For your patients
with SSTR+ GEP-NETs,[1-3]

START STRONG WITH LUTATHERA

1ST radioligand therapy with **1st-line** evidence demonstrated in a phase 3 study[1,4,5]

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

INDICATION

LUTATHERA® (lutetium Lu 177 dotatate) 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.

NOVARTIS

LUTATHERA was studied as 1L therapy* in newly diagnosed, well-differentiated, grade 2 or 3 advanced GEP-NETs[1,4]

NETTER-2 is a phase 3, randomized, open-label, multicenter study[4]

Select Inclusion Criteria[1]

- ✓ Newly diagnosed, SSTR+, metastatic or advanced GEP-NET (diagnosis within 6 months of screening)
- ✓ Well-differentiated grade 2 or 3 tumors
- ✓ Ki-67 index ≥10% and ≤55%
- ✓ Karnofsky Performance Score ≥60

Stratification Factors

- **Tumor grade:** grade 2 vs grade 3
- **Site of origin:** pNET vs other primary tumor site

Randomization 2:1 (N=226)

LUTATHERA + 30 mg octreotide LAR (n=151)[1,4]

LUTATHERA: 4 cycles, 7.4 GBq (200 mCi) every 8 weeks (+/-1 week)

Octreotide LAR: 30 mg every 8 weeks during LUTATHERA treatment and every 4 weeks after

60 mg octreotide LAR (n=75)†

Octreotide LAR: 60 mg every 4 weeks

*SSA-naive patients were eligible, as well as patients previously treated with SSAs in the absence of progression.[1]
†Patients received an initial single dose at 30 mg before stepping up to 60 mg octreotide.[1]

Primary end point[1]

- PFS (centrally assessed according to RECIST v1.1 and defined as time from randomization to first documented progression or death due to any cause)

Secondary end points[1]

- Objective response rate (ORR)
- Overall survival (OS)
- Time to deterioration (TTD) in select QOL scales
- Disease control rate
- Duration of response
- Safety

Additional information[1]

- Patients previously treated with an SSA without documented progression were allowed
- Crossover from the 60-mg octreotide LAR arm to LUTATHERA was allowed after patients experienced progression
- In the LUTATHERA arm, investigators had the option of enrolling patients for re-treatment with LUTATHERA if they had previously received and benefited from 4 doses as initial treatment (offering an additional 2-4 cycles of LUTATHERA)
- If progression occurred after the Week 72 primary end point analysis, the re-treatment decision was based on local assessment

1L, first line; GBq, gigabecquerel; LAR, long-acting release; mCi, millicurie; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; RECIST, Response Evaluation Criteria in Solid Tumors; SSA, somatostatin analog; QOL, quality of life.

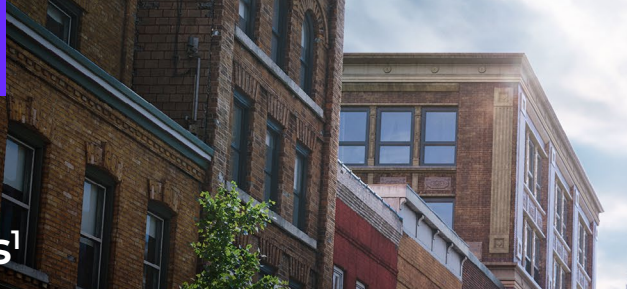
IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Myelosuppression:** In the NETTER-1 clinical trial, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide compared with patients receiving high-dose long-acting octreotide (all grades/grade 3/4): anemia (81%/0 vs 54%/1%), thrombocytopenia (53%/1% vs 17%/0), and neutropenia (26%/3% vs 11%/0). In NETTER-1, platelet nadir occurred at a median of 5.1 months following the first dose. Of the 59 patients who developed thrombocytopenia, 68% had platelet recovery to baseline or normal levels. The median time to platelet recovery was 2 months. Fifteen of the 19 patients in whom platelet recovery was not documented had post-nadir platelet counts. Among these 15 patients, 5 improved to grade 1, 9 to grade 2, and 1 to grade 3. Monitor blood cell counts. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of myelosuppression.

