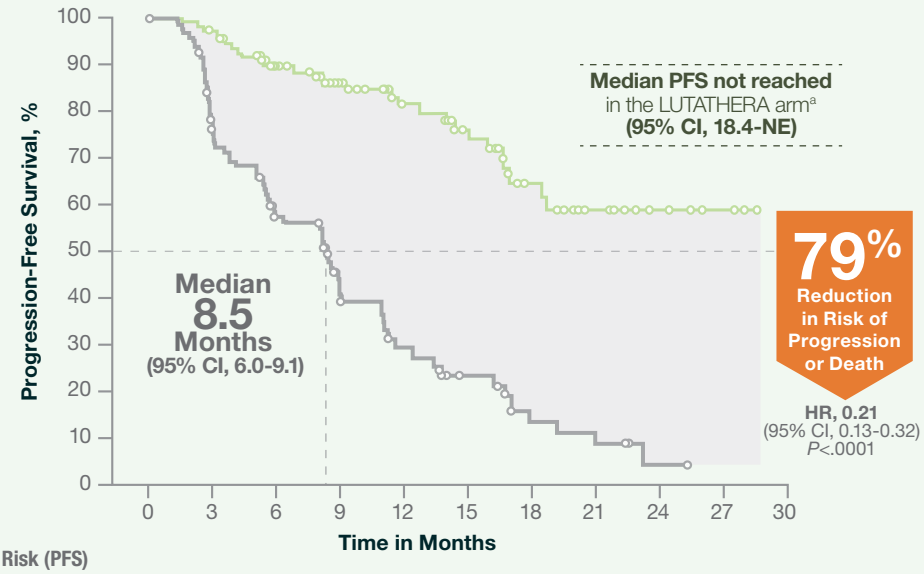
A 79% reduction in the risk of disease progression or death with LUTATHERA vs active control[1]

WE COULDN'T BELIEVE IT EITHER

Median PFS for LUTATHERA not reached at primary analysis (vs active control at 8.5 months, HR, 0.21 [95% CI, 0.13-0.32]; *P*<.0001)[1]

Progression-Free Survival[1]



No. at Risk (PFS)

LUTATHERA with long-acting octreotide (30 mg)	116	102	84	66	48	38	22	13	6	3	0
Long-acting octreotide (60 mg)	113	84	57	35	21	14	6	4	1	0	0

—○— LUTATHERA with long-acting octreotide 30 mg —○— Long-acting octreotide 60 mg

	LUTATHERA With Long-Acting Octreotide (n=116)	Long-Acting Octreotide (n=113)
Events, n (%)	27 (23%)	78 (69%)
Progressive disease, n (%)	15 (13%)	61 (54%)
Deaths, n (%)	12 (10%)	17 (15%)

[a]At primary analysis detailed in Prescribing Information for LUTATHERA.[1]

NETTER-1 (N=229) was a pivotal, phase 3, randomized, multicenter, open-label trial studying the efficacy of LUTATHERA with long-acting octreotide (n=116)* vs high-dose, long-acting octreotide (n=113)† in patients with locally advanced, inoperable, or metastatic SSTR-positive midgut NETs that had progressed following treatment with long-acting octreotide. The primary end point was PFS,‡ as determined by an IRC; secondary end points included OS and safety.[1,2]

In NETTER-1, after centrally confirmed disease progression, discontinuation of study treatment without confirmed progression, or completion of the 18-month treatment period, patients entered long-term follow-up. In total, 200 (87%) of 231 patients entered long-term follow-up, including 101 (86%) of 117 patients in the LUTATHERA arm and 99 (87%) of 114 patients in the control arm.§ Median duration of follow-up was 76.3 months (range, 0.4–95.0 months) in the LUTATHERA arm and 76.5 months (range, 0.1–92.3 months) in the control arm.[3]

*7.4 GBq (200 mCi) LUTATHERA every 8 weeks (±1 week for a total of 4 IV doses, maximum cumulative dose of 29.6 GBq) plus long-acting octreotide 30 mg IM 4 to 24 hours after each dose of LUTATHERA and every 4 weeks after completion of treatment with LUTATHERA until disease progression or until Week 76 of the study.[1]

†High-dose, long-acting octreotide (60 mg IM every 4 weeks).[1]

‡Defined as the time from randomization to documented disease progression (as evaluated per RECIST v1.1 by independent central review by radiologists who were unaware of the treatment) or death from any cause.[1,2]

§Included 2 patients randomized after the primary PFS analysis data cutoff (July 24, 2015).[3]

GBq, gigabecquerel; HR, hazard ratio; IM, intramuscular; IRC, independent review committee; IV, intravenous; mCi, millicurie; NE, not evaluable; NETs, neuroendocrine tumors; PFS, progression-free survival; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; SSTR, somatostatin receptor.

INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Radiation Exposure:** Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices, patient management procedures, Nuclear Regulatory Commission patient release guidance, and instructions to the patient for follow-up radiation protection at home.

