Coverage policy

AmeriHealth Caritas considers the use of peptide receptor radionuclide therapy (PRRT) with lutetium Lu 177 dotatate (Lutathera®, Advanced Accelerator Applications USA, Inc.) to be clinically proven and, therefore, medically necessary when the following criteria are met (NETTER-1 2018, Dannoon 2017, Singh 2016, Papamichail 2016, Kim 2015, Bodei 2013, Kam 2012, Gulenchyn 2012):

- When prescribed as treatment of inoperable or metastasized somatostatin receptor-positive gastro-enteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors (NETs) in adults.

Limitations:

All other uses of peptide receptor radionuclide therapy with lutetium Lu 177 dotatate are not medically necessary and are considered investigational.
Alternative covered services:

Routine patient evaluation and management by a network healthcare provider.

Background

Neuroendocrine tumors are a heterogeneous group of neoplasms with a common embryological origin and diverse biological behavior, derived from the neuroendocrine system, specifically from the amine precursor uptake and decarboxylation (APUD) cells. They are characterized by overexpression of all five somatostatin receptors (SSTR1-SSTR5), particularly type 2 (SST2).

Treatment with radiolabelled somatostatin analogues is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. Surgical resection of the tumor is the treatment option, with a possibility of complete remission in patients with limited disease. Somatostatin analogs (octreotide and lanreotide) are the treatment of choice in patients with residual disease, particularly when it comes to neuroendocrine tumors non-pancreatic origin. Systemic chemotherapy is administered primarily to patients with poorly differentiated carcinomas. Peptide receptor radionuclide therapy (PRRT) treatment is recommended in case of non-responsiveness of the disease. The ideal candidates for PRRT are patients with unresectable disease of high and intermediate differentiation.

On January 26, 2018, the Food and Drug Administration (FDA) approved lutetium Lu 177 dotatate (Lutathera®, Advanced Accelerator Applications USA, Inc.) a radiolabeled somatostatin analog, for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. The recommended dose of lutetium Lu 177 dotatate is 7.4 GBq (200 mCi) as an intravenous infusion over 30 minutes every 8 weeks for a total of 4 doses.

Searches

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on April 3, 2018. Search terms were: “somatostatin analog,” “neuroendocrine tumors,” and “peptide receptor radionuclide therapy.”

We included:

- Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use
predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- Guidelines based on systematic reviews.
- Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A multicenter, open-label, active-controlled trial (NETTER-1 2018) in 229 patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumors randomized patients to receive either lutetium Lu 177 dotatate (7.4 GBq [200 mCi] every 8 weeks for up to 4 administrations; maximum cumulative dose of 29.6 GBq) with long-acting octreotide (30 mg by intramuscular injection every 4 weeks) or high-dose long-acting octreotide (60 mg by intramuscular injection every 4 weeks). The major outcome measure was progression free survival (PFS). The median progression free survival was not reached for lutetium Lu 177 dotatate and was 8.5 months in the high-dose long-acting octreotide arm (p<0.0001). The most common grade 3-4 adverse reactions occurring with a greater frequency among patients receiving lutetium Lu 177 dotatate with long-acting octreotide compared to patients receiving high-dose octreotide alone included lymphopenia (44 percent), increased gamma glutamyl transferase (20 percent), vomiting (7 percent), nausea and elevated transaminases, hyperglycemia, and hypokalemia (4 percent each). In NETTER-1, with a median follow-up of 24 months, myelodysplastic syndrome was reported in 2.7 percent of patients receiving lutetium Lu 177 dotatate with long-acting octreotide; no patients receiving high-dose octreotide developed myelodysplastic syndrome.

Dosimetry studies (Kam 2012) with lutetium Lu 177 dotatate as well as the limited side effects with additional cycles of 177Lu-dotatate suggest that more cycles lutetium Lu 177 dotatate can be safely given. Also, if kidney-protective agents are used, the side effects of this therapy are few and mild and less than those from the use of 90Y-[DOTA0,Tyr3]octreotide (dotatoc). Besides objective tumor responses, the median progression-free survival is more than 40 months. The patients' self-assessed quality of life increased significantly after treatment with lutetium Lu 177 dotatate. Lastly, compared to historical controls, there is a benefit in overall survival of several years from the time of diagnosis in patients treated with lutetium Lu 177 dotatate. These findings compare favorably with the limited number of alternative therapeutic approaches. Symptomatic improvement may also occur with 177Lu-labelled somatostatin analogues that have been used for peptide receptor radionuclide therapy.