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

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



LUTATHERA has evidence across a range of patients with SSTR+ GEP-NETs[1]

NETTER-2 demographics and disease characteristics were well balanced between arms[4]

Baseline Demographics and Disease Characteristics

	LUTATHERA + 30 mg octreotide LAR (n=151)	60 mg octreotide LAR (n=75)
Age (median), years	**61**	**60**
Sex, no. (%)		
Male	81 (53.6)	40 (53.3)
Female	70 (46.4)	35 (46.7)
Karnofsky PS, no. (%)		
60	0	1 (1.3)
70-80	28 (18.5)	10 (13.3)
90-100	123 (81.5)	64 (85.3)
Primary tumor site, no. (%)		
Pancreas	82 (54.3)	41 (54.7)
Small intestine	45 (29.8)	21 (28.0)
Other	24 (15.9)	13 (17.3)
Extent of tumor burden[a], no. (%)		
Limited	17 (11.3)	9 (12.0)
Moderate	69 (45.7)	36 (48.0)
Extensive	65 (43.0)	29 (38.7)
Histopathology grade, no. (%)		
Grade 2	99 (65.6)	48 (64.0)
Grade 3	52 (34.4)	27 (36.0)
Ki-67, mean (SD)	**19.7 (10.08)**	**20 (10.42)**
SSTR tumor uptake score (highest[b]), no. (%)		
Grade 3	56 (37.1)	25 (33.3)
Grade 4	95 (62.9)	50 (66.7)

PS, performance score; SSTR, somatostatin receptor.

[a]Extent of tumor burden was based on central assessment.
[b]Highest SSTR tumor uptake score is based on local assessment.

IMPORTANT SAFETY INFORMATION (continued)

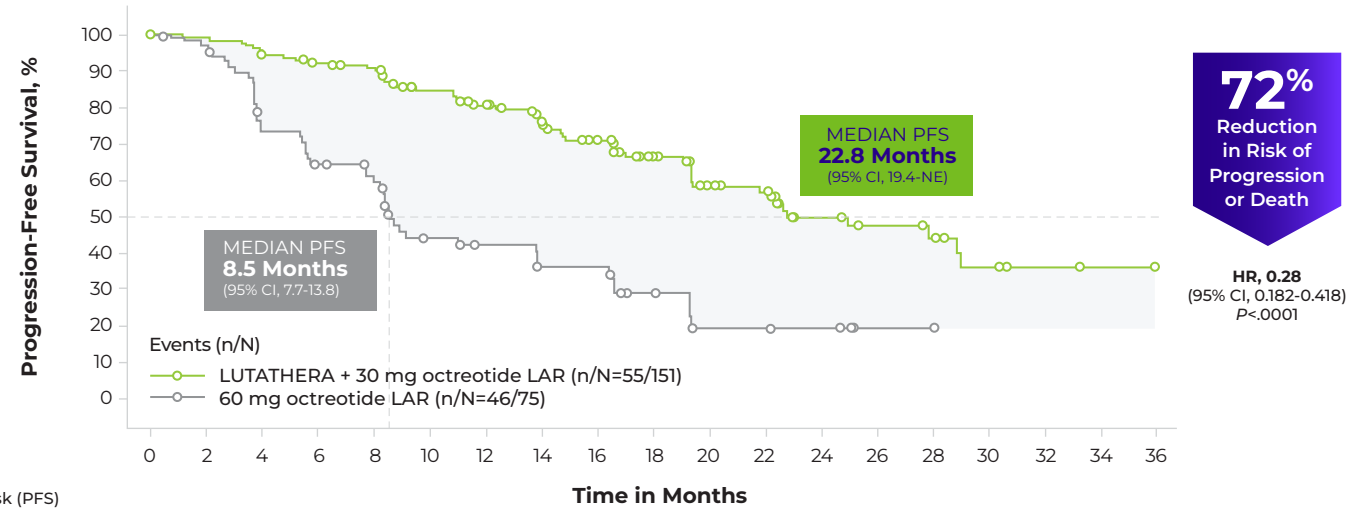
WARNINGS AND PRECAUTIONS (continued)

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

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

The potential to prolong PFS from the start with the power of LUTATHERA + SSA[1,2,4]

Statistically Significant Improvement in PFS (Primary End Point)



No. at Risk (PFS)

LUTATHERA + 30 mg octreotide LAR	151	143	138	129	125	104	92	80	68	53	41	37	23	19	13	9	4	2	0
60 mg octreotide LAR	75	67	49	42	37	24	21	16	16	10	5	5	4	1	1	0	0	0	0

- PFS was defined as the time from randomization to first documented disease progression or death due to any cause. Centrally assessed according to RECIST v1.1 criteria[1]
- The primary PFS analysis data cutoff was July 20, 2023. Median duration of follow-up was 23.2 months (from randomization to cutoff date)[4]
- Follow-up for overall survival is ongoing. Data will be collected for a planned final analysis of OS in the follow-up period after patients complete their treatment, re-treatment, or crossover phase (follow-up period: at least 6 months and up to 3 years, or until end of study, whichever comes first)[1]

