Subject: Lutathera (lutetium Lu 177 dotatate)	**Original Effective Date:** 9/13/2018
Policy Number: MCP-322	**Revision Date(s):**
Review Date: Q2 2020	
MCPC Approval Date: 9/13/2018, Q2 2020	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Lutathera (lutetium Lu 177 dotatate)** for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults when appropriate criteria are met.

The intent of the Lutathera (lutetium Lu 177 dotatate) policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

- **Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)**
  - Rare tumors originating in the neuroendocrine cells of numerous organs, including the gastrointestinal tract (such as the stomach, intestines, colon and rectum), pancreas and lung
  - Approximately one out of 27,000 people are diagnosed with GEP-NETs per year
  - Some patients develop symptoms arising from the excessive production of hormones by neuroendocrine tumor cells, while others remain clinically silent for years
  - The estimated incidence, or rate of new cases, of NETs in the United States is approximately 6.98/100,000 per year, while the estimated prevalence for 2014, based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, was 171,321. (Dasari A. et al. 2017)
  - Patient survival with advanced GEP-NETs depends on stage and histology. Patients with well- and moderately-differentiated tumors and distant metastases have a 5-year survival probability of 35%. (Yao JC, et al. 2008)

- **Lutathera (lutetium Lu 177 dotatate)**
  - A radiolabeled somatostatin analog that binds to and is internalized by somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors. The highest affinity is for subtype 2 receptors (SSRT2). Beta emission from lutetium Lu 177 dotatate causes cellular damage via formation of free radicals in the somatostatin receptor-positive cells and in neighboring cells

- Lutathera received orphan drug designation from the FDA, is **a first-in-class drug and the first available FDA-approved Peptide Receptor Radionuclide Therapy (PRRT),** a form of targeted treatment comprising a targeting molecule that carries a radioactive component

- The approval of lutetium Lu 177 dotatate was supported by two studies: NETTER-1 (phase III) and ERASMUS (phase I/II)

  - **NETTER-1 Trial** was a randomized, pivotal phase III clinical trial in 229 patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumors (N=229) treatment with lutetium Lu 177 dotatate. Patients in the trial either received Lutathera with octreotide or octreotide alone. (Strosberg et al. 2017)

    Progression-free survival was longer for patients taking Lutathera with octreotide compared to patients who received octreotide alone. This means the risk of tumor growth or patient death was lower for patients who received Lutathera with octreotide compared to that of patients who received only octreotide. (Strosberg et al. 2017)
    - Eligible patients were adults who had midgut neuroendocrine tumors that had metastasized or were locally advanced, that were inoperable, that were histologically confirmed and centrally verified, and that showed disease progression on either CT or MRI over the course of a maximum period of 3 years during treatment with octreotide LAR (20 to 30 mg every 3 to 4 weeks for at least 12 weeks before randomization).
    - Patients were required to have a Karnofsky performance-status score of at least 60, have somatostatin receptors present on all target lesions, and have well-differentiated histologic features. Well-differentiated histologic features defined as a Ki67 index (% of cells that are positive for Ki67 as determined by immunostaining of the primary tumor) of 20% or less.
    - Patients were randomly assigned 1:1 to receive Lutathera plus best standard of care (Sandostatin® LAR Depot [octreotide] 30 mg after each Lutathera dose and every four weeks after completion of Lutathera treatment) (n=116) **OR** 60 mg of octreotide LAR every four weeks alone (n=113).
    - Median time since diagnosis was 3.8 years in treatment group vs 4.8 years in control group. Ileum (73%) was the primary tumor site. The major efficacy outcome was progression free survival (PFS).
    - **The NETTER-1 study met its primary endpoint, showing a 79% reduction in risk of disease progression or death using Lutathera compared to 60 mg octreotide LAR (hazard ratio 0.21, 95% CI: 0.13-0.32; p<0.0001).**
      - Lutetium Lu 177 dotatate significantly lowered the risk of disease progression or death by 79% compared to the high-dose long-acting octreotide (60 mg of octreotide LAR) alone
      - Additionally, an interim analysis of overall survival showed 14 deaths in the lutetium Lu 177 dotatate group compared with 26 for control—estimated risk of death was **60% lower risk of death in the lutetium Lu 177 dotatate group compared with the control group**
      - Objective tumor response was classified as "complete" in 1% of the lutetium Lu 177 dotatate group and 0% of the control group and as "partial" in 17% and 3%, respectively. The objective response rate (sum of partial responses and complete responses) was 18% and 3% respectively, in the lutetium Lu 177 dotatate group and control group.
      - Treatment-related adverse events occurred in 86% in the lutetium Lu 177 dotatate group and 31% for control
      - The most common Grade 3-4 adverse reactions occurring with a greater frequency among patients in the NETTER-1 study receiving Lutathera with octreotide compared to patients receiving high-dose octreotide include: lymphopenia (44%), increased gamma-glutamyl transferase (20%), vomiting (7%), nausea and elevated aspartate aminotransferase (5% each), and increased alanine aminotransferase, hyperglycemia and hypokalemia (4% each).

