YOUR GUIDE TO LUTATHERA TREATMENT
About LUTATHERA

LUTATHERA is the first approved medicine from a class of drugs called peptide receptor radionuclide therapy (PRRT). It is a prescription treatment for adults with a type of cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs). GEP-NETs are tumors of the neuroendocrine cells in the stomach, gut, or pancreas that make hormones, which may cause symptoms such as flushing and diarrhea. LUTATHERA targets somatostatin receptor-positive tumors.

LUTATHERA is a medicine that uses radiation to induce damage to the cancer cells that are positive for the hormone receptor somatostatin. It works differently than most other cancer medicines.\(^1\)\(^2\)

What is LUTATHERA?
LUTATHERA is a prescription medicine used to treat adults with a type of cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that are positive for the hormone receptor somatostatin, including GEP-NETs in the foregut, midgut, and hindgut.

IMPORTANT SAFETY INFORMATION:

What are the possible serious side effects of LUTATHERA?
LUTATHERA can cause serious side effects and if you experience these side effects, your healthcare provider may need to adjust or stop your treatment. You should always follow your healthcare provider’s instructions. Serious side effects may include:

- Radiation exposure: Treatment with LUTATHERA will expose you to radiation which can contribute to your long-term radiation exposure. Overall radiation exposure is associated with an increased risk for cancer. The radiation will be detectable in your urine for up to 30 days following administration of the drug. It is important to minimize radiation exposure to household contacts consistent with good radiation safety practices.

How does LUTATHERA work?

1. LUTATHERA is administered directly into the bloodstream.
2. LUTATHERA contains a tumor-targeting part that helps find cells with somatostatin receptors, including GEP-NET cancer cells.
3. Once it finds these cells, LUTATHERA binds to and enters the cell.
4. Once inside the cell, LUTATHERA delivers beta radiation.
5. This radiation causes damage to the somatostatin-positive cancer cells, as well as to some nearby cells.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for LUTATHERA.
In a clinical trial of 229 patients that compared patients with midgut neuroendocrine tumors (NETs) who received LUTATHERA in combination with 30-mg, long-acting octreotide to those who received 60 mg of long-acting octreotide alone:

• LUTATHERA reduced the relative risk of the cancer getting worse or death by 79% compared with patients treated with 60 mg of long-acting octreotide alone

• More patients treated with LUTATHERA had their tumors shrink or disappear compared with patients treated with 60 mg of long-acting octreotide alone

Percent of patients who had their tumors shrink or disappear

<table>
<thead>
<tr>
<th></th>
<th>LUTATHERA + long-acting octreotide 30 mg group</th>
<th>Long-acting octreotide 60 mg group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response (tumors shrink):</td>
<td>12% (14 of 116 patients)</td>
<td>4% (4 of 113 patients)</td>
</tr>
<tr>
<td>Complete Response (tumors disappear):</td>
<td>1% (1 of 116 patients)</td>
<td>0% (0 of 113 patients)</td>
</tr>
</tbody>
</table>

EFFECTIVENESS OF LUTATHERA® (lutetium Lu 177 dotatate)

IMPORTANT SAFETY INFORMATION (Continued):

• Bone marrow problems: Treatment with LUTATHERA increases the risk of myelosuppression, a condition in which bone marrow activity is decreased, resulting in drop in blood cell counts. You may experience blood-related side effects such as low red blood cells (anemia), low numbers of cells that are responsible for blood clotting (thrombocytopenia), and low numbers of a type of white blood cells (neutrophils). People with low blood cell counts are at higher risk of developing serious side effects associated with LUTATHERA. Speak with your healthcare provider if you experience any signs or symptoms of infection, fever, chills, dizziness, shortness of breath or increased bleeding or bruising. Your healthcare provider may need to adjust or stop your treatment accordingly.

• Secondary bone marrow and blood cancers: Other serious conditions that you may develop as a direct result of treatment with LUTATHERA include blood and bone marrow disorders known as secondary myelodysplastic syndrome and cancer known as acute leukemia. Your healthcare provider will routinely check your blood counts and tell you if they are too low.

• Kidney problems: Treatment with LUTATHERA will expose your kidneys to radiation and may impair their ability to work as normal. You may be at an increased risk for lower kidney function after LUTATHERA treatment if you already have kidney impairment before treatment. In some cases, patients have experienced kidney failure after treatment with LUTATHERA. Your healthcare provider will monitor changes and provide you with an amino acid solution before, during, and after LUTATHERA to help protect your kidneys. You should stay well hydrated before, during, and after your treatment. You should urinate frequently during and after administration of LUTATHERA. Your doctor will monitor your kidney function and may withhold, reduce, or stop your LUTATHERA treatment accordingly.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for LUTATHERA.
Once you agree to receive LUTATHERA

RECEIVING LUTATHERA® (lutetium Lu 177 dotatate)

It’s important to tell your healthcare provider everything about your disease and health status. This should include:

✓ Symptoms you may have
✓ Any changes in your daily habits
✓ If you are trying to get pregnant, if you are already pregnant, or breastfeeding
✓ If you have trouble controlling when you urinate or have a bowel movement
✓ All the medicines you are taking

It is especially important to tell your healthcare provider if you are taking a type of medicine called a somatostatin analog. If you are taking one, you might have to stop or change your treatment for a short time before and while receiving LUTATHERA. For more information, see “What other medicines may interact with LUTATHERA?” on page 17.

Understanding radiation

Your doctor will provide you with tips to minimize radiation exposure to those around you throughout your treatment with LUTATHERA.

Reproductive safety

Females of reproductive potential must use birth control during treatment with LUTATHERA and for 7 months after the final dose. Males with female partners of reproductive potential must use birth control during treatment and for 4 months after the final dose.

