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Last P&T Approval/Version: 04/30/2025
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Policy Number: C29411-A

Therapeutic Radiopharmaceuticals

PRODUCTS AFFECTED

Azedra (iobenguane I-131), Lutathera (lutetium Lu 177 dotatate), Pluvicto (lutetium Lu 177 vipivotide tetraxetan), Quadramet (samarium Sm 153 lexidronam), Strontium Chloride Sr-89 (strontium-89 chloride), Xofigo (radium Ra 223 dichloride), Zevalin Y-90 (ibritumomab tiuxetan)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
FDA labeled, compendial or consortium supported

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ALL INDICATIONS:

1. Must have a documented diagnosis for a medically accepted indication including: Use of a drug which is FDA-approved. Use of which is supported by one or more citations included or approved for inclusion in any of the compendia: Society of Nuclear Medicine and Molecular Imaging, American College of Radiology, American Hospital Formulary Service Drug Information, DRUGDEX Information System, National Comprehensive Cancer Network (Categories 1 or 2A only), or pediatric consortium (e.g., Children's Oncology Group [COG], St. Jude Consortium, Dana-Farber Cancer Institute [DFCI]).
   NOTE: *A category 2B therapy/regimen may be authorized on an exception basis with documented Molina Healthcare medical director or Molina Healthcare oncologist consultation.*
   AND
2. Documentation of dose and dates of all previous therapies and the resulting outcomes where applicable
   AND
3. Documentation that the proper succession of the therapies has been considered OR have been tried and failed (i.e., serious side effects, contraindication, or progression)
   NOTE: *The proper succession for this element can be found within compendia monographs, FDA label or NCCN guidelines; If compendia monographs, FDA label or NCCN guidelines have a formulary/preferred product at therapeutic parity with requested agent a formulary/preferred product should be used first where state regulations allow.*
   MOLINA REVIEWER NOTE: For Mississippi Marketplace, please see Appendix. AND
4. Documentation of related lab work, test results, or clinical markers supporting the diagnosis, initiation, and/or continuation of treatment.

CONTINUATION OF THERAPY: A.
ALL INDICATIONS:

1. Documented clinically significant improvements in the disease state, stability on treatment, or lack of disease progression
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:
Initial authorization: 3 months, Continuation of Therapy: 9 months or maximum duration per FDA label or NCCN guideline or compendium, whichever is shorter
MOLINA REVIEWER NOTE: For Connecticut Marketplace or Mississippi Marketplace, please see Appendix.

PRESCRIBER REQUIREMENTS:
Prescribed by a board-certified oncologist, hematologist, or other specialist treating cancer

AGE RESTRICTIONS:
Azedra and Lutathera: 12 years of age and older
Al others: 18 years of age and older

QUANTITY:
FDA-labeled, NCCN, NCI, or AHFS supported dosing regimens or dosing schedules will be evaluated for approval

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Intravenous

DRUG CLASS:

Antineoplastic Radiopharmaceuticals, Antineoplastic -Antibody for Radiopharmaceutical Therapy

FDA-APPROVED USES:

Azedra (iobenguane I-131): Indicated 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.

Lutathera (lutetium Lu 177 dotatate): Indicated for the treatment of adult and pediatric patients 12 years and older with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEPNETs), including foregut, midgut, and hindgut neuroendocrine tumors.
Metastron (strontium chloride Sr-89): Indicated for the relief of bone pain in patients with painful skeletal metastases.

Pluvicto (lutetium Lu 177 vipivotide tetraxetan): Indicated for the treatment of adult patients with prostatespecific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibitor (ARPI) therapy and are considered appropriate to delay taxane-based chemotherapy or have received prior taxane-based chemotherapy.

Strontium Chloride Sr-89 (strontium-89 chloride): Indicated for the relief of bone pain in patients with painful skeletal metastases. The presence of bone metastases should be confirmed prior to therapy.

Quadramet (samarium Sm 153 lexidronam): Indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan.

Xofigo (radium Ra 223 dichloride): Indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease

ZevalinY-90 (ibritumomab tiuxetan): Indicated for the treatment of adult patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma, or previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy.

