitation medication and equipment are available *[see Warnings and Precautions (5.6)]*.

2.2 Recommended Dosage

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

2.3 Premedication and Concomitant Medications

Somatostatin Analogs

- Before initiating LUTATHERA: Discontinue long-acting somatostatin analogs (e.g., long-acting octreotide) 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 at least 24 hours before each LUTATHERA dose.
- Following LUTATHERA treatment: Continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing LUTATHERA until disease progression or for up to 18 months following treatment initiation.

Antiemetic

Administer antiemetics before the recommended amino acid solution.

Amino Acid Solution

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

Table 1. Amino Acid Solution

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

Hypersensitivity Prophylaxis

Premedicate patients who have had prior Grade 1 or 2 hypersensitivity reactions to LUTATHERA. Do not re-challenge patients who experience a Grade 3 or 4 hypersensitivity reactions to LUTATHERA *[see Warnings and Precautions (5.6)]*.

2.4 Dosage Modifications for Adverse Reactions

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

Table 2. Recommended Dosage Modifications of LUTATHERA for Adverse Reactions

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

Adverse Reaction	Severity of Adverse Reaction[a]	Dose Modification
Renal Toxicity *[see Warnings and Precautions (5.4)]*	Defined as: • Creatinine clearance less than 40 mL/min; calculate using Cockcroft Gault with actual body weight, or • 40% increase in baseline serum creatinine, or • 40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.	Withhold dose until complete resolution or return to baseline. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution or return to baseline. If reduced dose does not result in renal toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for renal toxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent renal toxicity	Permanently discontinue LUTATHERA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Defined as: • Bilirubinemia greater than 3 times the upper limit of normal (Grade 3 or 4), or • Serum albumin less than 30 g/L with international normalized ratio (INR) > 1.5.	Withhold dose until complete resolution or return to baseline. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution or return to baseline. If reduced LUTATHERA dose does not result in hepatotoxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for hepatotoxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent hepatotoxicity	Permanently discontinue LUTATHERA.
Hypersensitivity Reactions[b] *[see Warnings and Precautions (5.6)]*	Grade 3 or 4	Permanently discontinue LUTATHERA.
Other Non-Hematologic Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher adverse reactions requiring treatment delay of 16 weeks or longer.
	Recurrent Grade 3 or 4	Permanently discontinue LUTATHERA.
[a]Grading of severity is defined in the most current Common Terminology Criteria for Adverse Events (CTCAE). [b]Including allergic reaction and anaphylaxis.		

2.5 Preparation and Administration

- Use aseptic technique and radiation shielding when administering the LUTATHERA solution. Use tongs when handling the 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 under a shielded screen for particulate matter and discoloration prior to administration. Discard the vial if particulates or discoloration are present.

Administration Instructions

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

Instructions for Gravity Method

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

Instructions for Infusion Pump Method

- Insert a 2.5 cm, 20 gauge needle (short venting needle) into the LUTATHERA vial. Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient or the infusion pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic infusion pump according to manufacturer's instruction.
- Prime the line by opening the 3-way stopcock valve and pumping the LUTATHERA solution through the tubing until it reaches the exit of the valve.
- Prime the intravenous catheter that will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the primed intravenous catheter to the patient and set the 3-way stopcock valve such that the LUTATHERA solution is in line with the infusion pump.
- Infuse an appropriate volume of LUTATHERA solution over a 30-40 min period to deliver the desired radioactivity.
- When the desired LUTATHERA radioactivity has been delivered, stop the infusion pump and then change the position of the 3-way stopcock valve so that the infusion pump is in line with the 0.9% sterile sodium chloride solution. Restart the infusion pump and infuse an intravenous flush of 25 mL of 0.9% sterile

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