IMPORTANT SAFETY INFORMATION® (Continued):

• Liver problems: In clinical studies of LUTATHERA, less than 1% of patients were reported to have tumor bleeding (hemorrhage), swelling (edema) or tissue injury (necrosis) to the liver. If you have tumors in your liver, you may be more likely to experience these side-effects. Signs that you may be experiencing liver damage include increases in blood markers called ALT, AST and GGT. Your healthcare provider will monitor your liver using blood tests and may need to withhold, reduce, or stop your LUTATHERA treatment accordingly.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for LUTATHERA.

Before your first infusion

A few weeks before your first LUTATHERA infusion, your healthcare provider may conduct a few tests to make sure you are ready for treatment. They will check your liver, kidneys, and blood. Depending on the results, they may hold off on administering LUTATHERA until you are ready.

The day of therapy

You will go to your healthcare provider’s treatment center to have LUTATHERA administered. This is usually done in the nuclear medicine department. The doctors and nurses in this department are specially trained to use medicines like LUTATHERA.

The infusion

The infusion process lasts about 5 hours.

Approximately 1 hour before you are given LUTATHERA: You will be given a medicine that will help with vomiting or an upset stomach that you may experience because of the treatment.

30 minutes before you are given LUTATHERA: You will be given amino acids through an intravenous (IV) infusion to help protect your kidneys. This infusion will take at least 4 hours. It will continue during and after you receive LUTATHERA.

The LUTATHERA infusion: Will take 30 to 40 minutes and is given as an IV infusion.

After the infusion

Because LUTATHERA treatment uses radiation, you will have to wait a short while before you can leave the treatment center. The more you urinate, the faster the radiation will leave your body. A healthcare provider will let you know when it’s safe for you to leave the treatment center. Within a day of receiving LUTATHERA, you will be given an injection of long-acting octreotide 30 mg. You will receive an injection of long-acting octreotide 30 mg after each LUTATHERA infusion.

Your next infusion

You may receive LUTATHERA up to 3 more times after your first infusion. These doses will be between 8 and 16 weeks apart.

Between each dose, your healthcare provider may check your liver, kidneys, and blood again.

After your last dose

Your healthcare provider may check your liver, kidneys, and blood on a routine basis after your last LUTATHERA dose. You will continue receiving long-acting octreotide 30 mg until your cancer spreads, grows, or gets worse for up to 18 months since you started LUTATHERA treatment.
Since LUTATHERA is a nuclear medicine therapy, there are some things you should do to keep everyone safe and minimize exposure to family members and the general public.

At the treatment center:
- While you are taking LUTATHERA, you will be kept away from other patients in the treatment center to limit their exposure. Your family members and caregivers may be with you during your treatment away from patients or staff, but they may be asked to leave for 30 to 40 minutes while LUTATHERA is being given.

After leaving the treatment center:
- Your healthcare provider may provide further instructions to help minimize radiation exposure to others. You should always follow your healthcare provider’s instructions.

LUTATHERA Treatment Card:
- Your healthcare provider may fill out a LUTATHERA treatment card and give it to you after treatment. This card will list your name, the amount of medicine that you received, and a treatment center contact name and phone number. You should keep this card with you for a few days after your treatment, especially if you are traveling through an airport.

Care providers:
- If a care provider helps you in the bathroom, they should wear disposable gloves for the first few days after you are given LUTATHERA.

Showering:
- Daily showering is recommended for at least the first few days after receiving LUTATHERA.

Breastfeeding:
- You should not breastfeed during LUTATHERA treatment and for 2.5 months after your final LUTATHERA infusion.

Using the toilet:
- You should drink plenty of fluids on the days you receive LUTATHERA and after. The more you urinate, the faster you will get rid of the radiation from your body.
- For a few days after you receive LUTATHERA, use the toilet in a seated position, even for men, and use toilet paper each time.
- Flush toilet paper and/or wipes down the toilet and flush twice.
- Wash your hands every time you use the toilet.

Birth control:
- You should use effective birth control during LUTATHERA treatment and for 7 months after your final dose if you are a woman, or for 4 months after your final dose if you are a man with a female partner who is able to become pregnant.

IMPORTANT SAFETY INFORMATION (Continued):
- Hormonal gland problems (carcinoid crisis): During your treatment you may experience certain symptoms that are related to hormones released from your cancer. These symptoms may include flushing, diarrhea, difficulty breathing (bronchospasm), and low blood pressure (hypotension), and may occur during or within the 24 hours after your first LUTATHERA treatment. Your healthcare provider will monitor you closely. Speak with your healthcare provider if you experience any of these signs or symptoms.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for LUTATHERA.
SIDE EFFECTS OF LUTATHERA® (lutetium Lu 177 dotatate)

Serious side effects of LUTATHERA

LUTATHERA may cause side effects. Some of these side effects can be serious. If you experience these side effects, your care team may need to adjust or stop your treatment. You should always follow your care team’s instructions. Serious side effects may include:

- Bone marrow problems
- Secondary bone marrow and blood cancers
- Kidney problems
- Liver problems
- Hormonal gland problems (hormonal crisis)
- Infertility

Please see additional warnings below regarding pregnancy, breastfeeding, and use of birth control.

The most common side effects of LUTATHERA

In clinical trials, the most common side effects in people taking LUTATHERA included:

- Vomiting
- Nausea
- Decreased blood cell counts
- Increased liver enzymes
- Decreased blood potassium levels
- Increased glucose in the bloodstream

Talk to your doctor if you have a side effect that bothers you or does not go away. There are other possible side effects of LUTATHERA. For more information, and to learn more about LUTATHERA, talk to your doctor or healthcare provider.