HR, hazard ratio; NE, not evaluable.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Renal Toxicity:** In ERASMUS, 8 patients (<1%) developed renal failure 3 to 36 months following LUTATHERA. Two of these patients had underlying renal impairment or risk factors for renal failure (eg, diabetes or hypertension) and required dialysis. Administer the recommended amino acid solution before, during, and after LUTATHERA to decrease the reabsorption of lutetium Lu 177 dotatate through the proximal tubules and decrease the radiation dose to the kidneys. Advise patients to hydrate and to urinate frequently before, on the day of, and on the day after administration of LUTATHERA. Monitor serum creatinine and calculated creatinine clearance. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of renal toxicity. Patients with baseline renal impairment may be at increased risk of toxicity due to increased radiation exposure; perform more frequent assessments of renal function in patients with baseline mild or moderate impairment. LUTATHERA has not been studied in patients with baseline severe renal impairment (creatinine clearance <30 mL/min) or those with end-stage renal disease.
- **Hepatotoxicity:** In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with 1 patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, serum albumin, and the international normalized ratio during treatment. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of hepatotoxicity.

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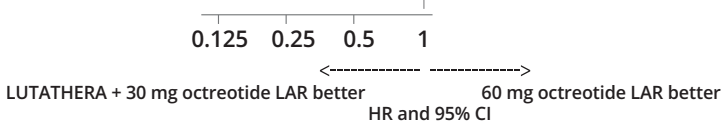
LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Consistent PFS benefit was shown with LUTATHERA + SSA across key clinical subgroups[4]

PFS Across Key Subgroups of Interest (Full Analysis Set)

	Hazard ratio (95% CI)	LUTATHERA + 30 mg octreotide LAR events, n/N (%)	60 mg octreotide LAR events, n/N (%)
Tumor grade			
Grade 2 (n=147)	0.31 (0.18-0.53)	29/99 (29.3)	25/48 (52.1)
Grade 3 (n=79)	0.27 (0.14-0.49)	26/52 (50.0)	21/27 (77.8)
Tumor origin			
pNET (n=123)	0.34 (0.20-0.56)	39/82 (47.6)	27/41 (65.9)
Other (n=103)	0.23 (0.12-0.46)	16/69 (23.2)	19/34 (55.9)
Small intestine (n=66)	0.30 (0.13-0.74)	11/45 (24.4)	10/21 (47.6)
Age group			
<65 years (n=134)	0.26 (0.16-0.45)	30/86 (34.9)	30/48 (62.5)
≥65 years (n=92)	0.37 (0.20-0.71)	25/65 (38.5)	16/27 (59.3)
Sex			
Female (n=105)	0.30 (0.16-0.55)	26/70 (37.1)	19/35 (54.3)
Male (n=121)	0.32 (0.18-0.54)	29/81 (35.8)	27/40 (67.5)

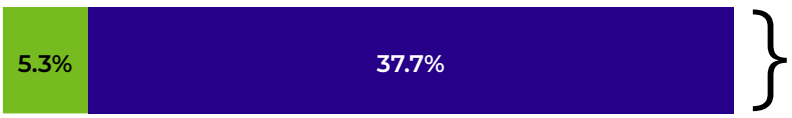


Statistically significant increase (>4X) in overall response rate (ORR) with LUTATHERA + 30 mg octreotide LAR

Overall Response Rate (Full Analysis Set)

LUTATHERA + 30 MG OCTREOTIDE LAR

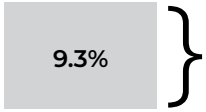
- Complete responses: **5.3%**
- Partial responses: **37.7%**



