

Medical Drug Clinical Criteria

Subject: Radioimmunotherapy and Somatostatin
Receptor Targeted Radiotherapy (Azedra, Lutathera, Pluvicto, Zevalin)

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Overview

This document addresses the use of somatostatin receptor targeted radiotherapies and radioimmunotherapies that involves the combination of somatostatin analogue (targeted monoclonal antibody) with a radionuclide primarily used to treat various types of cancer depending on agent.

The Food and Drug Administration (FDA) has approved the following somatostatin receptor targeted therapies and radioimmunotherapies:

- Zevalin (ibritumomab tiuxetan), CASI Pharmaceuticals, Rockville, MD
- Azedra (iobenguane I 131), Progenics Pharmaceuticals, Inc., New York, NY
- Lutathera (lutetium Lu 177 dotatate), Advanced Accelerator Applications USA, Inc., NJ
- Pluvicto (lutetium Lu 177 vipivotide tetraxetan), Novartis Pharmaceuticals Corporation, Millburn, NJ

Zevalin (Ibritumomab tiuxetan)

Zevalin binds to the CD20 antigen of pre-B and mature B lymphocytes primarily used to treat B-cell non-Hodgkin's lymphomas (NHL).

The FDA approved indications for ibritumomab tiuxetan include:

1. Individuals with CD20+ relapsed or refractory, low-grade or follicular B-cell NHL
2. Individuals with previously untreated CD20+ follicular NHL who achieve a partial or complete response to first-line chemotherapy

Azedra (Iobenguane I 131)

Azedra acts similar to norepinephrine (NE) and taken up by NE transporter in adrenergic nerve terminals and accumulates in adrenergically innervated tissues including tumors of the neural crest. Iobenguane is primary used to treat pheochromocytoma and paraganglioma (PPGL).

The FDA approved indications for Azedra include individuals 12 years and older with iobenguane (such as iodine-123 meta-iodobenzylguanidine [MIBG]) scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Lutathera (Lutetium Lu 177 dotatate)

Lutathera binds to somatostatin subtype 2 receptors (SSRT2) primarily used to treat somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

The FDA approved indications for Lutathera include:

1. Individuals with locally advanced, inoperable or metastatic well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults
2. Individuals with locally unresectable or metastatic pheochromocytoma or paraganglioma

Pluvicto (Lutetium Lu 177 vipivotide tetraxetan)

The FDA approved indications for Pluvicto include treatment of adult patients with prostate-specific membrane antigen (PSMA)- positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of individuals with locally advanced or distant metastatic bronchopulmonary or thymus neuroendocrine tumors.

Other Uses

Zevalin (Ibritumomab tiuxetan)

Zevalin has been investigated for other uses including progressive generalized extracutaneous disease in primary cutaneous B-cell lymphoma and high-dose chemotherapy and hematopoietic stem cell support in individuals with relapsed diffuse large cell lymphoma, but there have currently been no randomized trials that have reported an agent-containing pre-transplant regimen is associated with improved outcomes. Given gaps in published data, NCCN consensus no longer recommends use of ibritumomab tiuxetan as a conditioning regimen for hematopoietic stem cell transplants to treat individuals with NHL.

There are black box warnings with Zevalin for serious infusion reactions, prolonged and severe cytopenias and severe cutaneous and mucocutaneous reactions. Serious infusion reactions due to rituximab component of ibritumomab tiuxetan therapeutic regimen. Infusion reactions can be potentially fatal, associated with hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock.

Azedra (Iobenguane I 131)

There are warnings with iobenguane I 131 for radiation exposure risk, myelosuppression, secondary myelodysplastic syndrome, leukemia and other malignancies, hypothyroidism, renal toxicity and pneumonitis due to system treatment.