IMPORTANT SAFETY INFORMATION1 (Continued):

- Pregnancy warning: Tell your healthcare provider if you are pregnant or you or your partner plan to become pregnant before taking LUTATHERA. LUTATHERA can harm your unborn baby. Females should use an effective method of birth control during treatment and for 7 months after the final dose of LUTATHERA. Males with female partners should use an effective method of birth control during treatment and for 4 months after the final dose of LUTATHERA.
- Breastfeeding warning: You should not breastfeed during treatment with LUTATHERA and for 2.5 months after your final dose of LUTATHERA.

AAA PatientCONNECT™ PATIENT ASSISTANCE FOR LUTATHERA

Go to www.aaapatientconnect.com for more information about AAA PatientCONNECT™

AAA PatientCONNECT™ may help facilitate your access to LUTATHERA treatment. This may include:

- Patient financial assistance
  - Uninsured patient assistance
  - Commercial patient copay assistance
- Other assistance
  - Insurance benefits verification
  - Prior authorization eligibility check

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for LUTATHERA.
Financial assistance for uninsured patients

AAA PatientCONNECT™ may provide LUTATHERA at no cost to patients who are uninsured and meet certain eligibility criteria.* You may qualify for assistance if:

• You are uninsured for LUTATHERA treatment
• You meet financial criteria based on adjusted gross household income. Documentation of income is required when applying. Speak with a patient navigator to learn more about acceptable forms of documentation
• Your LUTATHERA treatment is being provided in an outpatient setting
• You are a permanent resident of the United States, including any of its territories, or the District of Columbia

Copay assistance is not available through the AAA PatientCONNECT™ program for patients who have public or government insurance, such as insurance available as through Medicare, Department of Veterans Affairs, or the Department of Defense. AAA PatientCONNECT™ is not an insurance program and is not a substitute for medical insurance.

*Eligibility restrictions may apply. For full terms and conditions, please call AAA PatientCONNECT™ at 1-844-NETS-AAA. Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the copayment support provided under this program, e.g. copay refunds, participating patients and pharmacies are obligated to inform insurance companies and third party payers of any benefits they receive and the value of this program, as required by contract or otherwise. Void where prohibited by law or restricted.

For more information, contact AAA PatientCONNECT™ at 1-844-NETS-AAA (1-844-639-7222).

Financial assistance for patients with commercial insurance

AAA PatientCONNECT™ may provide copay assistance for LUTATHERA treatment to patients who have commercial insurance and meet certain eligibility criteria.* You may qualify for assistance if:

• You have commercial insurance
• Your LUTATHERA treatment is being provided in an outpatient setting
• You are a permanent resident of the United States, including any of its territories, or the District of Columbia

Copay assistance is not available through the AAA PatientCONNECT™ program for patients who have public or government insurance, such as insurance available as through Medicare, Department of Veterans Affairs, or the Department of Defense. AAA PatientCONNECT™ is not an insurance program and is not a substitute for medical insurance.

*Eligibility restrictions may apply. For full terms and conditions, please call AAA PatientCONNECT™ at 1-844-NETS-AAA. Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the copayment support provided under this program, e.g. copay refunds, participating patients and pharmacies are obligated to inform insurance companies and third party payers of any benefits they receive and the value of this program, as required by contract or otherwise. Void where prohibited by law or restricted.

For more information, contact AAA PatientCONNECT™ at 1-844-NETS-AAA (1-844-639-7222).

Enrolling in copay assistance

To enroll in financial assistance for commercial insurance, your healthcare provider must submit a completed and signed copay assistance application to AAA PatientCONNECT™ on your behalf. Copay assistance applications are available online at www.aaapatientconnect.com.

By signing this application, you agree that if approved, all copay assistance funds distributed will be used only for the cost of LUTATHERA.

Receiving copay financial assistance

Upon approval, AAA PatientCONNECT™ will send an approval letter and outline of the copay assistance funds that are available for your treatment. Proof of treatment and claims must be submitted to AAA PatientCONNECT™ to receive a distribution of copay assistance funds. Upon receipt, copay assistance funds will be processed and distributed to you for payment of your LUTATHERA treatment copay. Eligible patients will be responsible for the first $25.00 per infusion and then may receive up to a maximum of $15,000 over the course of treatment (4 LUTATHERA infusions).

Enrolling in financial assistance for uninsured patients

To enroll in financial assistance for uninsured patients, your healthcare provider must submit a completed and signed assistance application to AAA PatientCONNECT™ on your behalf. Assistance applications are available online at www.aaapatientconnect.com.

For more information, contact AAA PatientCONNECT™ at 1-844-NETS-AAA (1-844-639-7222).

IMPORTANT SAFETY INFORMATION (Continued):

• Fertility problems: Treatment with LUTATHERA may cause infertility. This is because radiation absorbed by your testes and ovaries over the treatment period falls in the range of exposure where temporary or permanent infertility may occur.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for LUTATHERA.
FIND A GEP-NET SUPPORT ORGANIZATION

The Carcinoid Cancer Foundation (CCF)
333 Mamaroneck Avenue #492
White Plains, NY 10605
1-888-722-3132
www.carcinoid.org

The Healing NET Foundation
200 Hill Avenue, Suite 4
Nashville, TN 37210
615-369-6463
www.thehealingnet.org

Los Angeles Carcinoid Neuroendocrine Tumor Society (LACNETS)
info@lacnets.org
www.lacnets.org

Northern California CarciNET Community (NorCal CarciNET)
946 North Ripon Road
Ripon, CA 95366
www.norcalcarcinet.org

The Neuroendocrine Cancer Awareness Network (NCAN)
3074 Brookchase Boulevard
Fort Mill, SC 29707
1-866-850-9555
help@netcancerawareness.org
www.netcancerawareness.org

To learn more about treatment with LUTATHERA® (lutetium Lu 177 dotatate) and to find a treatment center near you, visit LUTATHERA.com.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for LUTATHERA.

What is LUTATHERA?