43% ORR
(65/151)
P<.0001

60 MG OCTREOTIDE LAR

- Partial responses: **9.3%**



9.3% ORR
(7/75)
There were no complete responses in this arm

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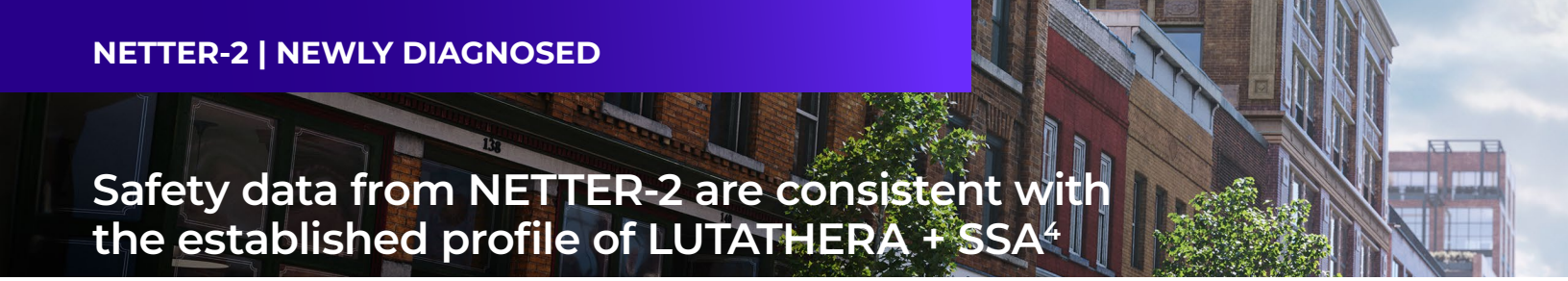

Safety data from NETTER-2 are consistent with the established profile of LUTATHERA + SSA[4]

Adverse Events (Irrespective of Causality) by Preferred Term (≥10% Incidence in Either Arm) (Safety Set)

	LUTATHERA + 30 mg octreotide LAR (n=147)		60 mg octreotide LAR (n=73)	
Preferred term	**All grades, no. (%)**	**Grade ≥3, no. (%)**	**All grades, no. (%)**	**Grade ≥3, no. (%)**
Patients with at least 1 event	136 (92.5)	52 (35.4)	69 (94.5)	20 (27.4)
Nausea	40 (27.2)	1 (0.7)	13 (17.8)	0
Diarrhea	38 (25.9)	2 (1.4)	25 (34.2)	1 (1.4)
Anemia	29 (19.7)	1 (0.7)	5 (6.8)	1 (1.4)
Fatigue	29 (19.7)	0	13 (17.8)	0
Asthenia	28 (19.0)	1 (0.7)	9 (12.3)	0
COVID-19	28 (19.0)	0	10 (13.7)	0
Abdominal pain	26 (17.7)	4 (2.7)	20 (27.4)	3 (4.1)
Platelet count decreased	25 (17.0)	2 (1.4)	4 (5.5)	0
Alopecia	22 (15.0)	0	1 (1.4)	0
Vomiting	21 (14.3)	1 (0.7)	6 (8.2)	1 (1.4)
Hyperglycemia	20 (13.6)	0	11 (15.1)	2 (2.7)
Decreased appetite	19 (12.9)	0	7 (9.6)	0
White blood cell count decreased	19 (12.9)	3 (2.0)	3 (4.1)	0
Weight increased	18 (12.2)	2 (1.4)	5 (6.8)	0
Edema peripheral	17 (11.6)	0	6 (8.2)	1 (1.4)
ALT increased	16 (10.9)	1 (0.7)	10 (13.7)	2 (2.7)
AST increased	16 (10.9)	1 (0.7)	8 (11.0)	2 (2.7)
Headache	16 (10.9)	0	5 (6.8)	0
Lymphocyte count decreased	16 (10.9)	8 (5.4)	0	0
Constipation	15 (10.2)	1 (0.7)	6 (8.2)	0
GGT increased	12 (8.2)	7 (4.8)	8 (11.0)	2 (2.7)

- The most common adverse events (>20% in either arm) were nausea (27.2% vs 17.8%), diarrhea (25.9% vs 34.2%), and abdominal pain (17.7% vs 27.4%) for LUTATHERA + 30 mg octreotide LAR vs 60 mg octreotide LAR, respectively[4]
- The most common grade 3/4 adverse events (≥3% in either arm) were lymphocyte count decreased (5.4% vs 0%), GGT increased (4.8% vs 2.7%), small intestinal obstruction (3.4% vs 0%), and abdominal pain (2.7% vs 4.1%) for LUTATHERA + 30 mg octreotide LAR vs 60 mg octreotide LAR, respectively[4]
- 4.8% of patients discontinued LUTATHERA + 30 mg octreotide LAR due to adverse events vs 2.7% for patients treated with 60 mg octreotide LAR[4]

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

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

Incidence of Laboratory Abnormalities (Safety Set)[4]