- **ERASMUS** was based on data from 1,214 patients with somatostatin receptor-positive tumors, including GEP-NETS, who received Lutathera at an international, single-institution, single-arm, open-label trial conducted by Erasmus Medical Center in Rotterdam, Netherlands. The product labeling provides a brief description of this retrospective trial, which involved 360 patients with gastroenteropancreatic neuroendocrine tumors of foregut, midgut, and hindgut (N=360) from a single site in the Netherlands. (Product Information 2017)
  - Patients received lutetium Lu 177 dotatate 7.4 GBq (200 mCi) IV every 6 to 13 weeks for up to 4 doses.
  - **Complete or partial tumor shrinkage was reported in 16 percent of a subset of 360 patients with GEP-NETs who were evaluated for response by the FDA. Of the responders, the median duration of response was 35 months (95% CI: 17, 38). Less than 1% of patients were complete responders.**
  - Patients initially enrolled in the study at ERASMUS Medical Center received Lutathera as part of an expanded access program. *Expanded access is a way for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives to gain access to investigational drugs for treatment use.*

Summary of Clinical Evidence

- Treatment with lutetium Lu 177 dotatate significantly improved progression free survival compared with high-dose long-acting octreotide in a randomized study; however, treatment-related adverse events were higher with lutetium Lu 177 dotatate (Strosberg J, et al; NETTER-1 Trial).
- Additionally, treatment with lutetium Lu 177 dotatate in patients with GEP-NETs resulted in an investigator-assessed overall response rate of 16% in a retrospective study (ERASMUS).[Micromedex 2018]

CLASSIFICATION: Antineoplastic Agents; Therapeutic Radiopharmaceuticals; Peptide Receptor Radionuclide Therapy (PRRT)

FDA INDICATIONS

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

- *FDA granted **Priority Review** for this application and previously granted **Orphan Drug designation** to lutetium Lu 177 dotatate for treatment of GEP-NETs.*

Available as: 370 MBq/mL (10 mCi/mL) in single-dose vial

- *Lutathera injection containing 370 MBq/mL (10 mCi/mL) of lutetium Lu 177 dotatate is a preservative-free and clear, colorless to slightly yellow solution supplied in a colorless 30 mL, single-dose glass vial containing 7.4 GBq (200 mCi) ±10% at the time of injection. The vials are stored in lead-shielded container placed in a plastic sealed container. Store below 25°C (77°F). It has a shelf life of 72 hours and must be appropriately discarded at 72 hours*

FDA Approved: January 26, 2017

Black Box Warnings: None at the time of this writing

REMS: No REMS is required for lutetium Lu 177 dotatate

RECOMMENDATIONS/COVERAGE CRITERIA

Lutathera (lutetium Lu 177 dotatate) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, hematologist/oncologist or physician who specializes in the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and has 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

2. Diagnosis/Indication [ALL]
Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis **[A OR B]**

A. Diagnosis of **gastroenteropancreatic neuroendocrine tumor (GEP-NET)** [includes tumors arising from the foregut (gastroduodenal), midgut (distal small intestine and proximal colon), hindgut (distal colorectal) and pancreas] **AND** ALL of the following: [ALL]

- ❒ **Well-differentiated tumor*** as documented by a **pathology report.**
  ***NOTE:**
  - Well-differentiated neuroendocrine tumors include **low-grade (G1)** and **intermediate-grade (G2) tumors,** which correlate with a defined Ki-67 proliferation index, as determined by an immunohistochemical stain.
  - Well-differentiated, low grade neuroendocrine tumors have a Ki-67 index of <3%, and well-differentiated, intermediate-grade neuroendocrine tumors have a Ki-67 index of 3-20%.