LUTATHERA® (lutetium Lu 177 dotatate) is a prescription medicine used to treat adults with a type of cancer known as gastrointestinal pancreatic neuroendocrine tumors (GEP-NETs) that are positive for the hormone receptor somatostatin, including GEP-NETs in the foregut, midgut, and hindgut.

IMPORTANT SAFETY INFORMATION:

What are the possible serious side effects of LUTATHERA?

LUTATHERA can cause serious side effects and if you experience these side effects, your healthcare provider may need to adjust or stop your treatment. You should always follow your healthcare provider’s instructions. Serious side effects may include:

- Radiation exposure: Treatment with LUTATHERA will expose you to radiation which can contribute to your long-term radiation exposure. Overall radiation exposure is associated with an increased risk for cancer. The radiation will be detectable in your urine for up to 30 days following administration of the drug. It is important to minimize radiation exposure to household contacts consistent with good radiation safety practices.

- Bone marrow problems: Treatment with LUTATHERA increases the risk of myelosuppression, a condition in which bone marrow activity is decreased, resulting in drop in blood cell counts. You may experience blood-related side effects such as low red blood cells (anemia), low numbers of cells that are responsible for blood clotting (thrombocytopenia), and low numbers of a type of white blood cells (neutropenia). People with low blood cell counts are at higher risk of developing serious side effects associated with LUTATHERA. Speak with your healthcare provider if you experience any signs or symptoms of infection, fever, chills, dizziness, shortness of breath or increased bleeding or bruising. Your healthcare provider may need to adjust or stop your treatment accordingly.

- Secondary bone marrow and blood cancers: Other serious conditions that you may develop as a direct result of treatment with LUTATHERA include blood and bone marrow disorders known as secondary myelodysplastic syndrome and cancer known as acute leukemia. Your healthcare provider will routinely check your blood counts and tell you if they are too low.
IMPORTANT SAFETY INFORMATION (Continued):

What are the possible serious side effects of LUTATHERA?

• Kidney problems: Treatment with LUTATHERA will expose your kidneys to radiation and may impair their ability to work as normal. You may be at an increased risk for lower kidney function after LUTATHERA treatment if you already have kidney impairment before treatment. In some cases, patients have experienced kidney failure after treatment with LUTATHERA. Your healthcare provider will monitor changes and provide you with an amino acid solution before, during, and after LUTATHERA to help protect your kidneys. You should stay well hydrated before, during, and after your treatment. You should urinate frequently during and after administration of LUTATHERA. Your doctor will monitor your kidney function and may withhold, reduce, or stop your LUTATHERA treatment accordingly.

• Liver problems: In clinical studies of LUTATHERA, less than 1% of patients were reported to have tumor bleeding (hemorrhage), swelling (edema) or tissue injury (necrosis) to the liver. If you have tumors in your liver, you may be more likely to experience these side-effects. Signs that you may be experiencing liver damage include increases in blood markers called ALT, AST and GGT. Your healthcare provider will monitor your liver using blood tests and may need to withhold, reduce, or stop your LUTATHERA treatment accordingly.

• Hormonal gland problems (carcinoid crisis): During your treatment you may experience certain symptoms that are related to hormones released from your cancer. These symptoms may include flushing, diarrhea, difficulty breathing (bronchospasm), and low blood pressure (hypotension), and may occur during or within the 24 hours after your first LUTATHERA treatment. Your healthcare provider will monitor you closely. Speak with your healthcare provider if you experience any of these signs or symptoms.

• Pregnancy warning: Tell your healthcare provider if you are pregnant or you or your partner plan to become pregnant before taking LUTATHERA. LUTATHERA can harm your unborn baby. Females should use an effective method of birth control during treatment and for 7 months after the final dose of LUTATHERA. Males with female partners should use an effective method of birth control during treatment and for 4 months after the final dose of LUTATHERA.

• Breastfeeding warning: You should not breastfeed during treatment with LUTATHERA and for 2.5 months after your final dose of LUTATHERA.

• Fertility problems: Treatment with LUTATHERA may cause infertility. This is because radiation absorbed by your testes and ovaries over the treatment period falls in the range of exposure where temporary or permanent infertility may occur.

What other medicines may interact with LUTATHERA?

Tell your healthcare provider if you are taking any other medications, including somatostatin analogs. Somatostatin analogs may affect how your LUTATHERA treatment works. Your healthcare provider may ask you to stop taking your long-acting somatostatin analogs 4 weeks before LUTATHERA treatment. You may continue taking short-acting somatostatin analogs up to 24 hours before your LUTATHERA treatment.

What are the most common side effects of LUTATHERA?

The most common and most serious side effects of LUTATHERA include: vomiting, nausea, decreased blood cell counts, increased liver enzymes, decreased blood potassium levels, and increased glucose in the bloodstream.

Talk to your doctor if you have a side effect that bothers you or does not go away. There are other possible side effects of LUTATHERA. For more information, and to learn more about LUTATHERA, talk to your doctor or healthcare provider.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Prescribing Information for LUTATHERA.

Distributed by: Advanced Accelerator Applications USA, Inc., NJ 07041

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

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AAA-Lu177-US-0181 | 03/2020
LUTATHERA.com
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Revised: 07/2018
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Instructions

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

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

2.2 Recommended Dosage

The recommended LUTATHERA dose is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. Administer pre- and concomitant medications and administer LUTATHERA as recommended [see Dosage and Administration (2.3, 2.5)].

2.3 Premedication and Concomitant Medications

Somatostatin 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 30 minutes before the recommended amino acid solution.

