Therapeutic Radiopharmaceuticals in Oncology

Policy # 00634
Original Effective Date: 09/19/2018
Current Effective Date: 04/13/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider lutetium 177 dotatate (Lutathera®)‡ or iobenguane i-131 (Azedra®)‡ for the treatment of appropriate locally advanced or metastatic tumors to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of lutetium 177 dotatate (Lutathera) or iobenguane i-131 (Azedra) will be considered when ALL of the specific drug's criteria are met:

- For Lutathera requests:
    - Patient is greater than or equal to 18 years of age; AND
    - Patient has documented low or intermediate grade (Ki-67 index ≤20%), locally advanced or metastatic, gastroenteropancreatic (including foregut, midgut, and hindgut) or bronchopulmonary or thymus neuroendocrine tumor; AND
      *(Note: The portion of this criterion requiring the tumor to be lower or intermediate grade and locally advanced or metastatic is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - Patient has documented somatostatin receptor expression of a neuroendocrine tumor as detected by somatostatin receptor-based imaging or somatostatin receptor scintigraphy; AND
    - Patient has documented disease progression while on octreotide long-acting release therapy; AND
      *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- Patient is not receiving long-acting somatostatin analogues for at least 4 weeks prior to initiating Lutathera; AND
- The patient does not have severe renal impairment [defined as a creatinine clearance <30 milliliters per minute(mL/min)]; AND
- The patient has adequate bone marrow and hepatic function as determined by the treating physician; AND
- Patient has documented Karnofsky Performance Status score of 60 or greater; AND *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- The dose will not exceed 7.4 gigabecquerels (GBq) [200 millicuries (mCi)] every 8 weeks for a total of 4 doses; AND
- Patient is not pregnant or breast-feeding; AND
- If patient is of reproductive potential, patient agrees to use effective contraception during and after treatment according to recommendations in package insert.

- For Azedra requests:
  - Patient is greater than or equal to 12 years of age; AND
  - Patient has diagnosis of pheochromocytoma or paraganglioma that is unresectable, locally advanced, or metastatic; AND
  - Disease is iobenguane (MIBG) scan positive; AND
  - No more than 3 doses (one dosimetric dose and two therapeutic doses) will be administered; AND
  - Patient requires systemic therapy; AND
  - Patient has progressed on or is not a candidate for prior chemotherapy; AND *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Platelet count is at least 80,000 cells/mm^3 and absolute neutrophil count (ANC) is at least 1200/mm^3 before the first therapeutic dose; AND
  - Patient does not have severe renal impairment (defined as creatinine clearance <30 mL/min); AND
  - Patient is not pregnant or breast-feeding; AND
  - If patient is of reproductive potential, patient agrees to use effective contraception during and after treatment according to recommendations in package insert.

When Services Are Considered Not Medically Necessary

Based on review of available data, the use of lutetium 177 dotatate (Lutathera) when the patient's tumor(s) is not low or intermediate grade and locally advanced or metastatic, the patient has not had disease progression while on octreotide long-acting release therapy, or the Karnofsky Performance Status score is less than 60 is considered to be **not medically necessary.****

Based on review of available data, the use of iobenguane i-131 (Azedra) when the patient is a candidate for chemotherapy and has not previously failed standard chemotherapy is considered to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers lutetium 177 dotatate (Lutathera) and iobenguane i-131 (Azedra) to be **investigational*** when the patient selection criteria (other than those considered to be **not medically necessary****) are not met.

Background/Overview

Therapeutic radiopharmaceuticals are a new class of drugs that combine a radioisotope with an organic molecule which targets the radioisotope to specific organs, tissues, or cells. Currently available radiopharmaceuticals include the radiolabeled somatostatin analogue, Lutathera, and the radiolabeled norepinephrine analogue, Azedra.