  APPENDIX 1: 'Well-differentiated GEP-NETs

- ❒ Locally advanced, inoperable, or metastatic carcinoid tumor
  - *The general treatment approach to well-differentiated GEP-NETs involves resecting potentially resectable disease, including metastasectomy. Unresectable, asymptomatic disease may involve observation, especially if tumor burden is limited, or initial therapy with a somatostatin analog if tumor burden is high.*

- ❒ Karnofsky performance-status score of at least 60* or equivalent

  *The Karnofsky Performance Status Scale classifies patients based on their functional impairment. The scale ranges from 0 (death) to 100 (normal, no evidence of disease).
  The Karnofsky Performance Scale (Karnofsky, 1948)

100	Normal; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work
60	**Requires occasional assistance, but is able to care for most of their personal needs**
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Death

- ❒ Presence of somatostatin receptors-positive foregut, midgut and hindgut GEP-NETS on all target lesions confirmed by an appropriate imaging study has been performed to document over-expression of somatostatin receptors by the target lesions (such as NETSPOT or Octreoscan)

B. For member(s) new to Molina Healthcare and being treated with Lutathera (lutetium Lu 177 dotatate) ONLY: [ALL]

- ❒ Member is currently being treated with Lutathera (lutetium Lu 177 dotatate). Documentation required.
- ❒ Prescriber indicates member is at risk if therapy is changed. Documentation required.
- ❒ Requested dosing or frequency is within the FDA-recommended dosing and frequency
- ❒ Member has not exceeded quantity limit of 4 doses total. Refer to 'Quantity Limit' section of policy.

3. Age/Gender/Restrictions [ALL]

- ❒ At least 18 years of age
  - *Safety and efficacy of lutetium Lu 177 dotatate have not been established in pediatric patients*
- ❒ For women of reproductive potential: confirm member is not pregnant or breastfeeding
  - *There are no available data regarding lutetium Lu 177 dotatate use in pregnant women. Radiopharmaceuticals can cause fetal harm; therefore, females of reproductive potential should use effective contraception during treatment with lutetium Lu 177 dotatate and for 7 months after the final dose. Males receiving lutetium Lu 177 who have female partners of reproductive potential should use effective contraception during treatment and for 4 months after the final dose.*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Member did not have prior treatment with the following: [ANY]
  - ❍ Another peptide receptor radionuclide therapy
  - ❍ External radiation therapy to more than 25% of the bone marrow
- ❒ Laboratory values confirming the range (labs must be dated within 30 days of request): [ALL]
  - ❍ Estimated creatinine clearance > 50 mL/min (Cockcroft Gault equation) or serum creatinine < 1.7 mg/dL
  - ❍ No severe hepatic impairment (defined as total bilirubin > 3x upper limit of normal and any AST)
  - ❍ Albumin > 3 g/dL
  - ❍ Hemoglobin > 8 g/dL
  - ❍ White blood cell count > 2,000/mm^3
  - ❍ Platelet count > 75,000/mm^3

- ❒ Disease progression during treatment with: [ONE]
    - ❍ Long-acting somatostatin analogs [e.g. Sandostatin LAR depot (octreotide acetate for injectable suspension)]
    - ❍ Somatostatin analogue therapy (octreotide or lanreotide) documented by either CT or MRI
        - *Informational Note: Unresectable, symptomatic disease usually involves initial therapy with a somatostatin analog (e.g. octreotide), and dose escalation as needed for control of symptoms of carcinoid syndrome and control of tumor growth. Patients with radiologic or symptom progression despite somatostatin analog therapy may benefit from noncurative debulking therapy or nonsurgical liver-directed therapy. Patients with more widespread disease that is not eligible for liver-directed therapy may benefit from systemic treatment with molecularly targeted agents, such as everolimus.*
- ❒ Long-acting somatostatin analogs [e.g. Sandostatin LAR depot (octreotide acetate for injectable suspension)] have been, or will be, **discontinued at least 4 weeks prior to initiation of treatment** with the requested agent, Lutathera