Amino Acid Solution

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

Table 1. Amino Acid Solution

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

2.4 Dose Modifications for Adverse Reactions

Recommended dose modifications of LUTATHERA for adverse reactions are provided in Table 2.
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity of Adverse Reaction¹</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia [see Warnings and Precautions (5.2)]</td>
<td>Grade 2, 3 or 4</td>
<td>Withhold dose until complete or partial resolution (Grade 0 to 1). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td>Recurrent Grade 2, 3 or 4</td>
<td></td>
<td>Permanently discontinue LUTATHERA.</td>
</tr>
<tr>
<td>Anemia and Neutropenia [see Warnings and Precautions (5.2)]</td>
<td>Grade 3 or 4</td>
<td>Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 anemia or neutropenia, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td>Recurrent Grade 3 or 4</td>
<td></td>
<td>Permanently discontinue LUTATHERA.</td>
</tr>
<tr>
<td>Renal Toxicity [see Warnings and Precautions (5.4)]</td>
<td>Defined as:</td>
<td>Withhold dose until complete resolution. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution. If reduced dose does not result in renal toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for renal toxicity requiring a treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td>Recurrent renal toxicity</td>
<td></td>
<td>Permanently discontinue LUTATHERA.</td>
</tr>
<tr>
<td>Hepatotoxicity [see Warnings and Precautions (5.5)]</td>
<td>Defined as:</td>
<td>Withhold dose until complete resolution. Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete resolution. If reduced LUTATHERA dose does not result in hepatotoxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for hepatotoxicity requiring a treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td>Recurrent hepatotoxicity</td>
<td></td>
<td>Permanently discontinue LUTATHERA.</td>
</tr>
<tr>
<td>Other Non-Hematologic Toxicity</td>
<td>Grade 3 or 4</td>
<td>Withhold dose until complete or partial resolution (Grade 0 to 2). Resume LUTATHERA at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer LUTATHERA at 7.4 GBq (200 mCi) for next dose. Permanently discontinue LUTATHERA for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td>Recurrent Grade 3 or 4</td>
<td></td>
<td>Permanently discontinue LUTATHERA.</td>
</tr>
</tbody>
</table>

¹ National Cancer Institute, Common Toxicity Criteria for Adverse Events, version 4.03
2.5 Preparation and Administration

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

Administration Instructions

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

2.6 Radiation Dosimetry

The mean and standard deviation (SD) of the estimated radiation absorbed doses for adults receiving LUTATHERA are shown in Table 3. The maximum penetration in tissue is 2.2 mm and the mean penetration is 0.67 mm.
### Table 3. Estimated Radiation Absorbed Dose for LUTATHERA in NETTER-1

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

*N=18 (two patients excluded because the liver absorbed dose was biased by the uptake of the liver metastases)

**N=9 (female patients only)

***N=11 (male patients only)

3 DOSAGE FORMS AND STRENGTHS

Injection: 370 MBq/mL (10 mCi/mL) of lutetium Lu 177 dotatate as a clear and colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINdications

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk from Radiation Exposure

LUTATHERA contributes to a patient’s overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures [see Dosage and Administration (2.1)].

5.2 Myelosuppression

In NETTER-1, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide compared to patients receiving high-dose long-acting octreotide (all grades/grade 3 or 4): anemia (81%/0) versus (54%/1%); thrombocytopenia (53%/1%) versus (17%/0); and neutropenia (26%/3%) versus (11%/0). In NETTER-1, platelet nadir occurred at a median of 5.1 weeks following the first dose. Of the 59 patients who developed thrombocytopenia, 68% had platelet recovery to baseline or normal levels. The median time to platelet recovery was 2 months. Fifteen of the nineteen patients in whom platelet recovery was not documented had post-nadir platelet counts. Among these 15 patients, 5 improved to Grade 1, 9 to Grade 2, and 1 to Grade 3.

Monitor blood cell counts. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction [see Dosage and Administration (2.4)].
5.3 Secondary Myelodysplastic Syndrome and Leukemia

In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide. In ERASMUS, 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

5.4 Renal Toxicity

In ERASMUS, 8 patients (<1%) developed renal failure 3 to 36 months following LUTATHERA. Two of these patients had underlying renal impairment or risk factors for renal failure (e.g., diabetes or hypertension) and required dialysis.

Administer the recommended amino acid solution before, during, and after LUTATHERA [see Dosage and Administration (2.3)] to decrease reabsorption of lutetium Lu 177 dotate through the proximal tubules and decrease the radiation dose to the kidneys. Do not decrease the dose of the amino acid solution if the dose of LUTATHERA is reduced. Advise patients to urinate frequently during and after administration of LUTATHERA. Monitor serum creatinine and calculated creatinine clearance. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of reaction [see Dosage and Administration (2.4)].

Patients with baseline renal impairment may be at greater risk of toxicity; perform more frequent assessments of renal function in patients with mild or moderate impairment. LUTATHERA has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min).

5.5 Hepatotoxicity

In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure.

Monitor transaminases, bilirubin and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue LUTATHERA based on severity of reaction [see Dosage and Administration (2.2)].

5.6 Neuroendocrine Hormonal Crisis

Neuroendocrine hormonal crises, manifesting with flushing, diarrhea, bronchospasm and hypotension, occurred in 1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose. Two (<1%) patients were reported to have hypercalcemia.

Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release. Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, LUTATHERA can cause fetal harm [see Clinical Pharmacology (12.1)]. There are no available data on the use of LUTATHERA in pregnant women. No animal studies using lutetium Lu 177 dotate have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm.

Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA [see Dosage and Administration (2.1)].

Advise females and males of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose [see Use in Specific Populations (8.1, 8.3)].

