

Corporate Medical Policy

Therapeutic Radiopharmaceuticals in Oncology

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Description of Procedure or Service

Radiopharmaceuticals, also known as radionuclides, are composed of a radioisotope coupled to an organic molecule and are used for diagnostic and therapeutic purposes. The organic molecule targets the radioisotope to specific organs, tissues, or cells. Examples of radionuclides include peptide receptor radioligand therapy and metaiodobenzylguanidine (MIBG).

The peptide receptor radioligand therapy lutetium 177 (Lu 177) dotatate (Lutathera[®]) is a radiolabeled-somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults.

MIBG which is structurally similar to noradrenaline, is attached to radioactive iodine (I¹³¹) to produce ¹³¹I-MIBG. ¹³¹I-MIBG comes in a conventional form and a high-specific activity (HSA) form, the latter of which contains minimal amounts of unlabeled drug, and is known as iobenguane I 131 (Azedra[®]). Azedra is indicated for the treatment of iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma in adult and pediatric patients 12 years and older who require systemic anticancer treatment.

Gastroenteropancreatic Neuroendocrine Tumors

Neuroendocrine cells are widely distributed throughout the body, and tumors arising from these cells can occur in most organs. In the digestive system, including the tubular gastrointestinal tract and the pancreas, neuroendocrine tumors are generally divided into two major categories, well-differentiated neuroendocrine tumors (NETs) and poorly differentiated (high-grade) neuroendocrine carcinomas. These two major categories of neuroendocrine tumors behave differently in terms of biologic aggressiveness and in approach to treatment.

Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which have been referred to as carcinoid tumors or pancreatic islet cell tumors, are generally indolent, but 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.

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. 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

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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.

Lutetium 177 (Lu 177) dotatate (Lutathera[®]) is a targeted form of systemic radiotherapy that binds to cell surface somatostatin receptors, and once internalized, induces cellular damage by free radical formation. Most GEP-NETs express high-affinity receptors for somatostatin, and somatostatin-based imaging can provide information on tumor burden and location. Lutetium 177 (Lu 177) dotatate has been proposed as a treatment option in patients with GEP-NETs who progress despite first-line therapy.

Pheochromocytoma/Paraganglioma

Pheochromocytomas are rare catecholamine-secreting neuroendocrine tumors that are derived from chromaffin cells of the adrenal medulla in most cases. Presenting less frequently, ectopic or extra-adrenal pheochromocytomas that originate from para-aortic sympathetic ganglia are termed paragangliomas. However, both tumors are similar in clinical presentation and treatment approach and are often referred to collectively as PPGL (pheochromocytoma and paraganglioma). These tumors release catecholamines and associated norepinephrine metabolites, which result in hypertension, arrhythmia, and/or hyperglycemia, and occur in less than 0.2% of patients with hypertension. Other symptoms, which are often paroxysmal in presentation, include headaches, sweating, tachycardia, chest pain, nausea, vomiting, and anxiety.

Standard initial treatment of PPGL following diagnosis is surgical resection combined with pharmacological blood pressure control. Locally unresectable tumors and distant metastases are instead treated with radiation therapy and cytoreductive resection when possible, iobenguane I 131 therapy in iobenguane scan positive tumors, or systemic chemotherapy. In patients with distant metastases, curative surgery is not a treatment option and the five-year survival rate is approximately 12 percent. The goals of treatment for metastatic, recurrent, or unresectable disease are thus aimed at reducing symptoms and controlling tumor progression. Prior to the approval of iobenguane I 131 (Azedra[®]), there have been no FDA-approved treatments for metastatic, recurrent, or unresectable PPGL. Standard non-approved treatment options have included chemotherapy (e.g. cyclophosphamide, vincristine, and dacarbazine [CVD]) and conventional, low-specific-activity I 131 at high doses.

Lutetium 177 (Lu 177) dotatate and iobenguane I 131 are given by intravenous infusion. They are radiopharmaceuticals and must be handled with appropriate safety measures to minimize radiation exposure.