A meta-analysis (Dannoon 2017) studied the efficacy of peptide receptor radionuclide therapy for neuroendocrine tumors. Lutetium Lu 177 dotatate peptide receptor radionuclide therapy response rates ranged from 27.63 to 57.35 percent, with a pooled random effect of 33.41 percent, and disease control rates ranged between 71.88 and 100 percent, with a pooled fixed effect of 79.32 percent. As for tandem- peptide receptor radionuclide therapy, disease response rates ranged between 42.11 and
66.67 percent, with a pooled fixed effect of 50.52 percent, and the disease control rate ranged between 93.33 and 100 percent, with a pooled fixed effect of 98.97 percent.

A consortium of sixteen Canadian medical centers (Singh 2016) issued consensus recommendations on neuroendocrine tumors originating in the digestive system. The group opined that well-differentiated gastro-enteropancreatic neuroendocrine tumors may exhibit indolent clinical behavior and are often metastatic at diagnosis. Some neuroendocrine tumors patients will develop secretory disease requiring symptom control to optimize quality of life and clinical outcomes. Optimal management of gastro-enteropancreatic neuroendocrine tumors is in a multidisciplinary environment and is multimodal, requiring collaboration between medical, surgical, imaging and pathology specialties. Clinical application of advances in pathological classification and diagnostic technologies, along with evolving surgical, radiotherapeutic and medical therapies are critical to the advancement of patient care.

A narrative review (Papamichail 2016) noted that somatostatin analogs radiolabelled with Indium In-111, Yttrium Y-90, Lutetium Lu-177 and Bismuth Bi-213 are selectively concentrated in tumor cells, causing maximum tissue damage to tumors and with fewer effects on healthy tissue and the immune system. The authors posited that patients with unresectable grade 1 or 2 disease showed increased progression free survival (PFS) and overall survival (OS), while quality of life was improved after peptide receptor radionuclide therapy treatment as compared to somatostatin analogs, chemotherapy and other targeted therapies.

A meta-analysis (Kim 2015) evaluated the efficacy of Lutetium Lu-177 labelled peptide receptor radionuclide therapy in patients with inoperable or metastatic gastro-enteropancreatic tumors. Disease response rates ranged between 17.6 and 43.8 percent with a pooled effect of 29 percent. Disease control rates ranged from 71.8 to 100 percent. The random-effects model showed an average disease control rate of 81 percent. The second study group demonstrated disease response rates ranging between 7.0 and 36.5 percent with a pooled effect of 23 percent. Disease control rates ranged from 73.9 to 89.1 percent. The random-effects model showed an average disease control rate of 82 percent.

Bodei (2013) noted that the accumulated medical evidence from clinical experience indicates that these tumors can be subjected to a high absorbed dose which leads to partial or complete objective responses in up to 30 percent of treated patients. Survival analyses indicate that patients presenting with high tumor receptor expression at study entry and receiving Yttrium Y-90 or Lutetium Lu-177 dotatate treatment show significantly higher objective responses, leading to longer survival and improved quality of life. Side effects of peptide receptor radionuclide therapy are typically seen in the kidneys and bone marrow. These, however, are usually mild provided adequate protective measures are undertaken.