5.8 Risk of Infertility

LUTATHERA may cause infertility in males and females. The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy [see Dosage and Administration (2.6) and Use in Specific Populations (8.3)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Myelosuppression [see Warnings and Precautions (5.2)]
- Secondary Myelodysplastic Syndrome and Leukemia [see Warnings and Precautions (5.3)]
- Renal Toxicity [see Warnings and Precautions (5.4)]
- Hepatotoxicity [see Warnings and Precautions (5.5)]
- Neuroendocrine Hormonal Crisis [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in Warnings and Precautions reflect exposure to LUTATHERA in 111 patients with advanced, progressive midgut neuroendocrine tumors (NETTER-1). Safety data in Warnings and Precautions were also obtained in an additional 22 patients in a non-randomized pharmacokinetic substudy of NETTER-1 and in a subset of patients (811 of 1214) with advanced somatostatin receptor-positive tumors enrolled in ERASMUS [see Warnings and Precautions (5)].
NETTER-1
The safety data described below are from NETTER-1, which randomized (1:1) patients with progressive, somatostatin receptor-positive midgut carcinoid tumors to receive LUTATHERA 7.4 GBq (200 mCi) administered every 8 to 16 weeks concurrently with the recommended amino acid solution and with long-acting octreotide (30 mg administered by intramuscular injection within 24 hours of each LUTATHERA dose) (n = 111), or high-dose octreotide (defined as long-acting octreotide 60 mg by intramuscular injection every 4 weeks) (n = 112) [see Clinical Studies (14.1)]. Among patients receiving LUTATHERA with octreotide, 79% received a cumulative dose > 22.2 GBq (> 600 mCi) and 76% of patients received all four planned doses. Six percent (6%) of patients required a dose reduction and 13% of patients discontinued LUTATHERA. Five patients discontinued LUTATHERA for renal-related events and 4 discontinued for hematological toxicities. The median duration of follow-up was 24 months for patients receiving LUTATHERA with octreotide and 20 months for patients receiving high-dose octreotide.

Table 4 and Table 5 summarize the incidence of adverse reactions and laboratory abnormalities, respectively. The most common Grade 3-4 adverse reactions occurring with a greater frequency among patients receiving LUTATHERA with octreotide compared to patients receiving high-dose octreotide include: lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea and elevated AST (5% each), and increased ALT, hyperglycemia and hypokalemia (4% each).

<table>
<thead>
<tr>
<th>Adverse Reaction1</th>
<th>LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)</th>
<th>Long-Acting Octreotide (60 mg) (N = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>38</td>
<td>1</td>
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<tr>
<td>Fatigue</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
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<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>13</td>
<td>2</td>
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<tr>
<td>Pain in extremity</td>
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<td>Neck Pain</td>
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<tr>
<td>Nervous system disorders</td>
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<td>Headache</td>
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<tr>
<td>Dizziness</td>
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<td>Anxiety</td>
<td>12</td>
<td>1</td>
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<tr>
<td>Renal and urinary disorders</td>
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<td></td>
</tr>
<tr>
<td>Renal failure*</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Radiation-related urinary tract toxicity**</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
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<td>Vascular disorders</td>
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<tr>
<td>Flushing</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

*Includes the terms: Glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, renal impairment
**Includes the terms: Dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain and urinary incontinence

Table 4. Adverse Reactions Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-11
Table 5. Laboratory Abnormalities Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-1

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

* Values are worst grade observed after randomization

1 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays laboratory abnormalities occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2% (grades 3-4)]

ERASMS
Safety data are available from 1214 patients in ERASMS, an international, single-institution, single-arm, open-label trial of patients with somatostatin receptor-positive tumors (neuroendocrine and other primaries). Patients received LUTATHERA 7.4 GBq (200 mCi) administered every 6 to 13 weeks with or without octreotide. Retrospective medical record review was conducted on a subset of 811 patients to document serious adverse reactions. Eighty-one (81%) percent of patients in the subset received a cumulative dose ≥ 22.2 GBq (≥ 600 mCi). With a median follow-up time of more than 4 years, the following rates of serious adverse reactions were reported: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

7 **DRUG INTERACTIONS**

7.1 Somatostatin Analogs

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended [see Dosage and Administration (2.3)].

8 **USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LUTATHERA can cause fetal harm [see Clinical Pharmacology (12.1)]. There are no available data on LUTATHERA use in pregnant women. No animal studies using lutetium Lu 177 dotate have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm. Advise pregnant women of the risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
8.2 Lactation

Risk Summary
There are no data on the presence of lutetium Lu 177 dotatate in human milk, or its effects on the breastfed infant or milk production. No lactation studies in animals were conducted. Because of the potential risk for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose.

8.3 Females and Males of Reproductive Potential

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

Contraception

Females
LUTATHERA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the final dose of LUTATHERA.

Males
Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of LUTATHERA [see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)].

Infertility
The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy [see Dosage and Administration (2.6)].

8.4 Pediatric Use

The safety and effectiveness of LUTATHERA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 1325 patients treated with LUTATHERA in clinical trials, 438 patients (33%) were 65 years and older. The response rate and number of patients with a serious adverse event were similar to that of younger subjects.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild to moderate impairment. The safety of LUTATHERA in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The safety of LUTATHERA in patients with severe hepatic impairment (total bilirubin > 3 times upper limit of normal and any AST) has not been studied.

11 DESCRIPTION

LUTATHERA (lutetium Lu 177 dotatate) is a radiolabeled somatostatin analog. The drug substance lutetium Lu 177 dotatate is a cyclic peptide linked with the covalently bound chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to a radionuclide.

Lutetium Lu 177 dotatate is described as lutetium (Lu) 177-N-[4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl] acetyl]-D-phenylalanine-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic (2-7) disulfide. The molecular weight is 1609.6 Daltons and the structural formula is as follows:

![Structural formula of LUTATHERA](image)

LUTATHERA (lutetium Lu 177 dotatate) 370 MBq/mL (10 mCi/mL) Injection is a sterile, clear, colorless to slightly yellow solution for intravenous use. Each single-dose vial contains acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), sodium hydroxide (0.65...
mg/mL), ascorbic acid (2.8 mg/mL), diethylene triamine pentaacetic acid (0.05 mg/mL), sodium chloride (6.85 mg/mL), and Water for Injection (ad 1 mL). The pH range of the solution is 4.5 to 6.