COMPENDIAL APPROVED OFF-LABELED USES: None

APPENDIX

APPENDIX:

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information

State Marketplace

Connecticut (Source: House Bill No. 7023, State of Connecticut)

"Sec. 38a-510. Prescription drug coverage. Mail order pharmacies. Step therapy use. (a) *No insurance company*, hospital service corporation, medical service corporation, health care center or other entity delivering, issuing for delivery, renewing, amending or continuing an individual health insurance policy or contract that provides coverage for prescription drugs *may*:

(1) Require any person covered under such policy or contract to obtain prescription drugs from a mail order pharmacy as a condition of obtaining benefits for such drugs; or

(2) *Require*, if such insurance company, hospital service corporation, medical service corporation, health care center or other entity uses step therapy for such drugs, *the use of step therapy for* (A) any prescribed drug for longer than sixty days, or (B) *a prescribed drug for cancer treatment for an insured who has been diagnosed with stage IV metastatic cancer provided such prescribed drug is in compliance with approved federal Food and Drug Administration indications*."

Mississippi (Source: Mississippi Legislature)

"SECTION 13. Length of approvals. (1) A prior authorization approval shall be valid for the lesser of six (6) months after the date the health care professional or health care provider receives the prior authorization approval or the length of treatment as determined by the patient's health care professional or the renewal of the policy or plan, and the approval period shall be effective regardless of any changes, including any changes in dosage for a prescription drug prescribed by the health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his/her health care professional may extend a prior authorization approval for a longer period, by agreement. All dosage increases must be based on established evidentiary standards, and nothing in this section shall prohibit a health insurance issuer from having safety edits in place. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.

(2) Nothing in this section shall require a policy or plan to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment or services are medically necessary.

SECTION 14. Approvals for chronic conditions. (1) If a health insurance issuer requires a prior authorization for a recurring health care service or maintenance medication for the treatment of a chronic or long-term condition, including, but not limited to, chemotherapy for the treatment of cancer, the approval shall remain valid for the lesser of twelve (12) months from the date the health care professional or health care provider receives the prior authorization approval or the length of the treatment as determined by the patient's health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his or her health care professional may extend a prior authorization approval for a longer period, by agreement. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.

(2) Nothing in this section shall require a policy or plan to cover any care, treatment or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment, or services are medically necessary."

Mississippi (Source: House Bill 1143)

"BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF MISSISSIPPI:

SECTION 1. (1) As used in this section, the following terms shall be defined as provided in this subsection:

(a) "Associated conditions" means the symptoms or side effects associated with advanced, metastatic cancer or its treatment and which, in the judgment of the health care practitioner, further jeopardizes the health of a patient if left untreated.

(b) "Advanced, metastatic cancer" means cancer that has spread from the primary or original site of the cancer to nearby tissues, lymph nodes, or other areas or parts of the body.

(c) "Health benefit plan" means a policy, contract, certificate or agreement entered into, offered by or issued by an insurer to provide, deliver, arrange for, pay for or reimburse any of the costs of health care services.

(2) A health benefit plan that provides coverage for advanced, metastatic cancer and associated conditions may not require, before the health benefit plan provides coverage of a prescription drug approved by the United States Food and Drug Administration, that the enrollee: (a) Fail to successfully respond to a different drug; or (b) Prove a history of failure of a different drug.

(3) This section applies only to a drug the use of which is:

(a) Consistent with best practices for the treatment of advanced, metastatic cancer or an associated condition;

(b) Supported by peer-reviewed, evidence-based literature; and (c) Approved by the United States Food and Drug Administration.

SECTION 2. Section 83-9-36, Mississippi Code of 1972, is amended as follows:…

4) The provisions of Section 1 of this act shall supersede the provisions of this section to the extent of any conflict between Section 1 and this section."

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Radiopharmaceuticals are compounds composed of a radionuclide linked to a biologically active molecule that facilitates selective localization in specific tissues, organs, or cellular targets. In therapeutic applications, they deliver cytotoxic radiation (typically alpha or beta particles) directly to pathological cells, enabling targeted destruction while sparing surrounding healthy tissue. This mechanism is particularly effective in the treatment of malignancies such as differentiated thyroid carcinoma (using I-131), neuroendocrine tumors (with Lu-177–dotatate), and certain hematologic cancers (e.g., radioimmunotherapy in lymphomas). The therapeutic efficacy depends on factors such as the physical half-life of the radionuclide, the type and energy of emitted radiation, and the biological half-life of the radiopharmaceutical.