5. Contraindications*Exclusions/Discontinuations

**There are no contraindications listed in the manufacturer's labeling.*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to lutetium Lu 177 dotatate or any component of the formulation

Exclusions

- ❒ Requested dosing or frequency outside of the FDA-approved dosing and frequency
- ❒ Prior treatment with another peptide receptor radionuclide therapy
- ❒ Prior external radiation therapy to more than 25% of the bone marrow
- ❒ Lab results not within the following range: [ANY]
    - ❍ Estimated creatinine clearance > 50 mL/min (Cockcroft Gault equation) or serum creatinine < 1.7 mg/dL
    - ❍ No severe hepatic impairment (defined as total bilirubin > 3x upper limit of normal and any AST)
    - ❍ Albumin > 3 g/dL
    - ❍ Hemoglobin > 8 g/dL
    - ❍ White blood cell count > 2,000/mm^3
    - ❍ Platelet count > 75,000/mm^3

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

- ❒ Recommended dose is 7.4 gigabecquerel (GBq) [200 millicuries (mCi)] administered intravenously every 8 weeks for a total of 4 doses. Lutathera dosing may be modified based on adverse reactions.

- ❒ Administer pre- and concomitant medications as recommended.
  - Pre-medications include an amino acid infusion to prevent nephrotoxicity from radiation and antiemetics to reduce nausea from the amino acid infusion. Somatostatins may interfere with lutetium Lu 177 dotatate efficacy.
  - Prior to initiation, discontinue long-acting somatostatin analogs for at least 4 weeks prior to administration and administer short-acting octreotide as needed up to 24 hours prior to initiation

2. Authorization Limit [ALL]

- ❒ Quantity limit [ALL]

  - ❍ The prescribed regimen must be in compliance with FDA-approved dosing, with a dosing regimen of 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses

  - ❍ **One-time authorization of 4 doses (over a 12-month duration)**

- ❒ Duration of authorization: One-time authorization of 4 doses over **12 month duration.** Recommended duration is one dose every 8 weeks for a total of 4 doses which may be modified based on adverse reactions.

- ❒ Requests exceeding the above quantity limit: **NOT RECOMMENDED** however 'EXCEPTIONS' may be considered on an individual basis. Refer to 'EXCEPTIONS' section below.

EXCEPTIONS

A CASE-BY-CASE review by a Molina Medical Director may be considered in individual cases. ALL of the following criteria for re-treatment must be submitted with clinical documentation: [ALL]

- ❍ Progression experienced after a reasonable period of disease response or stability (generally defined as greater than 12 months). Documentation required. *UpToDate Recommendation*

  AND

- ❍ Member did not experience the following drug-related adverse event or toxicities: [ANY]
  - Moderate (or higher) in severity
  - Required an extensive treatment delay or treatment of toxicity

  AND

- ❍ **LIFETIME LIMIT: A total cumulative radiation dose of approximately 1600 mCi (eight courses of 200 mCi each** *UpToDate 2018*

3. Route of Administration [ALL]

- ❒ Lutathera (lutetium Lu 177 dotatate) is considered a **provider-administered** medication under the expertise and safety measures available in the nuclear medicine facility of an oncology center.

- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor or obtained by a specified route at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

This policy addresses the coverage of **Lutathera (lutetium Lu 177 dotatate)** for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults when appropriate criteria are met.