Lutathera (Lutetium Lu 177 dotatate)

Lutathera has been investigated for other uses including treatment of incompletely resected, locoregionally advanced and/or metastatic neuroendocrine bronchopulmonary/thymus tumors (carcinoid) if somatostatin receptor positive imaging and progression on octreotide or lanreotide in individuals with clinically significant tumor burden and low grade (typical) histology or evidence of progression, intermediate grade (atypical) histology, or progression on first-line therapy, and primary treatment for locally unresectable pheochromocytoma or paraganglioma with distant metastases if somatostatin receptor positive imaging. While NCCN provides 2A recommendations for these off-label uses, NCCN states the published peer reviewed literature for these are considered lower-level evidence, but appropriate.

Note: Somatostatin analogues that are not radiolabeled have diagnostic and clinical indications that are outside the scope of this document.

Definitions and Measures

Carcinoid Tumors: Rare, slow-growing tumors of the neuroendocrine cells (enterochromaffin or Kulchitsky cells) widely found in many organs of body, but usually originate in the digestive tract or lung; also called carcinoids or well-differentiated NETs.

Cytotoxic: Treatment that is destructive to cells, preventing their reproduction or growth.

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Malignant: Cancerous. Malignant cells can invade and destroy nearby tissue and spread to other parts of the body.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

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).

Non-Hodgkin Lymphoma (NHL): A group of malignant solid tumors or lymphoid tissues.

Phenotype: The total characteristics displayed by the tumor.

Radioisotope: A radioactive form of an element or isotope.

Radionuclide: An unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. Radionuclides may occur in nature or be made in a laboratory. In medicine, they are used in imaging tests and in treatment; also called radioisotope.

Radiotherapy: Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body.

Refractory Disease: Illness or disease that does not respond to treatment.

Somatostatin-receptor scintigraphy (SRS): A type of radionuclide scan used to find carcinoid and other types of tumors. Radioactive octreotide, a drug similar to somatostatin, is injected into a vein and travels through the bloodstream. The radioactive octreotide attaches to tumor cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide, and take pictures showing where the tumor cells are in the body; also called octreotide scan.

Unresectable: Unable to be removed with surgery.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Zevalin (ibritumomab tiuxetan)

Requests for Zevalin (ibritumomab tiuxetan) may be approved if the following criteria are met:

- I. Individual is 18 years of age or older; **AND**
- II. Individual has a diagnosis of one the following:
 - A. CD20+ relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's Lymphoma (NHL); **OR**
 - B. Previously untreated CD20+ follicular NHL who achieve a partial or complete response to first-line chemotherapy.

Azedra (iobenguane I 131)

Requests for Azedra (iobenguane I 131) may be approved if the following criteria are met:

- I. Individual has a diagnosis of unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma; **AND**
- II. Individual is 12 years or older; **AND**
- III. Individual has target lesions confirmed by an iobenguane scan (such as iodine-123 meta-iodobenzylguanidine [MIBG]); **AND**
- IV. Individual has an ECOG performance status of 0 to 2; **AND**
- V. Individual has not received prior treatment with radiolabeled somatostatin analog.

Lutathera (lutetium Lu 177 dotatate)

Requests for Lutathera (lutetium Lu 177 dotatate) may be approved if the following criteria are met:

- I. Individual has diagnosis of one of the following:
 - A. Locally advanced, inoperable or metastatic well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults;
- OR**
- B. Locally advanced or distant metastatic bronchopulmonary or thymus neuroendocrine tumors (NCCN 2A) when the following criteria are met;
 - ~~1. Individual is 18 years or older; AND~~
 - ~~2.1.~~ Tumor has progressed while receiving greater than or equal to 4 months of somatostatin analog therapy (such as octreotide LAR or lanreotide) with evidence of tumor progression on imaging; **AND**
 - ~~3.2.~~ Individual has target lesions overexpressing somatostatin receptors confirmed by an appropriate somatostatin receptor-based imaging study (such as ⁶⁸Ga-dotatate PET/CT or somatostatin receptor scintigraphy); **AND**
 - ~~4.3.~~ Individual has an ECOG performance status of 0 to 2; **AND**
 - ~~5.4.~~ Individual has not received prior treatment with a radiolabeled somatostatin analog.
- OR**
- C. Locally unresectable or metastatic pheochromocytoma or paraganglioma when the following criteria are met (NCCN 2A):
 - ~~1. Individual is 18 years or older; AND~~
 - ~~2.1.~~ Individual has target lesions overexpressing somatostatin receptors confirmed by an appropriate somatostatin receptor-based imaging study (such as ⁶⁸Ga-dotatate PET/CT or somatostatin receptor scintigraphy); **AND**
 - ~~3.2.~~ Individual has an ECOG performance status of 0 to 2; **AND**
 - ~~4.3.~~ Individual has not received prior treatment with a radiolabeled somatostatin analog.

Pluvicto (lutetium Lu 177 vipivotide tetraxetan)

Requests for Pluvicto (Lutetium Lu 177 vipivotide tetraxetan) may be approved if the following criteria are met:

- I. Individual is 18 years or older; **AND**
- II. Individual has a diagnosis of prostate-specific membrane antigen (PSMA)-positive metastatic, castration-resistant prostate cancer (mCRPC); **AND**
- III. Individual has been treated with androgen receptor (AR) pathway inhibition; **AND**
- IV. Individual has been treated with a taxane-based chemotherapy; **AND**
- V. Individual has been treated with a GnRH analog or bilateral orchiectomy; **AND**
- VI. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

The following criteria illustrate when each radioimmunotherapy *may not be approved*:

Requests for Zevalin (ibritumomab tiuxetan) may not be approved for the following:

- I. Individually or in combination with other forms of irradiation or chemotherapy when the criteria above are not met; **OR**
- II. As a repeat course of treatment; **OR**
- III. As part of CD20+ lymphoma pre-transplant conditioning regimen; **OR**
- IV. Individual has ≥ 25% bone marrow involvement and/or impaired bone marrow reserve.

Requests for Pluvicto (lutetium Lu 177 vipivotide tetraxetan) may not be approved for the following:

- I. Individual has severe renal impairment (CrCl 29ml/min or less) or end-stage renal disease; **OR**
- II. Individual has already received 6 doses of Pluvicto (lutetium Lu 177 vipivotide tetraxetan).

Requests for Azedra (jobenguane I 131), Lutathera (lutetium Lu 177 dotatate), Pluvicto (lutetium Lu 177 vipivotide tetraxetan), or Zevalin (ibritumomab tiuxetan) may not be approved when the above criteria are not met and for all other indications.

Requests for the use of other yttrium-labeled humanized antibody therapies may not be approved.

Requests for Somatostatin analogs (including octreotide, lanreotide and vapreotide) which are not FDA approved for use as therapeutic receptor targeted radionuclide therapy may not be approved.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement

policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Zevalin (ibritumomab tiuxetan)

HCPCS

A9543	Yttrium Y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 mCi [Zevalin therapeutic]
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CPT

79403	Radiopharmaceutical therapy, radiolabeled monoclonal antibody by intravenous infusion
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ICD-10 Diagnosis

C82.00-C82.99	Follicular lymphoma
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Azedra (iobenguane I 131)

HCPCS

A9590	Iodine I-131, iobenguane, 1 mCi [Azedra]
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CPT

79101	Radiopharmaceutical therapy, by intravenous administration [injection of Iobenguane I 131 (Azedra)]
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ICD-10 Diagnosis

C74.10-C74.12	Malignant neoplasm of medulla of adrenal gland
C74.90-C74.92	Malignant neoplasm of unspecified part of adrenal gland
C75.5	Malignant neoplasm of aortic body and other paraganglia

Lutathera (lutetium Lu 177 dotatate)