Related Policies:

Somatostatin Analogs

Radioembolization for Primary and Metastatic Tumors of the Liver

Cryosurgical Ablation of Primary and Metastatic Liver Tumors

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for lutetium 177 (Lu 177) dotatate (Lutathera[®]) and iobenguane I 131 (Azedra[®]) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Therapeutic Radiopharmaceuticals are covered

Lutetium 177 (Lu 177) dotatate (Lutathera) is considered medically necessary for the treatment of adult patients with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) or bronchopulmonary or thymus neuroendocrine tumors when the following criteria are met:

- The patient has unresectable, locally advanced or metastatic disease, **AND**
- The patient has had disease progression despite somatostatin analog therapy or molecularly targeted therapy (e.g. everolimus), **AND**
- An appropriate imaging study has been performed to document over-expression of somatostatin receptors by the target lesions, **AND**
- The tumor is well-differentiated with a Ki-67 index of 20% or less, as documented in a pathology report. (see Policy Guidelines)

High-specific activity (HSA) iobenguane I 131 (Azedra) is considered medically necessary for the treatment of adult and pediatric (age 12 years or older) patients with pheochromocytoma or paraganglioma when the following criteria are met:

- The patient has unresectable, locally advanced or metastatic disease, **AND**
- The patient has tried and failed, is unable to tolerate, or is not a candidate for prior systemic therapy for pheochromocytoma/paraganglioma, **AND**
- An appropriate imaging study has been performed to document that the tumor is MIBG-avid, **AND**
- For patients with pheochromocytoma-related hypertension, the patient has been on a stable antihypertensive medication for at least 30 days prior to therapy initiation.

When Therapeutic Radiopharmaceuticals are not covered

Lutetium 177 (Lu 177) dotatate (Lutathera) is considered **investigational** and therefore not covered when the above criteria are not met, including for the treatment of pheochromocytomas and paragangliomas.

HSA iobenguane I 131 (Azedra) is considered **investigational** and therefore not covered when the above criteria are not met.

Treatment with lutetium 177 (Lu 177) dotatate greater than a total of 4 doses as per the Food and Drug Administration (FDA)-approved regimen and treatment with HSA iobenguane I 131 greater than a total of 2 therapeutic doses as per the FDA-approved regimen are considered **investigational**.

Retreatment with lutetium 177 (Lu 177) dotatate or HSA iobenguane I 131 is considered **investigational**.

Policy Guidelines

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

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

GEP-NETs include those arising from the foregut (gastroduodenal), midgut (distal small intestine and proximal colon), hindgut (distal colorectal) and pancreas.

Lutetium 177 (Lu 177) dotatate (Lutathera)

The recommended Lutathera dosage is 7.4 GBq (200 mCi) administered intravenously every 8 weeks for a total of 4 doses. Lutathera dosing may be modified based on adverse reactions.

Before initiating Lutathera, discontinue any long-acting somatostatin analogs for at least 4 weeks and short-acting octreotide at least 24 hours prior to each Lutathera dose. During Lutathera treatment, administer long-acting octreotide 30 mg intramuscularly 4 to 24 hours after each Lutathera dose and short-acting octreotide for symptomatic management. Do not administer long-acting octreotide within 4 weeks of each subsequent Lutathera dose and withhold short-acting octreotide for at least 24 hours before each Lutathera dose. Following Lutathera treatment, continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing Lutathera until disease progression or for up to 18 months following treatment initiation.

Pre-medicate with antiemetics 30 minutes before recommended amino acid solution. Initiate recommended intravenous amino acid solution 30 minutes before Lutathera infusion; continue during and for 3 hours after Lutathera infusion.

According to the manufacturer's safety information, Lutathera must be handled with appropriate safety measures to minimize radiation exposure, and pregnancy status in females of reproductive potential should be verified prior to initiating Lutathera. Other warnings and precautions for Lutathera listed within the prescribing information include: myelosuppression, secondary myelodysplastic syndrome (MDS) and leukemia, renal toxicity, hepatotoxicity, neuroendocrine hormonal crisis, embryo-fetal toxicity, and infertility risk.