All other uses of Lutathera (lutetium Lu 177 dotatate) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF EVIDENCE

PIVOTAL TRIALS

The approval of lutetium Lu 177 dotatate was supported by two studies: NETTER-1 (phase III) and ERASMUS (phase I/II)

- **NETTER-1 Trial** was a randomized, pivotal phase III clinical trial in 229 patients with a certain type of advanced somatostatin receptor-positive GEP-NET. Patients in the trial either received Lutathera with octreotide or octreotide alone. Progression-free survival was longer for patients taking Lutathera with octreotide compared to patients who received octreotide alone. This means the risk of tumor growth or patient death was lower for patients who received Lutathera with octreotide compared to that of patients who received only octreotide. (Strosberg et al. 2017)
- **ERASMUS** was based on data from 1,214 patients with somatostatin receptor-positive tumors, including GEP-NETS, who received Lutathera at a single site in the Netherlands. Complete or partial tumor shrinkage was reported in 16 percent of a subset of 360 patients with GEP-NETs who were evaluated for response by the FDA. Patients initially enrolled in the study received Lutathera as part of an expanded access program. Expanded access is a way for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives to gain access to investigational drugs for treatment use.

NETTER-1 Trial (Strosberg J, et al. 2017)
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.

- Phase 3, randomized, open-label, multicenter study
- Patients either received Lutathera in combination with the drug octreotide or octreotide alone: *Lutetium Lu 177 Dotatate plus Best Supportive Care (Octreotide Long-Acting Repeatable [LAR]) vs. High-Dose Octreotide LAR*
- Subjects: 229 patients with well-differentiated, progressive, somatostatin receptor–positive midgut neuroendocrine tumors that had metastasized or were locally advanced and that were inoperable.
    - Disease progression had to have occurred during treatment with octreotide LAR (20 to 30 mg every 3 to 4 weeks for at least 12 weeks before randomization)
    - Patients were required to have a Karnofsky performance status score of at least 60 (on a scale from 0 to 100), a tumor with well-differentiated histologic features, and somatostatin receptors present on all target lesions.
- Key eligibility criteria include:
    - 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
- Exclusion criteria
    - Serum creatinine level greater than 1.7 mg/dL) or a creatinine clearance (CrCl) less than 50 mL/min;
    - Low hemoglobin level, white blood cell count, or platelet count; elevated total bilirubin level;
    - Serum albumin level more than 3 g/dL, unless prothrombin time value was within the normal range;
    - Treatment with more than 30 mg of octreotide LAR within 12 weeks before randomization;
    - Peptide receptor radionuclide therapy at any time before randomization; and
    - Any surgery, liver-directed transarterial therapy, or chemotherapy within 12 weeks before randomization

- Mean patient age: 63 years; equal distribution of males and females; mean body mass index was 25 kg/m^2; and median time since diagnosis was 3.8 to 4.8 years. At enrollment, the ileum was the primary tumor site (73% of patients), and most patients presented with metastases in the liver (83%), the lymph nodes (62%), or both. The 2 treatment groups were well balanced with respect to tumor grade (low-grade [grade 1] Ki67 proliferation index in 66% of patients in the lutetium Lu 177 dotatate group and in 72% in the control group) and with respect to highest uptake of tumor somatostatin radiotracer (high-grade [grade 4] uptake in 61% and 59%, respectively). The majority of patients had undergone previous surgery for their cancer (78% of the lutetium Lu 177 dotatate group and 82% of the control group). Systemic therapy other than somatostatin analog therapy had been used by 41% and 45%, respectively.

- Intervention
  - 229 patients were randomized (1:1) to receive *lutetium Lu 177 dotatate plus best supportive care, consisting of octreotide LAR 30 mg every 4 weeks for symptom control, or to receive high-dose octreotide LAR (60 mg) every 4 weeks (control group).
    *The dose of lutetium Lu 177 dotatate was 7.4 GBq (200 mCi) infused IV over a period of 30 minutes; patients received 4 infusions every 8 weeks (maximum total cumulative radioactivity, 29.6 GBq [800 mCi]) unless unacceptable toxicity, disease progression, or withdrawal occurred.
    *The lutetium Lu 177 dotatate patients also received an IV amino acid solution (*Aminosyn II 10%* [lysine 21 g and arginine 20.4 g in 2 L of solution] or *Vamin-18* [lysine 18 g and arginine 22.6 g in 2 L of solution]) administered concomitantly for at least 4 hours, starting 30 minutes before infusion of the radiopharmaceutical to decrease its renal toxicity. Approximately 24 hours after each lutetium Lu 177 dotatate infusion, an octreotide dose of 30 mg was administered intramuscularly (IM) and then monthly after completion of all 4 treatments. The control group received octreotide LAR 60 mg IM every 4 weeks. Both treatment groups were also allowed to receive subcutaneous rescue injections of octreotide in the event of hormonal symptoms (i.e., diarrhea, flushing) associated with their carcinoid syndrome.