11.1 Physical Characteristics

Lutetium (Lu 177) decays to stable hafnium (Hf 177) with a half-life of 6.647 days, by emitting beta radiation with a maximum energy of 0.498 MeV and photonic radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (6.4%). The main radiations are detailed in Table 6.

Table 6. Lu 177 Main Radiations

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Energy (keV)</th>
<th>Iβ%</th>
<th>Iγ%</th>
</tr>
</thead>
<tbody>
<tr>
<td>β^-</td>
<td>176.5</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>β^-</td>
<td>248.1</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>β^-</td>
<td>384.9</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>497.8</td>
<td>78.6</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>71.6</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>112.9</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>136.7</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>208.4</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>249.7</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>321.3</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

11.2 External Radiation

Table 7 summarizes the radioactive decay properties of Lu 177.

Table 7. Physical Decay Chart: Lutetium Lu 177 Half-life = 6.647 days

<table>
<thead>
<tr>
<th>Hours</th>
<th>Fraction Remaining</th>
<th>Hours</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.000</td>
<td>48 (2 days)</td>
<td>0.812</td>
</tr>
<tr>
<td>1</td>
<td>0.996</td>
<td>72 (3 days)</td>
<td>0.731</td>
</tr>
<tr>
<td>2</td>
<td>0.991</td>
<td>168 (7 days)</td>
<td>0.482</td>
</tr>
<tr>
<td>5</td>
<td>0.979</td>
<td>336 (14 days)</td>
<td>0.232</td>
</tr>
<tr>
<td>10</td>
<td>0.958</td>
<td>720 (30 days)</td>
<td>0.044</td>
</tr>
<tr>
<td>24 (1 day)</td>
<td>0.901</td>
<td>1080 (45 days)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lutetium Lu 177 dotatate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSRT2). Upon binding to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors, the compound is internalized. The beta emission from Lu 177 induces cellular damage by formation of free radicals in somatostatin receptor-positive cells and in neighboring cells.

12.2 Pharmacodynamics

Lutetium Lu 177 exposure-response relationships and the time course of pharmacodynamics response are unknown.

Cardiac Electrophysiology

The ability of LUTATHERA to prolong the QTc interval at the therapeutic dose was assessed in an open label study in 20 patients with somatostatin receptor-positive midgut carcinoid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of lutetium Lu 177 dotatate have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors. The mean blood exposure (AUC) of lutetium Lu 177 dotatate at the recommended dose is 41 ng.h/mL. [coefficient of variation (CV) 36 %]. The mean maximum blood concentration (Cmax) for lutetium Lu 177 dotatate is 10 ng/mL (CV 50%), which generally occurred at the end of the LUTATHERA infusion.

Distribution

The mean volume of distribution for lutetium Lu 177 dotatate is 460 L (CV 54%).

Within 4 hours after administration, lutetium Lu 177 dotatate distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid. The co-administration of amino acids reduced the median radiation dose to the kidneys by 47% (34% to 59%) and increased the mean beta-phase blood clearance of lutetium Lu 177 dotatate by 36%.

The non-radioactive form of lutetium dotatate is 43% bound to human plasma proteins.
Elimination
The mean clearance (CL) is 4.5 L/h (CV 31%) for lutetium Lu 177 dotatate. The mean (± standard deviation) effective blood elimination half-life is 3.5 (±1.4) hours and the mean terminal blood half-life is 71 (± 28) hours.

Metabolism
Lutetium Lu 177 dotatate does not undergo hepatic metabolism.

Excretion
Lutetium Lu 177 dotatate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following LUTATHERA administration. Prolonged elimination of lutetium Lu 177 dotatate in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium Lu 177 dotatate, greater than 99% will be eliminated within 14 days after administration of LUTATHERA (see Warnings and Precautions (5.1)).

Drug Interactions
The non-radioactive form of lutetium is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 in vitro. It is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or OCT1 in vitro.

13 NONCLINICAL TOXICOLOGY

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

13.2 Animal Toxicology and/or Pharmacology
The primary target organ in animal studies using a non-radioactive form of lutetium Lu 177 dotatate (lutetium Lu 175 dotatate) was the pancreas, a high SST2 expressing organ. Pancreatic acinar apoptosis occurred at lutetium Lu 175 dotatate doses ≥ 5 mg/kg in repeat dose toxicology studies in rats. Pancreatic acinar cell atrophy also occurred in repeat dose toxicology studies in dogs at doses ≥ 500 mg/kg. These findings were consistent with high uptake of the radiolabeled peptide in the pancreas in animal biodistribution studies.

14 CLINICAL STUDIES

14.1 Progressive, Well-differentiated or Metastatic Somatostatin Receptor-Positive Midgut Carcinoid Tumors
The efficacy of LUTATHERA in patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumors was established in NETTER-1 (NCT01578239), a randomized, multicenter, open-label, active-controlled trial. Key eligibility criteria included Ki67 index ≤ 20%, Karnofsky performance status ≥ 60, confirmed presence of somatostatin receptors on all lesions (OctreoScan uptake ≥ normal liver), creatinine clearance ≥ 50 mL/min, no prior treatment with peptide receptor radionuclide therapy (PRRT), and no prior external radiation therapy to more than 25% of the bone marrow.