A systematic review (Gulenchyn 2012) investigated the effects of therapeutic radiopharmaceuticals in patients with different types of advanced neuroendocrine tumors. Limited evidence from a historical comparison of studies supported that Lutetium Lu-177 dotatate might be associated with better clinical outcomes. The severe toxicities for Lutetium Lu-177 dotatate included hepatic insufficiency in 0.6 percent, myelodysplastic syndrome in 0.8 percent and renal insufficiency in 0.4 percent. The authors
concluded that peptide receptor radionuclide therapy seems to be an acceptable option and is relatively safe in adult advanced neuroendocrine tumor neuroendocrine tumors patients with receptor uptake positive on scintigraphy, but patients' renal function must be monitored.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>NETTER-1 (2018)</td>
<td>Key points:</td>
</tr>
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<td>• Enrollees were randomized to receive either lutetium Lu 177 dotatate (7.4 GBq [200 mCi] every 8 weeks for up to 4 administrations; maximum cumulative dose of 29.6 GBq) with long-acting octreotide (30 mg by intramuscular injection every 4 weeks) or high-dose long-acting octreotide (60 mg by intramuscular injection every 4 weeks).</td>
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<td>• The major outcome measure was PFS. The median PFS was not reached for lutetium Lu 177 dotatate and was 8.5 months in the high-dose long-acting octreotide arm (hazard ratio 0.21; 95 % CI: 0.13, 0.32; p&lt;0.0001).</td>
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<td>• The most common grade 3-4 adverse reactions occurring with a greater frequency among patients receiving lutetium Lu 177 dotatate with long-acting octreotide compared to patients receiving high-dose octreotide alone included lymphopenia (44 %), increased gamma glutamyl transferase (20 %), vomiting (7 %), nausea and elevated AST (5 % each), and increased ALT, hyperglycemia, and hypokalemia (4 % each).</td>
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| Papamichail (2016)  
Neuroendocrine tumors: Peptide receptors radionuclide therapy (PRRT) | **Key points:**  
- A narrative review noted that somatostatin analogs radiolabelled with Indium In - 111, Yttrium Y-90, Lutetium Lu-177 and Bismuth Bi-213 are selectively concentrated in tumor cells, causing maximum tissue damage to tumors and with fewer effects on healthy tissue and the immune system.  
- The authors posited that patients with unresectable grade 1 or 2 disease showed increased PFS and overall survival (OS), while quality of life was improved after PRRT treatment as compared to somatostatin analogs, chemotherapy and other targeted therapies. |
| Kim (2015)  
The efficacy of (177)Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis. | **Key points:**  
- A meta-analysis evaluated the efficacy of Lutetium Lu-177 labelled PRRT in patients with inoperable or metastatic NETs.  
- Disease response rates ranged between 17.6 and 43.8 % with a pooled effect of 29 % [95 % confidence interval (CI) 24-34 %].  
- Disease control rates ranged from 71.8 to 100 %.  
- The random-effects model showed an average disease control rate of 81 percent (95 % CI 71-91%).  
- The second study group demonstrated disease response rates ranging between 7.0 and 36.5 percent with a pooled effect of 23 % (95 % CI 11-38 %).  
- Disease control rates ranged from 73.9 to 89.1 %. The random-effects model showed an average disease control rate of 82 % (95 % CI 71-91 %). |
| Bodei (2013)  
The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. | **Key points:**  
- Bodei (2013) noted that the accumulated medical evidence from clinical experience indicates that these tumors can be subjected to a high absorbed dose which leads to partial or complete objective responses in up to 30 % of treated patients.  
- Survival analyses indicate that patients presenting with high tumor receptor expression at study entry and receiving Yttrium Y-90 or Lutetium Lu-177 dotatate treatment show significantly higher objective responses, leading to longer survival and improved quality of life.  
- Side effects of PRRNT are typically seen in the kidneys and bone marrow. These, however, are usually mild provided adequate protective measures are undertaken. |
| Kam (2012)  
Lutetium-labelled peptides for therapy of neuroendocrine tumours | **Key points:**  
- Dosimetry studies with lutetium Lu 177 dotatate as well as the limited side effects with additional cycles of 177Lu-dotatate suggest that more cycles lutetium Lu 177
dotatate can be safely given.

- Also, if kidney-protective agents are used, the side effects of this therapy are few and mild and less than those from the use of 90Y-[DOTA0,Tyr3]octreotide (dotatoc).
- Besides objective tumor responses, the median progression-free survival is more than 40 months.
- The patients' self-assessed quality of life increased significantly after treatment with lutetium Lu 177 dotatate.
- Lastly, compared to historical controls, there is a benefit in overall survival of several years from the time of diagnosis in patients treated with lutetium Lu 177 dotatate.
- These findings compare favorably with the limited number of alternative therapeutic approaches.
- Symptomatic improvement may also occur with 177Lu-labelled somatostatin analogues that have been used for PRRT.

Gulenchyn (2012)

Radionuclide therapy in neuroendocrine tumours: a systematic review

Key points:

- A systematic review investigated the effects of therapeutic radiopharmaceuticals in patients with different types of advanced NETs.
- Limited evidence from a historical comparison of studies supported that Lutetium Lu-177 dotatate might be associated with better clinical outcomes.
- The severe toxicities for Lutetium Lu-177 dotatate included hepatic insufficiency in 0.6 %, myelodysplastic syndrome in 0.8 % and renal insufficiency in 0.4 %.
- The authors concluded that PPRT seems to be an acceptable option and is relatively safe in adult advanced NET patients with receptor uptake positive on scintigraphy, but patients' renal function must be monitored.

References

Professional society guidelines/other:

FDA approves lutetium Lu 177 dotatate for treatment of GEP-NETS. FDA website: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm594105.htm

A Study Comparing Treatment With 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours (NETTER-1). Clinical Trials website: https://clinicaltrials.gov/ct2/show/NCT01578239

Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.
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<td>A9504</td>
<td>Technetium Tc-99m apcitide, diagnostic, per study dose, up to 20 millicuries</td>
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**Appendix A**

PerformRx


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No PerformRx policy identified as of the writing of this policy.