  - Patients were stratified by highest tumor uptake score on somatostatin receptor scintigraphy, OctreoScan tumor uptake score (*Grade 2, 3 or 4)
    *Grade 2, 3, or 4 on a scale ranging from 0 [no uptake by tumor] to 4 [very intense uptake by tumor], with higher grades indicating a higher level of expression of somatostatin receptors) and according to length of time that a patient had been receiving a constant dose of octreotide (6 months or less or longer than 6 months).

RESULTS

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).

END POINT(S)

Pre-specified subgroup analysis for disease progression or death showed a consistent treatment benefit with lutetium Lu 177 dotatate irrespective of stratification factors and prognostic factors, which included levels of radiotracer uptake on somatostatin receptor scintigraphy, tumor grade, age, gender, and tumor marker levels.

Primary End Point(s)

- Estimated rate of progression-free survival (PFS), defined as the time from randomization to documented disease progression or death from any cause, at month 20 was 65.2% (95% confidence interval [CI], 50% to 76.8%) in the lutetium Lu 177 dotatate group and 10.8% (95% CI, 3.5% to 23%) in the control group
- Median PFS had not been reached in the lutetium Lu 177 dotatate group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group
- Hazard ratio (HR) for disease progression or death with lutetium Lu 177 versus control was 0.21 (95% CI, 0.13 to 0.33; $P<0.001$).

Secondary End Point(s)

- Objective tumor response was classified as "complete" in 1% of the lutetium Lu 177 dotatate group and 0% of the control group and as "partial" in 17% and 3%, respectively. The objective response rate (sum of partial responses and complete responses) was 18% (95% CI, 10% to 25%) and 3% (95% CI, 0% to 6%; *P*<0.001).
- At the interim analysis for overall survival, there were 14 deaths in the lutetium Lu 177 dotatate group and 26 deaths in the control group. The estimated risk of death was 60% lower in the lutetium Lu 177 dotatate group compared with the control group; HR for death was 0.4 (*P*=0.004). However, the investigator determined the data were not sufficiently mature to provide an estimate of the median overall survival in either treatment group.

SUMMARY

Analyses of efficacy, demographics, and baseline characteristics used the intention-to-treat cohort (n=229). The safety analysis included 221 patients who underwent randomization and received at least 1 dose of study treatment, including 111 patients in the lutetium Lu 177 dotatate group and 110 in the control group. The majority (77%) of patients in the lutetium Lu 177 dotatate group received the 4 scheduled infusions of lutetium Lu 177 dotatate; 8 patients required a reduction in lutetium Lu 177 dotatate dose. Adverse reactions were common in both groups and led to premature withdrawal from the study in 6% of the lutetium Lu 177 dotatate group and 9% of the control group.

ERASMUS

The FDA considered additional data from a single-center in the Netherlands, ERASMUS. All patients received Lutathera with octreotide. Patients and health care providers knew which treatment was given. The benefit of Lutathera was evaluated by measuring if and how much the tumor size changed during treatment (the overall response rat*e).*

- An international, single-institution, single-arm, open-label trial
- A total of 1214 patients received lutetium Lu 177 dotatate, of which 601 (50%) were assessed per RECIST criteria. Of the 601 patients evaluated by investigators using RECIST criteria, 360 (60%) had gastroenteropancreatic neuroendocrine tumors (GEP-NETs).
- Lutetium Lu 177 dotatate 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 lutetium Lu 177 dotatate 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).