Two hundred twenty-nine (229) patients were randomized (1:1) to receive either LUTATHERA 7.4 GBq (200 mCi) every 8 weeks for up to 4 administrations (maximum cumulative dose of 29.6 GBq) or high-dose long-acting octreotide (defined as 60 mg by intramuscular injection every 4 weeks). Patients in the LUTATHERA arm also received long-acting octreotide 30 mg as an intramuscular injection 4 to 24 hours after each LUTATHERA dose and every 4 weeks after completion of LUTATHERA treatment until disease progression or until week 76 of the study. Patients in both arms could receive short-acting octreotide for symptom management; however, short-acting octreotide was withheld for at least 24 hours before each LUTATHERA dose. Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤ 6 or > 6 months). The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee (IRC) per RECIST v1.1. Additional efficacy outcome measures were overall response rate (ORR) by IRC, duration of response, and overall survival (OS).

Demographic and baseline disease characteristics were balanced between the treatment arms. Of the 208 patients, whose race/ethnicity was reported, 90% were White, 5% were Black, and 4% were Hispanic or Latino. The median age was 64 years (28 to 87 years); 51% were male, 74% had an illia primary, and 96% had metastatic disease in the liver. The median Karnofsky performance score was 90 (60 to 100); 74% received a constant dose of octreotide for > 6 months and 12% received prior treatment with everolimus. Sixty-nine percent of patients had Ki67 expression in ≤ 2% of tumor cells, 77% had CgA > 2 times the upper limit of normal (ULN), 65% had 5-HIAA > 2 x ULN, and 65% had alkaline phosphatase ≤ ULN. Efficacy results for NETTER-1 are presented in Table 8 and Figure 1.
### Table 8. Efficacy Results in NETTER-1

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

*a: Hazard ratio based on the unstratified Cox model  
b: Unstratified log rank test  
c: Median follow-up 10.5 months at time of primary analysis of PFS (range: 0 to 29 months)  
d: Interim analysis of OS not statistically significant based on pre-specified significance criteria  
e: Fisher’s Exact test  
NR: Not reached; NE: Not evaluable

**Figure 1. Kaplan-Meier Curves for Progression-Free Survival in NETTER-1**
14.2 Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

The efficacy of LUTATHERA in patients with foregut, midgut, and hindgut gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was assessed in 360 patients in the ERASMUS study. In ERASMUS, LUTATHERA was initially provided as expanded access under a general peptide receptor radionuclide therapy protocol at a single site in the Netherlands. A subsequent LUTATHERA-specific protocol written eight years after study initiation did not describe a specific sample size or hypothesis testing plan but allowed for retrospective data collection. A total of 1214 patients received LUTATHERA in ERASMUS, of which 601 (50%) were assessed per RECIST criteria. Of the 601 patients evaluated by investigators using RECIST criteria, 360 (60%) had gastroentero-pancreatic neuroendocrine tumors (GEP-NETs). LUTATHERA 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. The major efficacy outcome was investigator-assessed ORR. The median age in the efficacy subset was 61 years (25 to 88 years), 52% were male, 61% had a baseline Karnofsky performance status ≥ 90 (60 to 100), 60% had progressed within 12 months of treatment, and 15% had received prior chemotherapy. Fifty five percent (55%) of patients received a concomitant somatostatin analog. The median dose of LUTATHERA was 29.6 GBq (800 mCi). Baseline tumor assessments were obtained in 39% of patients. The investigator assessed ORR was 16% (95% CI 13, 20) in the 360 patients with GEP-NETs. Three complete responses were observed (< 1%). Median DoR in the 58 responding patients was 35 months (95% CI; 17, 38).

16 HOW SUPPLIED/STORAGE AND HANDLING

LUTATHERA Injection containing 370 MBq/mL (10 mCi/ml) of lutetium Lu 177 dotate is a sterile, preservative-free and clear, colorless to slightly yellow solution for intravenous use supplied in a colorless Type 1 glass 30 mL single-dose vial containing 7.4 GBq (200 mCi) ± 10% of lutetium Lu 177 dotate at the time of injection (NDC# 69488-003-01). The solution volume in the vial is adjusted from 20.5 mL to 25 mL to provide a total of 7.4 GBq (200 mCi) of radioactivity.

The product vial is in a lead shielded container placed in a plastic sealed container (NDC# 69488-003-01). The product is shipped in a Type A package (NDC# 69488-003-70).

Store below 25 °C (77 °F).

The shelf life is 72 hours. Discard appropriately at 72 hours.

17 PATIENT COUNSELING INFORMATION

Radiation Risks
Advise patients to minimize radiation exposure to household contacts consistent with institutional good radiation safety practices and patient management procedures [see Dosage and Administration (2.1), Warnings and Precautions (5.1)].

Myelosuppression
Advise patients to contact their healthcare provider for any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, or increased bleeding or bruising [see Warnings and Precautions (5.2)].

Secondary Myelodysplastic Syndrome and Acute Leukemia
Advise patients of the potential for secondary cancers, including myelodysplastic syndrome and acute leukemia [see Warnings and Precautions (5.3)].

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

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

Neuroendocrine Hormonal Crises
Advise patients to contact their health care provider for signs or symptoms that may occur following tumor-hormone release, including severe flushing, diarrhea, bronchospasmod, and hypotension [see Warnings and Precautions (5.6)].

Embryo-Fetal Toxicity
Advise pregnant women and males and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)].

Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose [see Use in Specific Populations (8.1, 8.3)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LUTATHERA and for 4 months after the final dose [see Use in Specific Populations (8.1, 8.3)].

Lactation
Advise females not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose [see Use in Specific Populations (8.2)].

Infertility
Advise female and male patients that LUTATHERA may impair fertility [see Warnings and Precautions (5.8), Use in Specific Populations (8.3)].
Manufactured by:
Advanced Accelerator Applications, S.r.l.
Via Ribes 5, 10010 Colleretto Giacosa (TO), Italy

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

Or

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

Distributed by:
Advanced Accelerator Applications USA, Inc., NJ 07041

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