In January 2018, the U.S. Food and Drug Administration approved Lutathera (lutetium Lu 177 dotatate) for the treatment of somatostatin receptor-positive GEP-NETs in adults, largely based on support from the NETTER-1 trial. This phase 3, open-label, randomized, multicenter clinical trial included 229 patients with advanced, progressive, well-differentiated midgut neuroendocrine tumors. Patients received either ¹⁷⁷Lu-Dotatate every 8 weeks for up to 4 infusions plus best supportive care including octreotide (n=116) or high-dose octreotide alone (n=113). The majority of patients in the ¹⁷⁷Lu-Dotatate group (77%) received all four infusions of ¹⁷⁷Lu-Dotatate. The treatment groups were well balanced in terms of clinical characteristics and tumor grade, with 83% of patients having metastatic disease to the liver. The ileum was the primary tumor site in 73% of patients. The primary end point was progression-free survival (PFS), which, at 20 months, was 65.2% (95% confidence interval [CI], 50.0-76.8) in the ¹⁷⁷Lu-Dotatate group versus 10.8% (95% CI, 3.5-23.0) in the control group. Median PFS was 8.4 months in the control group and not reached in the ¹⁷⁷Lu-Dotatate group (p<0.001). Secondary end points included objective tumor response rate, which was 18% in the ¹⁷⁷Lu-Dotatate group and 3% in the control group (p<0.001). The rates of grade 3 and 4 adverse events were similar between the groups; however, grade 3 or 4 neutropenia, thrombocytopenia and lymphopenia were reported in 1%, 2%, and 9% of patients, respectively, in the ¹⁷⁷Lu-Dotatate group versus none of control group patients.

Long-term safety and survival were evaluated in an investigator-sponsored, open-label, single-arm, single-institution (Erasmus) retrospective study of over 1200 patients with somatostatin receptor positive neuroendocrine tumors who received ¹⁷⁷Lu-Dotatate treatment. Primary tumor sites included bronchus, foregut, midgut, hindgut, pancreas and unknown. Patient populations were heterogeneous for baseline tumor status (progressive versus nonprogressive) and treatments received prior to ¹⁷⁷Lu-Dotatate. Of these patients, the safety analysis included 610 patients, 360 (60%) of which had metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs), treated with a cumulative dose of at least 100 mCi (3.7 GBq) ¹⁷⁷Lu-Dotatate. Median follow-up

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was 78 months. Long-term toxicity included acute leukemia in four patients (0.7%) and myelodysplastic syndrome in nine patients (1.5%). There was no therapy-related long-term renal or hepatic failure. Overall response rate, defined as complete or partial response, in patients with midgut and pancreatic NETs with progressive disease at baseline was 84% and 81%, respectively. Median overall survival for GEP-NETs was only reported for pancreas (71 months [95% CI 56-86]) and midgut (60 months [52-68]), due to small numbers of other gastrointestinal primaries. A subset analysis of PFS in patients with midgut tumors and progressive disease at baseline was 24 months [95% CI 18-30].

Lutetium 177 (Lu 177) dotatate (Lutathera) has not been approved by the FDA to treat pheochromocytomas and paragangliomas.

HSA iobenguane I 131 (Azedra)

Azedra is administered intravenously as a dosimetric dose followed by a total of two therapeutic doses given 90 days apart. The recommended dosimetric dose for patients weighing greater than 50 kg is 185 to 222 MBq (5 or 6 mCi), and 3.7 MBq/kg (0.1 mCi/kg) for patients weighing 50 kg or less. Following the dosimetric dose, the recommended therapeutic dose of Azedra is weight-based and reduced if needed based on dosimetry data. The recommended therapeutic dose per cycle is 18,500 MBq (500mCi) for patients weighing more than 62.5 kg, and 296 MBq/kg (8 mCi/kg) for patients weighing 62.5 kg or less. Azedra dosing may be modified based on adverse reactions.

Before initiating Azedra, inorganic iodine should be administered beginning at least 24 hours before and continuing for 10 days after each dose, in order to provide thyroid blockade. In addition, to decrease bladder irradiation, patients should increase fluid intake to at least 2 liters per day starting at least 1 day before and continuing for 1 week after each Azedra dose. Drugs that reduce catecholamine uptake or deplete catecholamine stores should be discontinued for at least 5 half-lives prior to Azedra administration and not taken again until at least 7 days after each dose. Pre-medicate with antiemetics 30 minutes before each Azedra dose.

According to the manufacturer's safety information, Azedra must be handled with appropriate safety measures to minimize radiation exposure, and pregnancy status in females of reproductive potential should be verified prior to initiating Azedra. Other warnings and precautions for Azedra listed within the prescribing information include: myelosuppression, secondary myelodysplastic syndrome (MDS) and leukemia, hypothyroidism, renal toxicity, elevated blood pressure, pneumonitis, embryo-fetal toxicity, and infertility risk.

