

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

### RECENT MAJOR CHANGES

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

### INDICATIONS AND USAGE

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

### DOSAGE AND ADMINISTRATION

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

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

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

### ADVERSE REACTIONS

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

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

### DRUG INTERACTIONS

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

### USE IN SPECIFIC POPULATIONS

**Lactation:** Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2020

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Important Safety Instructions

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

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

#### 2.2 Recommended Dosage

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

#### 2.3 Premedication and Concomitant Medications

##### Somatostatin Analogs

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

##### Antiemetic

Administer antiemetics before the recommended amino acid solution.

## Amino Acid Solution

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

**Table 1. Amino Acid Solution**

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

## 2.4 Dosage Modifications for Adverse Reactions

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

**Table 2. Recommended Dosage Modifications of LUTATHERA for Adverse Reactions**

Adverse Reaction	Severity of Adverse Reaction*	Dose Modification
Thrombocytopenia [see <i>Warnings and Precautions (5.2)</i> ]	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 <i>Warnings and Precautions (5.2)</i> ]	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

Adverse Reaction	Severity of Adverse Reaction*	Dose Modification
		<p>result in Grade 3 or 4 anemia or neutropenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose.</p> <p>Permanently discontinue LUTATHERA for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 16 weeks or longer.</p>
Renal Toxicity [ <i>see Warnings and Precautions (5.4)</i> ]	<p>Defined as:</p> <ul style="list-style-type: none"> <li>• Creatinine clearance less than 40 mL/min; calculate using Cockcroft Gault with actual body weight, or</li> <li>• 40% increase in baseline serum creatinine, or</li> <li>• 40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.</li> </ul>	<p>Withhold dose until complete resolution or return to baseline.</p> <p>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.</p> <p>Permanently discontinue LUTATHERA for renal toxicity requiring a treatment delay of 16 weeks or longer.</p>
Hepatotoxicity [ <i>see Warnings and Precautions (5.5)</i> ]	<p>Defined as:</p> <ul style="list-style-type: none"> <li>• Bilirubinemia greater than 3 times the upper limit of normal (Grade 3 or 4), or</li> <li>• Hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.</li> </ul>	<p>Withhold dose until complete resolution or return to baseline.</p> <p>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.</p> <p>Permanently discontinue LUTATHERA for hepatotoxicity requiring a treatment delay of 16 weeks or longer.</p>
Other Non-Hematologic Toxicity [ <i>see Adverse Reactions (6.1)</i> ]	Grade 3 or 4	<p>Withhold dose until complete or partial resolution (Grade 0 to 2).</p> <p>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.</p> <p>Permanently discontinue LUTATHERA for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.</p>
	Recurrent Grade 3 or 4	Permanently discontinue LUTATHERA.

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

## 2.5 Preparation and Administration

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

### Administration Instructions

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

### *Instructions for Gravity Method*

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

### *Instructions for Infusion Pump Method*

- Insert a 2.5 cm, 20 gauge needle (short venting needle) into the LUTATHERA vial. Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient or the infusion pump.

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