

MEDICAL POLICY



SUBJECT: PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)	EFFECTIVE DATE: 06/21/07
POLICY NUMBER: 7.01.78	REVISED DATE: 05/14/08, 04/16/09, 03/18/10, 03/17/11, 03/15/12, 02/21/13, 02/20/14, 02/19/15, 01/21/16, 01/19/17, 01/18/18, 08/14/18
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- *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*
- *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.*
- *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT:

- I. Based upon our criteria and assessment of peer-reviewed literature, peptide receptor radionuclide therapy using Lutathera (lutetium or Lu 177 dotatate) has been medically proven to be effective and is considered medically appropriate for the treatment of the following:
 - A. Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETS) of the foregut, midgut and hindgut in adults that are either inoperable or metastatic; or
 - B. Somatostatin receptor positive tumors of the pancreas that are either inoperable or metastatic.
- II. Based upon our criteria and assessment of peer-reviewed literature, peptide receptor radionuclide therapy has not been proven to medically effective and is considered **investigational** for all other indications.

Refer to Corporate Medical Policy # 7.01.69 regarding Selective Internal Radiation Therapy (SIRT).

Refer to Corporate Medical Policy # 11.01.03 regarding Experimental and Investigational Services.

Refer to Corporate Medical Policy # 11.01.10 regarding Clinical Trials.

POLICY GUIDELINES:

- I. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.
- II. Requirements for Lutathera therapy include all of the following:
 - A. Official pathology report documenting a neuroendocrine tumor of the foregut, midgut, hindgut or pancreas with Ki67 index less than 20%;
 - B. Positive somatostatin receptor scintigraphy with correlative MRI or CT imaging of metastatic measurable disease or 68-Ga-Dotate PET scan positive for metastatic disease;
 - C. In the absence of metastatic disease, a surgical or medical consult documenting the reason for inoperability; and
 - D. Completed Lutetium-177 (Lutathera) Worksheet.
- III. Contraindications of Lutathera include:
 - A. Serum creatinine: 1.7 mg per deciliter or creatinine clearance of 50 ml/minute;
 - B. Hgb: 8.0 g/dl; WBC less than 2000/mm³; platelets less than 75,000 mm³; and
 - C. Total bilirubin greater than 3 x upper limit of normal.
- IV. The current recommended dose of Lutathera is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses.

DESCRIPTION:

Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via an interaction with G-protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Five somatostatin receptors have been identified and characterized with each of the receptors activating distinct signaling mechanisms within cells. Analogs of somatostatin have been synthesized that are smaller,

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more potent, longer-lasting and more specific in their biologic effects than natural somatostatin. Examples of these analogs include octreotide, lanreotide and vapreotide. Some of these analogs have become useful as medications for the treatment of acromegly, or the treatment of diarrhea and flushing episodes associated with carcinoid syndrome.

Many types of neuroendocrine tumors express somatostatin receptors including, but not limited to, pancreatic islet cell tumors (e.g., gastrinomas, glucagonomas, GHRHomas, and nonfunctioning islet cell tumors), VIPomas, carcinoids, insulinomas, and some adrenal cortical and differentiated thyroid tumors. Somatostatin receptor (SSTR) scintigraphy has become an important image modality in patients with SSTR-positive tumors. SSTR scintigraphy involves the administration of a radiolabeled peptide tracer, which is targeted at the somatostatin receptor. A more intensified, targeted radiotherapy, known as peptide receptor radionuclide therapy (PRRT), has been proposed and investigated for those patients with inoperable or metastasized neuroendocrine tumors who suffer from debilitating symptoms, such as carcinoid syndrome.

Several radiolabeled somatostatin analogs are currently being investigated in the treatment of patients with SSTR-positive metastasized neuroendocrine tumors. These conjugates all consist of a somatostatin analog, such as octreotide or octreotate, a complexing moiety (or chelator) and a radionuclide. The chelator, which is attached to the somatostatin analog, allows a stable connection between the analog and the radionuclide. The basic principle of tumor-targeting after systemic administration of the conjugate involves binding to SSTRs, which are expressed on the cell surface of the tumor cell, followed by effective internalization of the radionuclide-peptide complex. The emitted radiation can damage the DNA, which may subsequently lead to the induction of cell death. Different combinations of radionuclides and somatostatin analogues are used to target the specific SSTR-positive tumor. These analogues differ from each other in their affinity for the various five SSTR subtypes. This variable affinity is important because it can have great influence on the clinical effectiveness of the radiolabeled somatostatin analog. Indium (111In), yttrium (90Y) and lutetium (177Lu) have been the most frequently used radionuclides for targeted radiotherapy in the various clinical trials thus far.