In July 2018, the U.S. Food and Drug Administration approved Azedra (iobenguane I 131) for the treatment of iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma. The efficacy of iobenguane I 131 (Azedra) was evaluated in a phase IB12B, multicenter, open-label, single-arm clinical trial (NCT00874614) of patients (n=74) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy. Patients included in the study were at least 12 years of age, had a diagnosis of PPGL, and were ineligible for curative surgery. Patients also had failed prior therapy for PPGL or were not candidates for chemotherapy. In addition, patients were required to have tumors with definitive iobenguane avidity, and to be stable on an antihypertensive medication for at least 30 days prior to the first therapeutic dose. A total of 74 patients received a dosimetric dose of Azedra of 185 to 222 MBq (5mCi to 6 mCi) for patients weighing > 50 kg and 3.7 MBq/kg (0.1 mCi/kg) for patients weighing ≤ 50 kg. Following dosimetry, 68 patients received at least one therapeutic dose and 50 patients received two therapeutic doses given at least 90 days apart. The therapeutic dose was 18,500 MBq (500 mCi) for patients weighing > 62.5 kg and 296 MBq/kg (8 mCi/kg) for patients weighing ≤ 62.5 kg. The study included a 12-month efficacy phase assessment followed by a 4-year long-term follow-up period. The primary endpoint was the proportion of patients with a reduction of all antihypertensive medication(s) by at least 50% for 6 months or more, which was observed in 25% of patients (95% CI, 16% to 37%). Other secondary endpoints included overall

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objective tumor response measured by RECIST (Response Evaluation Criteria in Solid Tumors version 1.0), tumor biomarker response, overall survival up to 5 years post-first therapeutic dose, and safety. Best confirmed overall tumor response per RECIST was partial response, which was achieved in 22% of patients (95%CI, 14% to 33%). Of these responders, 53% had a duration of response of at least 6 months.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbssc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: A9513, A9590

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 12/2018

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Specialty Matched Consultant Advisory Panel 5/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 6.01.60, 7/11/2019

Specialty Matched Consultant Advisory Panel 5/2020

Policy Implementation/Update Information

For Policy Titled: “Lutathera® (lutetium Lu 177 dotatate)”

- 4/13/18 New policy developed. Lutathera is considered medically necessary for the treatment of adult patients with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) when the following criteria are met: the patient has unresectable, locally advanced or metastatic disease, AND the patient has had disease progression despite somatostatin analog therapy or molecularly targeted therapy (e.g. everolimus), AND an appropriate imaging study has been performed to document over-expression of somatostatin receptors by the target lesions, AND the tumor is well-differentiated with a Ki-67 index of 20% or less, as documented in a pathology report (see Policy Guidelines). Added HCPCS code A9699 to “Billing/Coding” section. References added. Medical Director review 4/2018. (krc)
- 6/29/18 Added HCPCS code C9031 to Billing/Coding section. Specialty Matched Consultant Advisory Panel review 5/23/2018. No change to policy statement. (an)
- 11/30/18 Under “When Covered” section added additional indication for Lutathera for bronchopulmonary or thymus neuroendocrine tumors. Added HCPCS code A9513 to Billing/Coding section for effective date 1/1/2019. References added. Medical Director review 11/2018. (krc)

For Policy Re-titled: “Therapeutic Radiopharmaceuticals in Oncology”

- 12/31/18 Policy title revised from “Lutathera® (lutetium Lu 177 dotatate)” to “Therapeutic Radiopharmaceuticals in Oncology”. Updated Description section, Policy Statement, and Policy Guidelines to include newly approved Azedra with medical necessity statement: “High-specific activity (HSA) iobenguane I 131 (Azedra) may be considered medically necessary for the treatment of adult and pediatric (age 12 years or older) patients with pheochromocytoma or paraganglioma.” Added HCPCS code C9408 to Billing/Coding section and deleted code C9031 for effective date 1/1/2019. References added. Medical Director review 12/2018. (krc)

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- 6/11/19 References added. Specialty Matched Consultant Advisory Panel review 5/15/2019. No change to policy statement. (krc)
- 12/31/19 Added HCPCS code A9590 to Billing/Coding section and deleted codes A9699 and C9408 effective 1/1/2020. (krc)
- 6/23/20 Reference added. Specialty Matched Consultant Advisory Panel review 5/20/2020. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.