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

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

IMPORTANT SAFETY INFORMATION

INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Radiation Exposure:** Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices, patient management procedures, Nuclear Regulatory Commission patient release guidance, and instructions to the patient for follow-up radiation protection at home.
- **Myelosuppression:** In the NETTER-1 clinical trial, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide compared with patients receiving high-dose long-acting octreotide (all grades/grade 3/4): anemia (81%/0 vs 54%/1%), thrombocytopenia (53%/1% vs 17%/0), and neutropenia (26%/3% vs 11%/0). In NETTER-1, platelet nadir occurred at a median of 5.1 months following the first dose. Of the 59 patients who developed thrombocytopenia, 68% had platelet recovery to baseline or normal levels. The median time to platelet recovery was 2 months. Fifteen of the19 patients in whom platelet recovery was not documented had post-nadir platelet counts. Among these 15 patients, 5 improved to grade 1, 9 to grade 2, and 1 to grade 3. Monitor blood cell counts. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of myelosuppression.
- **Secondary Myelodysplastic Syndrome and Leukemia:** In NETTER-1, with a median follow-up time of 76 months in the main study, myelodysplastic syndrome (MDS) was reported in 2.3% of patients receiving LUTATHERA with long-acting octreotide compared with no patients receiving high-dose long-acting octreotide. In ERASMUS, a phase 2 clinical study, 16 patients (2.0%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to onset was 29 months (range, 9-45 months) for MDS and 55 months (range, 32-125 months) for acute leukemia.
- **Renal Toxicity:** In ERASMUS, 8 patients (<1%) developed renal failure 3 to 36 months following LUTATHERA. Two of these patients had underlying renal impairment or risk factors for renal failure (eg, diabetes or hypertension) and required dialysis. Administer the recommended amino acid solution before, during, and after LUTATHERA to decrease the reabsorption of lutetium Lu 177 dotatate through the proximal tubules and decrease the radiation dose to the kidneys. Advise patients to hydrate and to urinate frequently before, on the day of, and on the day after administration of LUTATHERA. Monitor serum creatinine and calculated creatinine clearance. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of renal toxicity. Patients with baseline renal impairment may be at increased risk of toxicity due to increased radiation exposure; perform more frequent assessments of renal function in patients with baseline mild or moderate impairment. LUTATHERA has not been studied in patients with baseline severe renal impairment (creatinine clearance <30 mL/min) or those with end-stage renal disease.
- **Hepatotoxicity:** In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with 1 patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, serum albumin, and the international normalized ratio during treatment. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of hepatotoxicity.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema, occurred in patients treated with LUTATHERA. Monitor patients closely for signs and symptoms of hypersensitivity reactions, including anaphylaxis, during and following LUTATHERA administration for a minimum of 2 hours in a setting in which cardiopulmonary resuscitation medication and equipment are available. Discontinue the infusion upon the first observation of any signs or symptoms consistent with a severe hypersensitivity reaction and initiate appropriate therapy. Premedicate patients with a history of grade 1/2 hypersensitivity reactions to LUTATHERA before subsequent doses. Permanently discontinue LUTATHERA in patients who experience grade 3/4 hypersensitivity reactions.
- **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.

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

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (continued)

- **Embryo-Fetal Toxicity:** LUTATHERA can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating LUTATHERA. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with LUTATHERA and for 4 months after the last dose.
- **Risk of Infertility:** LUTATHERA may cause infertility in males and females. Radiation absorbed by testes and ovaries from the recommended cumulative LUTATHERA dose falls within the range in which temporary or permanent infertility can be expected following external beam radiotherapy.

ADVERSE REACTIONS

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

In ERASMUS, the following serious adverse reactions have been observed with a median follow-up time of >4 years after treatment with LUTATHERA: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%). Patients should be counseled and monitored in accordance with the LUTATHERA Prescribing Information.

DRUG INTERACTIONS

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

Glucocorticoids can induce downregulation of subtype 2 somatostatin receptors. Avoid repeated administration of high doses of glucocorticoids during treatment with LUTATHERA.

SPECIFIC POPULATIONS

Lactation: Because of the potential risk for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LUTATHERA and for 2.5 months after the last dose.

References: 1. Lutathera. Prescribing information. Advanced Accelerator Applications. **2.** Strosberg J, El-Haddad G, Wolin E, et al; for the NETTER-1 trial investigators. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376(2):125-135. **3.** Strosberg JR, Caplin ME, Kunz PL, et al; NETTER-1 investigators. ^{177}Lu-dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2021;22(12):1752-1763.

ESTABLISHED SAFETY PROFILE IN CLINICAL TRIALS

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


Not an actual patient.

LUTATHERA safety profile from primary analysis of NETTER-1[1]

- **In the primary analysis, the most common grade 3/4 adverse reactions with a higher incidence in the LUTATHERA arm were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), increased AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%)**
- **6% (7 of 111) of patients required a dose reduction, and 13% (14 of 111) of patients discontinued LUTATHERA**

No new safety signals were reported in the 5-year, long-term follow-up for NETTER-1[3]*

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

*Cutoff date for final analysis was January 18, 2021.[3]

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

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; MDS, myelodysplastic syndrome.

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

Scan the QR code or go to LUTATHERA-HCP.com to find a list of LUTATHERA treatment centers in the United States.

LEARN MORE ABOUT THE LUTATHERA SAFETY PROFILE AT LUTATHERA-SAFETYPROFILE.COM

NOVARTIS

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

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

© 2023 Novartis