RATIONALE:

Advanced Accelerator Applications (AAA), located in France, received FDA approval in late January 2018 for Lutetium Lu 177 Dotatate (Lutathera®). Lutathera is approved for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors, in adults. Lutathera, which 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 treatment comprising of a targeting molecule that carries a radioactive component. Currently, there are no other radiolabeled somatostatin analog conjugates that are FDA approved specifically for use in PRRT.

The FDA approval for the use of Lutathera is based on the results of two published studies. NETTER 1 compared treatment with Lutathera to octreotide in patients with inoperable, progressive somatostatin receptor-positive midgut carcinoid tumors. Eligibility included a Ki67 index of 20% or lower, OctreoScan uptake greater than or equal to that of the normal liver, creatinine clearance of 50 mL/min or greater, no prior treatment with Peptide Receptor Radionuclide Therapy (PRRT), and no prior external radiation therapy to more than 25% of the bone marrow. The primary outcome was progression free survival (PFS). A total of 229 patients were randomized to Lutathera 200 mCi for four infusions every 8 weeks concurrently with long-acting octreotide (30 mg) or high-dose octreotide alone (60 mg). Baseline characteristics were balanced between the groups. It was noted that 74% of patients had an ileal primary and 96% had metastatic disease in the liver.

At the data-cutoff date for the primary analysis, PFS at 20 months was 65.2% in the 177-Lu arm vs 10.8% in the control group. The response rate was 18% in the 177-Lu group vs 3% in the control group. In an updated analysis, progressive disease was seen in 23% of the 177-Lu group and 69% of the control group. Median progression free survival was not reached for the experimental group and was 8.5 months for the control group. Median overall survival was also not reached in the experimental group but was 27.4 months in the control arm.

The ERASMUS study included 1214 patients who received Lutathera, 610 of whom were treated with a cumulative dose of at least 100 mCi for safety analysis. Another subgroup of 443 Dutch patients were treated with a cumulative dose of at least 600 mCi. The objective response rate (ORR) of the combined group was 39%. Stable

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disease was seen in 43%. Progression free survival was 29 months. Overall survival was 63 months. The group included not only gastrointestinal tumors but also pancreatic and bronchial neuroendocrine tumors. Toxicity included acute leukemia in 0.7% and myelodysplastic syndrome in 1.5%.

Clinical studies investigating neuroendocrine tumors, in particular, those treated with other ~~90Y~~ and ~~177Lu~~ labelled somatostatin analogues, are very encouraging in terms of tumor shrinkage and palliation of symptoms. However, complete responses are unusual and there have been no demonstrated improvements in survival. Differences in treatment protocols, such as administered doses, dosing schemes, the tumor response criteria, and the heterogeneity of the patient sample population in the various studies have made it impossible to come to any definitive conclusions regarding the overall health benefit of this therapy. Therefore, trials with better defined protocols and patient populations are necessary to determine the optimal PRRT and treatment scheme.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

*** No specific codes exist for PRRT, but the following codes could be billed:**

CPT:

78800	Radiopharmaceutical localization of tumor, or distribution of radiopharmaceutical agent(s); limited area
78801	multiple areas
78802	whole body, single day imaging
78803	tomographic (SPECT)
78804	whole body, requiring two or more days imaging

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HCPCS:

A4641	Radiopharmaceutical, diagnostic, not otherwise classified
A9699	Radiopharmaceutical, therapeutic, not otherwise classified
C9031	Lutetium Lu 177, dotatate, therapeutic, 1 mCi
J2354	Injection, octreotide, nondepot form for subcutaneous or intravenous injection, 25 mcg

ICD10: Multiple diagnosis codes

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* key article

KEY WORDS:

Lutathera, Peptide receptor radionuclide therapy, PRRT, PRRNT, Receptor-mediated radiotherapy, Radiolabeled nuclide therapy, somatostatin analog, ⁹⁰Y-DOTATOC, ¹⁷⁷Lu-DOTA0,Tyr3, ⁹⁰Y-DOTA0,Tyr3

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based on our review, peptide receptor radionuclide therapy is not specifically mentioned in any National or Regional Medicare coverage determinations or policies.