CLINICAL PRACTICE GUIDELINES

European Neuroendocrine Tumor Society (ENETS): Consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas (2016)

- Chemotherapy (e.g., cisplatin plus etoposide, carboplatin plus irinotecan) is the starting point for a multimodality approach to localized neuroendocrine carcinomas and the mainstay of care in advanced disease.
- The purpose of these guidelines is to assist physicians caring for patients with neuroendocrine neoplasia in considering eligibility criteria for peptide receptor radionuclide therapy (PRRT) and in defining the minimum requirements for PRRT.
- The guidelines discuss the randomized controlled trial, NETTER-1 and makes recommendations on what minimal patient, tumor, and treatment outcome characteristics should be reported for PRRT to facilitate robust comparisons between studies.
- These guidelines do not give recommendations on the use of specific radiolabeled somatostatin analogues for PRRT as different analogues are being used, and their availability is governed by varying international regulations.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)
Neuroendocrine and Adrenal Tumors Version 2.2018: Principles of Peptide Receptor Radionuclide Therapy (PRRT) with Lu-Dotatate

Lutetium Lu 177 Dotatate (Lu-Dotatate) is a radiolabeled somatostatin analog used as PRRT (peptide receptor radionuclide therapy). It is approved by the FDA for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (NET) including foregut, midgut, and hindgut NET in adults.

Key Eligibility
- Low or intermediate grade NET (Ki-67 < 20%)
- Somatostatin receptor expression of NET as detected by somatostatin receptor based imaging (i.e. Ga-dotatate PET/CT preferred or somatostatin receptor scintigraphy)
- Adequate bone marrow, renal and hepatic function

Timing of Somatostatin Analogs (SSAs) (Octreotide or Lanreotide) in relation to Lu-Dotatate
- Most patients treated with PRRT will have progressed on a first-line SSA
- Generally, patients with hormonally functional tumors should continue octreotide or lanreotide along Lu-dotatate. It is unclear whether patients with nonfunctional tumors benefit from continuation of SSA treatment during and after Lu-dotatae treatment.
- There are theorectical concerns regarding the competition between SSAs and Lu-dotatate for somatostatin receptor binding. Therefore, the following is recommended:
    - Do not administer long-acting SSAs for 4-6 weeks prior to each Lu-dotatate treatment
    - Stop short-acting SSAs 24 hours before each Lu-dotatate treatment
    - SSAs (short and long-acting) can be resumed 4-24 hours after each Lu-dotatate treatment

HAYES
At the time of this writing in July 2018, a Hayes Directory report addressing the place of 'Lutathera (lutetium Lu 177 dotatate)' therapy is not available.

DEFINITIONS

Neuroendocrine tumor (NET): A tumor that forms from cells that release hormones into the blood in response to a signal from the nervous system. NETs may make higher-than-normal amounts of hormones, which can cause many different symptoms. These tumors may be benign (not cancerous) or malignant (cancerous) (NCI, 2018).

APPENDIX

Appendix 1: Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which have been referred to as carcinoid tumors or pancreatic islet cell tumors, are generally indolent, however, all are potentially malignant, and the clinical course may be highly variable. Symptomatic disease may be due to either tumor bulk, including pain and/or bowel obstruction, or due to secretion of serotonin and other vasoactive substances, sometimes referred to as carcinoid syndrome.

- Well-differentiated neuroendocrine tumors include low-grade (G1) and intermediate-grade (G2) tumors, which correlate with a defined Ki-67 proliferation index, as determined by an immunohistochemical stain.

- Well-differentiated, low grade neuroendocrine tumors have a Ki-67 index of <3%, and well-differentiated, intermediate-grade neuroendocrine tumors have a Ki-67 index of 3-20%.

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
NA	

HCPCS	Description
A9699	Radiopharmaceutical, therapeutic, not otherwise classified
C9031	Lutetium Lu 177, dotatate, therapeutic, 1 mCi [Lutathera] (Note: code effective 07/01/2018)
J3590	Unclassified biologics
J9999	Not otherwise classified, antineoplastic drugs

*CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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Policy History	Approval
Policy Developed *Peer Review: AMR Peer Review Network. 2/5/2018. Practicing Physician. Board certified in Neurology, Sleep Medicine*	MCPC 9/13/2018
Annual Review* No coverage criteria changes or notable revisions with this annual reviewP&T	P&T Q2 2020

**Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy revised/updated as appropriate.*