	LUTATHERA + 30 mg octreotide LAR (n=147)		60 mg octreotide LAR (n=73)	
Biochemical laboratory abnormalities	**All grades, no. (%)**	**Grade ≥3, no. (%)**	**All grades, no. (%)**	**Grade ≥3, no. (%)**
Creatinine increase	30 (20.4)	0	15 (20.5)	1 (1.4)
Albumin decrease	25 (17.0)	0	17 (23.3)	1 (1.4)
Bilirubin increase	26 (17.7)	4 (2.7)	17 (23.3)	4 (5.5)
Alkaline phosphatase increase	79 (53.7)	7 (4.8)	40 (54.8)	3 (4.1)
AST increase	75 (51.0)	4 (2.7)	40 (54.8)	5 (6.8)
ALT increase	63 (42.9)	6 (4.1)	38 (52.1)	3 (4.1)
GGT increase	102 (69.4)	38 (25.9)	56 (76.7)	21 (28.8)
Sodium increase	5 (3.4)	0	6 (8.2)	0
Sodium decrease	32 (21.8)	1 (0.7)	12 (16.4)	1 (1.4)
Potassium increase	33 (22.4)	3 (2.0)	16 (21.9)	3 (4.1)
Potassium decrease	13 (8.8)	4 (2.7)	10 (13.7)	2 (2.7)
Calcium corrected increase	9 (6.1)	0	8 (11.0)	1 (1.4)
Hematological laboratory abnormalities				
Leukocytes increase	0	0	0	0
Leukocytes decrease	92 (62.6)	6 (4.1)	15 (20.5)	0
Lymphocytes increase	4 (2.7)	0	3 (4.1)	0
Lymphocytes decrease	142 (96.6)	56 (38.1)	45 (61.6)	2 (2.7)
Neutrophils decrease	55 (37.4)	5 (3.4)	9 (12.3)	0
Platelets decrease	81 (55.1)	3 (2.0)	15 (20.5)	0
Hemoglobin increase	4 (2.7)	0	2 (2.7)	0
Hemoglobin decrease	116 (78.9)	2 (1.4)	42 (57.5)	2 (2.7)

Incidence based on worst post-baseline CTC grade.
CTC, Common Terminology Criteria.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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

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

LUTATHERA was studied in well-differentiated grade 1 or 2 advanced GEP-NETs at SSA progression[2,3]

NETTER-1 was a pivotal, phase 3, randomized, open-label, multicenter study[2,3]

Select Inclusion Criteria[2,3]

- SSTR+ metastatic, inoperable, or locally advanced midgut GEP-NETs that had progressed during SSA treatment
- Well-differentiated grade 1 or 2 tumors
- Ki-67 index ≤20%
- Karnofsky Performance Score ≥60

Stratification Factors[3]

- **SSTR uptake:** grade 2, 3, or 4
- **Time receiving constant dose of octreotide:** ≤6 months vs >6 months

Randomization 1:1 (N=229)

LUTATHERA + 30 mg octreotide LAR (n=116)[2,3]

LUTATHERA: 4 cycles, 7.4 GBq (200 mCi) every 8 weeks (+/-1 week), maximum cumulative dose 29.6 GBq

Octreotide LAR: 30 mg 4 to 24 hours after each LUTATHERA dose and then every 4 weeks after completion of treatment with LUTATHERA until disease progression or until Week 76 of the study

60 mg octreotide LAR (n=113)

Octreotide LAR: 60 mg every 4 weeks

Primary end point[3]

- PFS (independent central review by radiologists unaware of the treatment according to RECIST v1.1), defined as time from randomization to documented disease progression or death from any cause[2,3]

Secondary end points[2,3]

- ORR
- Duration of response
- OS
- Safety

Additional information

- 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 dose of LUTATHERA[2]
- **Final Analysis:** After centrally confirmed disease progression, discontinuation of the 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 60-mg octreotide LAR 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 60-mg octreotide arm[6]

*Included 2 patients randomized after the primary PFS analysis data cutoff (July 24, 2015).[6]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Neuroendocrine Hormonal Crisis:** Neuroendocrine hormonal crises, manifesting with flushing, diarrhea, bronchospasm, and hypotension, occurred in <1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose. Two (<1%) patients were reported to have hypercalcemia. Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction, or other signs and symptoms of tumor-related hormonal release. Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.