HCPCS

A9513	Lutetium Lu 177, dotatate, therapeutic, 1 mCi [Lutathera]
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CPT

79101	Radiopharmaceutical therapy, by intravenous administration [when specified as injection of lutetium Lu 177 dotatate (Lutathera)]
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ICD-10 Diagnosis

C25.4	Malignant neoplasm of endocrine pancreas
C74.10-C74.12	Malignant neoplasm of medulla of adrenal gland
C74.90-C74.92	Malignant neoplasm of unspecified part of adrenal gland
C75.5	Malignant neoplasm of aortic body and other paraganglia
C7A.00-C7A.8	Malignant carcinoid tumors
C7B.00-C7B.09	Secondary carcinoid tumors
C7B.8	Other secondary neuroendocrine tumors
E34.0	Carcinoid syndrome
Z85.020	Personal history of malignant carcinoid tumor of stomach

Z85.030	Personal history of malignant carcinoid tumor of large intestine
Z85.040	Personal history of malignant carcinoid tumor of rectum
Z85.060	Personal history of malignant carcinoid tumor of small intestine
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.110	Personal history of malignant carcinoid tumor of bronchus and lung
Z85.230	Personal history of malignant carcinoid tumor of thymus
Z85.858	Personal history of malignant neoplasm of other endocrine glands

Pluvicto (lutetium Lu 177 vipivotide tetraxetan)

HCPCS

A9607	Lutetium lu 177 vipivotide tetraxetan, therapeutic, 1 mCi [Pluvicto]
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ICD-10 Diagnosis

C61	Malignant neoplasm of prostate
C63.00-C63.9	Malignant neoplasm of other and unspecified male genital organs
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C77.0-C77.9	Secondary and unspecified malignant neoplasm of lymph nodes
C78.00-C78.89	Secondary malignant neoplasm of lung
C79.00-C79.9	Secondary malignant neoplasm of kidney and renal pelvis
Z19.2	Hormone resistant malignancy status

Document History

Revised: 06/10/2024

Document History:

- 06/10/2024 – Select Review: Remove age requirements on Lutathera for updated FDA approval, wording change. Coding Reviewed: Updated coding description for HCPCS A9607, A9513, A9543. Corrected HCPCS code range from C77.00-C77.9 to C77.0-C77.9 for Pluvicto. Removed from Zevalin the following HCPCS C83.00-C83.99, C85.10-C85.99, C88.4.
- 02/23/2024- Annual Review: Remove NCCN recommendations from Zevalin to treat follicular lymphoma. Coding Reviewed: No changes.
- 02/24/2023 – Annual Review: add second and subsequent therapy for follicular lymphoma. Coding Reviewed: Added ICD-10-CM C82.00-C82.97. Code range C82.00-C82.97 has been removed from Pluvicto ICD-10-CM code list.
- 05/20/2022 – Select Review: Add new criteria for Pluvicto. Coding Reviewed: Added HCPCS A9699. Added ICD-10-CM: C61, C63.00-C63.9, C69.90, C77.00-C77.9, C78.00-C78.89, C79.00-C79.9, Z19.2. Effective 10/1/2022 Added HCPCS A9607. Removed HCPCS A9699.
- 02/25/2022 – Annual Review: wording and formatting change. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Update may not be approved criteria for Zevalin. Coding Reviewed: Removed A9699 for Azedra.
- 02/21/2020 – Annual Review: Update Zevalin criteria for use in adults only. Update may not be approved criteria with bone marrow criteria. Wording and formatting updates. Coding reviewed: Added HCPCS A9590, Delete C9407, C9408
- 05/17/2019 – Annual Review: Initial review of Radioimmunotherapy and Somatostatin Receptor Targeted Radiotherapy (Azedra, Lutathera, Zevalin). Added clarifications for disease states. Wording and formatting changes. Coding Reviewed: Added A9513 Effective 1/1/19. Deleted A9699 for Lutathera on 12/31/18.

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