Lutathera binds to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors. It is then internalized and beta particle emission from the drug induces cellular damage by formation of free radicals in somatostatin receptor-positive and neighboring cells. It is dosed at 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. Each dose should be preceded by an infusion of amino acids to protect the patient's kidneys and the infusion should continue during and for at least 3 hours after Lutathera infusion. Because there are theoretical concerns regarding the competition between somatostatin analogues and Lutathera for somatostatin receptor binding, long-acting somatostatin analogues should not be administered for 4 to 6 weeks

prior to each Lutathera treatment. In addition, short-acting somatostatin analogues should be stopped 24 hours before each Lutathera treatment. Both long-acting and short-acting somatostatin analogues can be resumed 4 to 24 hours after each Lutathera treatment.

Azedra is structurally similar to norepinephrine (NE) and is subject to the same uptake and accumulation pathways as NE. It is internalized by the NE transporter in adrenergic nerve terminals and accumulates in adrenergically innervated tissues, such as the heart, lungs, adrenal medulla, salivary glands, liver, and spleen as well as tumors of neural crest origin (pheochromocytomas and paragangliomas). Prior to therapeutic dosing with Azedra, patients must be given a smaller dosimetric dose of 3.7 MBq/kg (max of 222MBq) to determine the radiation dose estimates to normal organs and tissues and subsequently the dose for the two therapeutic doses. More information regarding dose calculation can be found in the drug's FDA-approved package insert. In addition, a number of pre-medications are required before each dose. Patients should be treated with inorganic iodine to protect the thyroid, fluid intake should be increased by at least 2 liters a day starting 1 day before and continuing for 1 week after each dose to minimize irradiation to the bladder, drugs that reduce catecholamine uptake or deplete catecholamine stores should be discontinued at least 5 half-lives before Azedra dosing, and antiemetics should be given 30 minutes prior to administering the Azedra dose.

Both Lutathera and Azedra can cause fetal harm and should not be used in pregnant or breastfeeding females. In addition, females of reproductive potential should be advised to use effective contraception during treatment and for 7 months after the final dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for 4 months after the final dose.

Neuroendocrine Tumors
Neuroendocrine tumors are a heterogeneous group of tumors that originate from the neuroendocrine cells in the diffuse neuroendocrine system anywhere in the body. Approximately 61% of all neuroendocrine tumors originate from the gastrointestinal system or pancreas and are referred to as gastroenteropancreatic neuroendocrine tumors. Lung neuroendocrine tumors may also be referred to as pulmonary neuroendocrine tumors, pulmonary carcinoids, or bronchopulmonary neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors may further be characterized as functional or nonfunctional based on whether they secrete hormones that result in clinical

symptoms, particularly serotonin which results in "carcinoid syndrome" characterized by flushing and diarrhea.

Diagnosis of neuroendocrine tumors is difficult due to the rarity of the condition and the fact that symptoms are often nonspecific and mimic other disorders such as irritable bowel syndrome or asthma. For this reason, the average diagnosis delay is 5-7 years after symptom onset. Most of these tumors express somatostatin receptors that can be imaged using a radiolabeled form of the somatostatin analogue, octreotide. Neuroendocrine tumors are often staged with the Ki-67 index, and only patients with a Ki-67 index of 20% or less were included in the randomized trial of Lutathera.

There is a general lack of prospective data to guide treatment of neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors are chemotherapy-responsive neoplasms, and platinum-based chemotherapy represents the backbone of treatment for both early and advanced-stage tumors. Surgery alone or followed by chemotherapy along with treatment of hormone-related symptoms may be the initial approach for localized disease. For asymptomatic patients with slow progression, observation with routine surveillance imaging is an option. The prognosis for patients with metastatic disease is highly variable. The median overall survival from diagnosis for patients with metastatic pancreatic neuroendocrine tumors has been reported to range from 2 to 4.8 years while the median overall survival for small bowel neuroendocrine tumors has been reported as 7.9 years. Somatostatin analogues (e.g., octreotide, lanreotide) were initially developed to manage the hormonal symptoms related to neuroendocrine tumors, and they are a first-line treatment option for these patients. They were also found to exert antiproliferative activity and result in prolonged progression-free survival in patients with neuroendocrine tumors. However, the role of somatostatin analogues in patients with nonfunctioning neuroendocrine tumors is unclear. Currently, there are no data to support a specific sequence of second-line therapies and only streptozocin, everolimus, and sunitinib are FDA approved for treatment of pancreatic neuroendocrine tumors.