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

LUTATHERA has evidence across a range of patients with SSTR+ GEP-NETs[2]

NETTER-1 demographics and disease characteristics were well balanced between arms[2,3]

Baseline Demographics and Disease Characteristics

	LUTATHERA + 30 mg octreotide LAR (n=116)	60 mg octreotide LAR (n=113)
Age (median), years	**63±9**	**64±10**
Sex, no. (%)		
Male	63 (54)	53 (47)
Female	53 (46)	60 (53)
Karnofsky PS (mean + SD)	**88.6±9.32**	**88±9.56**
Primary tumor site, no. (%)		
Jejunum	6 (5)	9 (8)
Ileum	86 (74)	82 (73)
Small intestine	11 (9)	12 (11)
Appendix	1 (1)	2 (2)
Right colon	3 (3)	1 (1)
Midgut (NOS)	9 (8)	7 (6)
Site of metastasis, no. (%)		
Liver	97 (84)	94 (83)
Lymph nodes	77 (66)	65 (58)
Mesentery	17 (15)	8 (7)
Bone	13 (11)	12 (11)
Other	15 (13)	10 (9)
Peritoneum	7 (6)	10 (9)
Lungs	11 (9)	5 (4)
Ovaries	1 (1)	9 (8)
Tumor grade, no. (%)		
Grade 1	76 (66)	81 (72)
Grade 2	40 (35)	32 (28)
SSTR uptake score (highest[a]), no. (%)		
Grade 2	11 (9)	12 (11)
Grade 3	34 (29)	34 (30)
Grade 4	71 (61)	67 (59)

[a]Highest SSTR tumor uptake score was based on the Krenning scale.
NOS, not otherwise specified.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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

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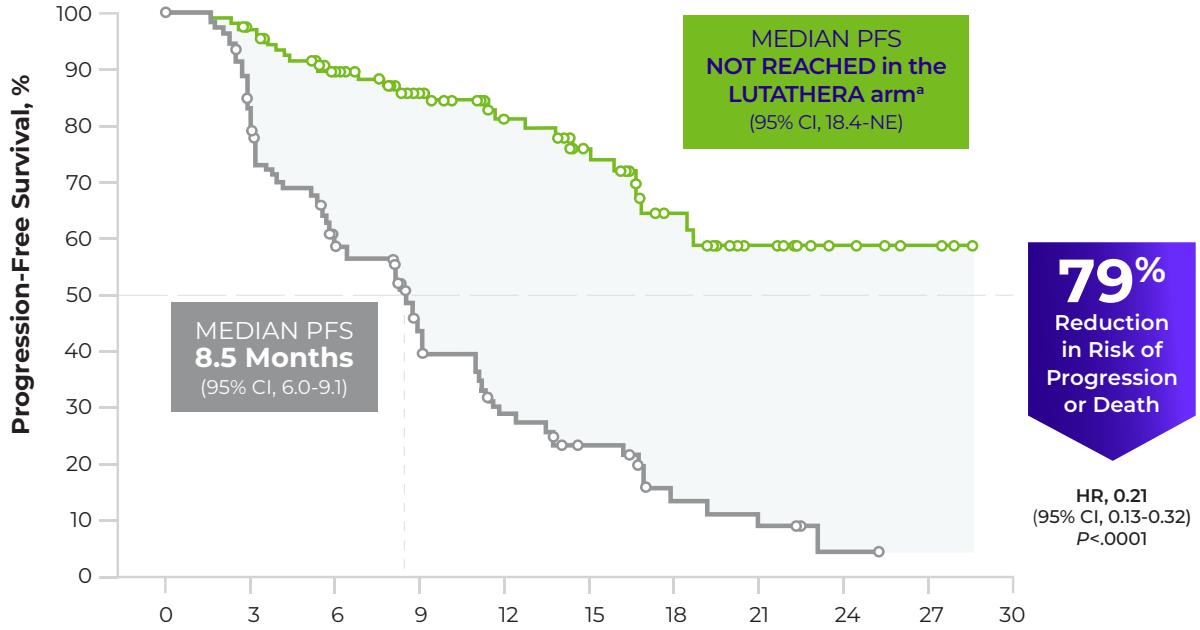
injection, for intravenous use

At SSA progression, prolong PFS with the power of LUTATHERA[2]

Statistically Significant Improvement in PFS (Primary End Point)



No. at Risk (PFS)

LUTATHERA + 30 mg octreotide LAR	116	102	84	66	48	38	22	13	6	3	0
60 mg octreotide LAR	113	84	57	35	21	14	6	4	1	0	0

LUTATHERA + 30 mg octreotide LAR — 60 mg octreotide LAR

	LUTATHERA + 30 mg octreotide LAR (n=116)	60 mg octreotide LAR (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.[2]

Primary PFS analysis

- PFS (as assessed by independent central review according to RECIST v1.1 by radiologists unaware of the treatment), defined as the time from randomization to documented disease progression or death from any cause[3]
- The primary PFS analysis data cutoff was July 24, 2015. Median duration of follow-up was 14 months[3]