Pheochromocytoma and 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 such as epinephrine, norepinephrine, and dopamine; which result in hypertension, arrhythmia, and/or hyperglycemia, and occur in 0.2-0.6% 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 or systemic chemotherapy. In patients with distant metastases, curative surgery is not a treatment option and the five-year survival rate is approximately 12%. 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 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) and conventional, low-specific-activity I 131 at high doses.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

On January 26, 2018, Lutathera was approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors, including foregut, midgut, and hindgut neuroendocrine tumors in adults.

On July 30, 2018, Azedra was approved for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Lutathera
Approval of Lutathera was based on an open-label study in patients with midgut carcinoid tumors (NETTER-1), and the portion of the retrospective ERASMUS study that evaluated patients with gastroenteropancreatic neuroendocrine tumors.

In the NETTER-1 trial, patients with a Ki-67 index of 20% or less, Karnofsky Performance Status score of 60 or greater, confirmed presence of somatostatin receptors on all lesions (octreoscan uptake ≥normal liver) and creatinine clearance for 50 mL/min or greater were included. The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee. Additional efficacy outcome measures were overall response rate, duration of response, and overall survival. Results showed a consistent statistically significant and clinically meaningful effect on overall response rate, PFS, and overall survival among patients given Lutathera compared with those given high-dose long-acting octreotide. The median PFS was not reached in the Lutathera group and was 8.5 months in the control group (HR=0.21[0.13-0.32]).

In the ERASMUS study, 1214 patients with heterogeneous etiologies in terms of primary tumor site received Lutathera as part of expanded access protocol at a single center in the Netherlands. From this cohort, 360 patients with foregut, midgut, or hindgut gastroenteropancreatic neuroendocrine tumors were respectively identified and analyzed. The major efficacy outcome was investigator-assessed overall response rate. 55% of patients received a concomitant somatostatin analogue. The investigator-assessed overall response rate was found to be 16% and the median duration of response was 35 months among 58 responders.

The ERASMUS study also included 25 individuals with treatment-refractory bronchopulmonary or thymus neuroendocrine tumors who received Lutathera. Among the 23 patients with bronchopulmonary neuroendocrine tumor, the median progression-free survival was 20 months, median time to progression was 25 months, and median overall survival was 52 months. Stratified results of 2 patients with thymus neuroendocrine tumors were not reported.

Azedra
The efficacy of Azedra in patients with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma which require systemic anticancer therapy was established in Study IB12B, an open-label, single-arm, multicenter clinical trial. Patients were at least 12 years of age, were ineligible for curative therapy, and had progressed on prior chemotherapy

or were not candidates for chemotherapy. Other eligibility criteria required patients' tumors to have definitive iobenguane avidity; at least one tumor site identified by CT, MRI, or iobenguane I 131 scan; Karnofsky performance status ≥60; absence of active CNS lesions, and no changes to their antihypertensive regimen in the 30 days prior to the first therapeutic dose.

The major efficacy outcome measure was the proportion of patients who experienced a 50% or greater reduction of all antihypertensive medication(s) lasting for at least 6 months. Of the 74 patients who received the dosimetric dose of Azedra, 68 received at least one therapeutic dose and 50 received two therapeutic doses administered at least 90 days apart. Of the patients who received at least one therapeutic dose, 25% (95% CI: 16-37%) met the primary endpoint.

References

1. Lutathera [package insert]. Advanced Accelerator Applications USA. Millburn, NJ. February 2018.
2. Azedra [package insert]. Progenics Pharmaceuticals, Inc. New York, NY. August 2018.
3. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Therapeutic Radiopharmaceuticals in Oncology", Policy #6.01.60, August 2019.

Policy History

Original Effective Date: 09/19/2018
Current Effective Date: 04/13/2020

09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. New policy.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Added new drug, Azedra, to policy with relevant background information.
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 03/2021

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	A9513 Code added eff 1/1/2020: A9590 Code deleted eff 1/1/2020: C9408
ICD-10 Diagnosis	C7A.00-C7A.8, C7B.00-C7B.09, C7B.8

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.