Final OS analysis (secondary end point)

- OS was analyzed at the final analysis, which occurred 66 months after the primary PFS analysis. There was no statistically significant difference in OS between the 2 treatment arms. Because the assumptions for the Cox model for OS were not fulfilled, the HR is uninterpretable[2,6]
- Prespecified OS analysis was completed 5 years after the last patient was randomized (data cutoff: January 18, 2021)[6]
- Median duration of follow-up was 76.3 months in the LUTATHERA + 30 mg octreotide LAR arm and 76.5 months in the 60 mg octreotide LAR arm[6]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Risk of Infertility:** LUTATHERA may cause infertility in males and females. Radiation absorbed by testes and ovaries from the recommended cumulative LUTATHERA dose falls within the range in which temporary or permanent infertility can be expected following external beam radiotherapy.

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

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

Established safety profile for LUTATHERA + SSA[2]

Most of the adverse reactions seen with LUTATHERA + SSA were grade 1 or 2

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

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

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

[b]Includes the terms glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, and renal impairment.

[c]Includes the terms dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain, and urinary incontinence.

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LUTATHERA®
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Long-term safety profile of LUTATHERA[6]

No new safety signals were reported in the 5-year, long-term follow-up for NETTER-1[6,*]

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[6]
Grade ≥3 Treatment-Related SAEs During the Entire Study	**7 (6%) of 111 patients treated in the LUTATHERA arm[6]**
Incidence of Treatment-Related SAEs During the Long-Term Follow-Up Period	**3 (3%) of 111 patients treated with LUTATHERA[6]** — 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[6]** — 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[2,6] — 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[2,a]
Diffuse Large B-Cell Lymphoma	One patient developed diffuse large B-cell lymphoma during long-term follow-up that was deemed unrelated to treatment with LUTATHERA[6]
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[6]**

*Cutoff date for final analysis was January 18, 2021.[6]

[a]ERASMUS study design: Retrospective safety data are available from 1214 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with SSTR-positive tumors (neuroendocrine and other primaries). The median duration of follow-up was >4 years.[2]

AEs, adverse events; MDS, myelodysplastic syndrome.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

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

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.

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

LUTATHERA®
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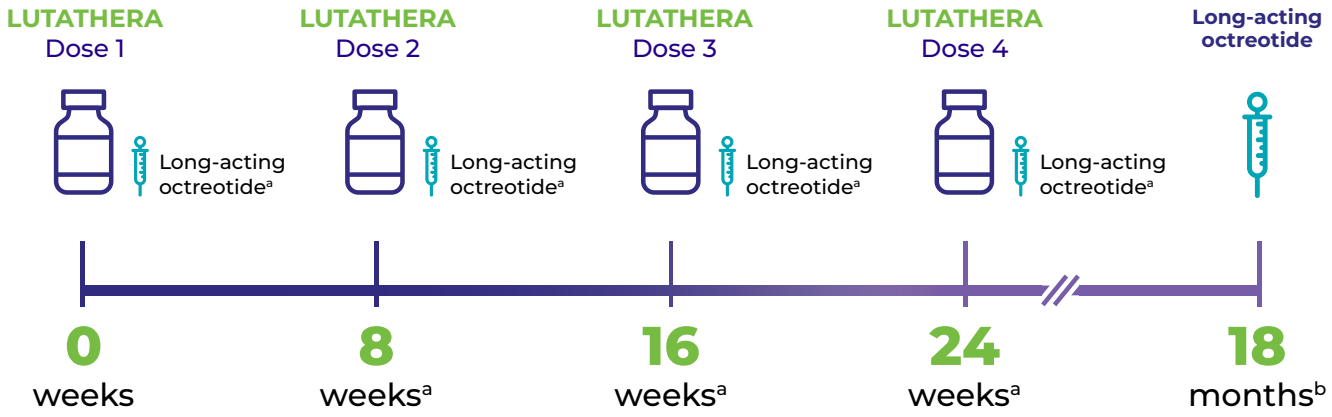
The defined 4-dose treatment regimen for LUTATHERA is available at treatment centers nationwide[2]

Recommended Treatment Regimen With LUTATHERA[1]



Long-acting SSAs should be discontinued for at least 4 weeks prior to initiating LUTATHERA.[2]

Short-acting octreotide may be given for symptomatic management during treatment with LUTATHERA, but must be withheld for at least 24 hours before each dose of LUTATHERA.[2]

LUTATHERA dosage should be modified based on hematologic, renal, hepatic, hypersensitivity, or other adverse reactions (see full Prescribing Information).[2]

For reduced dose administration instructions, refer to section 2.5 (Preparation and Administration) of the full Prescribing Information.

In NETTER-2
88% of patients completed all 4 doses of LUTATHERA[4]

In NETTER-1
77% of patients completed all 4 doses of LUTATHERA[3]

[a]Administer long-acting octreotide 30 mg IM between 4 to 24 hours after each dose of LUTATHERA. Do not administer long-acting octreotide within 4 weeks prior to each subsequent dose of LUTATHERA. The interval between infusions may be extended up to 16 weeks in the case of a dose modification due to an adverse reaction. Permanently discontinue LUTATHERA in patients who experience grade 3/4 hypersensitivity reactions. Please see the Prescribing Information for additional information on dose modifications.[2]
[b]Continue long-acting octreotide 30 mg IM every 4 weeks after completing LUTATHERA until disease progression or for 18 months following treatment initiation at the discretion of the physician.[2]
IM, intramuscular.

Find a LUTATHERA treatment center near your patients

IMPORTANT SAFETY INFORMATION (continued)

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.

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

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

Novartis Patient Support

Support to help your patients start and stay on therapy

Designed to provide support in the following areas:

- Access & Reimbursement
- Affordability
- Acquisition
- Patient Education

Novartis Patient Support Co-pay Savings

We help make treatment more affordable for your patients through co-pay savings.

$25 CO-PAY*

Eligible patients may pay as little as $25 per dose.*

Enrollment in Novartis Patient Support is required to determine eligibility and participation.

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

Here's How to Enroll

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

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

Additional Educational Support Is Available for Your Patients

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

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

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

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

LUTATHERA®
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injection, for intravenous use

INDICATION

LUTATHERA® (lutetium Lu 177 dotatate) 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 the 19 patients in whom platelet recovery was not documented had post-nadir platelet counts. Among these 15 patients, 5 improved to grade 1, 9 to grade 2, and 1 to grade 3. Monitor blood cell counts. Withhold dose, reduce dose, or permanently discontinue LUTATHERA based on the severity of myelosuppression.
- **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.

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LUTATHERA®
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- **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.

Please see full Prescribing Information.

References: 1. Data on file. Novartis Pharmaceuticals Corp; 2021. **2.** Lutathera. Prescribing information. Novartis Pharmaceuticals Corp. **3.** 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. **4.** Data on file. Novartis Pharmaceuticals Corp; 2023. **5.** US Food and Drug Administration. FDA approves new treatment for certain digestive tract cancers [press release]. Updated January 26, 2018. Accessed November 30, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-certain-digestive-tract-cancers **6.** 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.

The potential to prolong PFS from the start with the power of LUTATHERA + SSA[1,2,4]

Statistically significant improvement in PFS demonstrated in 2 clinical trials[2,4]

NETTER-2 (1L)[1,4]:
Studied in newly diagnosed, well-differentiated grade 2 or 3 SSTR+ GEP-NETs

72%
REDUCTION
in the risk of disease progression or death

with LUTATHERA + 30 mg octreotide LAR vs 60 mg octreotide LAR

(HR, 0.28 [95% CI 0.18-0.42]; *P*<.0001)

NETTER-1 (2L)[2,3]:
Studied in well-differentiated grade 1 or 2 SSTR+ GEP-NETs at SSA progression

79%
REDUCTION
in the risk of disease progression or death

with LUTATHERA + 30 mg octreotide LAR vs 60 mg octreotide LAR

(HR, 0.21 [95% CI 0.13-0.32]; *P*<.0001)

NETTER-2
Newly Diagnosed[1,4]

- Newly diagnosed (within last 6 months), well-differentiated SSTR+ GEP-NET
- **Karnofsky PS:** 90 to 100
- **Ki-67 index:** ≥10% to ≤55% (tumor grade 2/3)
- **Disease burden:** moderate to extensive

NETTER-1
At SSA Progression[2,3]

- Well-differentiated SSTR+ GEP-NET and progression on SSA
- **Karnofsky PS:** 75 to 95
- **Ki-67 index:** <10% (tumor grade 1/2)

LUTATHERA + SSA: Demonstrated clinical benefit across a range of patients with SSTR+ GEP-NETs[1,3]

2L, second line.

Learn more about LUTATHERA at LUTATHERA-HCP.COM >

INDICATION

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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