Gastrointestinal and pancreatic neuroendocrine tumors (GEP-NET) are a type of neuroendocrine tumor that originates in the gastrointestinal tract and pancreas. Neuroendocrine tumors are a type of tumor that forms from cells that release hormones into the blood, causing higher than normal levels of certain hormones. There are 3 types of GEP-NETs categorized by their locations in the GI tract/ pancreas: the foregut, midgut, and hindgut. Foregut GEP-NETs originate in the esophagus stomach, proximal duodenum, liver, and the pancreas. Midgut GEP-NETs originate in the distal duodenum, ileum, jejunum, ascending colon, appendix, and in the proximal two-thirds of the transverse colon. Hindgut GEP-NETs originate in the distal one-third of the transverse colon, descending colon, sigmoid colon, and the rectum. Some symptoms patients may experience are nausea, vomiting, bloating, cramps, weight loss, and fatigue. Treatment for GEP-NETs varies; ideally the tumor is removed, but depending on feasibility and clinician judgement, treatment options like chemotherapy, hormone therapy, and radiotherapy are also available. Lutathera is a treatment option for members with GEP-NETs as outlined by the NCCN Neuroendocrine tumor guidelines and has also proven to be effective. In the NETTER-1 study (NCT01578239), Lutathera combined with Octreotide proved to significantly reduction disease progression and death in patients [HR 0.21 (95% CI, 0.13 - 0.32); $p < 0.0001$].

Non-Hodgkin's Lymphoma (NHL) is a type of cancer that forms in the lymph system. The lymph system is a part of the immune system and consists of cells like B-lymphocytes, T-lymphocytes, and Natural killer cells. The types of NHL typically arise from 2 main groups: B-cell and T-cell lymphomas. Some symptoms patients may experience are swollen lymph nodes, fever, drenching night sweats, weight loss, and fatigue. Typical treatment includes surgery, chemotherapy, immunotherapy, and radiation therapy. Zevalin is a radiotherapy treatment option specifically indicated for relapsed or refractory Follicular Lymphoma, primary

cutaneous diffuse large B-cell lymphoma leg type, Nodal Marginal Zone Lymphoma, Splenic Marginal Zone Lymphoma, Gastric and Non-gastric MALT Lymphoma. In the FIT study (NCT00185393), Zevalin was administered to patients who had undergone chemotherapy. This study demonstrated that patients experienced significantly higher progression-free survival when treated with Zevalin compared to no further treatment groups [HR R 0.46 (95% CI: 0.35, 0.60); p<0.0001].

Pheochromocytoma/ Paraganglioma are also neuroendocrine tumors. However, they typically originate from chromaffin cells outside of the adrenal gland. Pheochromocytomas originate from the adrenal medulla, while Paragangliomas originate from the neural crest progenitor cells. Their symptoms tend to vary quite widely, but most patients will experience hypertension or hypotension, headaches, truncal sweating, flushing, palpitations, anxiety, fatigue, nausea/ vomiting, weight loss, or visual disturbances. Typical treatment can include surgery, chemotherapy, tyrosine kinase inhibitors, and radiotherapy. Azedra is a type of radiotherapy that has proven effective in treating Pheochromocytomas/ Paragangliomas through Study IB12B (NCT00874614). In this study, 25% of the patients experienced a durable reduction in baseline antihypertensive medication use (95% CI, 16-37%), and 68% of patients had confirmed complete or partial responses after 12 months of treatment.

Prostate cancer is a type of adenocarcinoma, that specifically originates from the prostate gland cells. Patients will typically experience symptoms like pain in the hips or back areas, weakness or numbness of the legs/ feet, and loss of bowel/ bladder control, in addition to weight loss and fatigue. Prostate cancer can be treated with surgery, chemotherapy, hormone therapy, immunotherapy, and radiotherapy. The two radiopharmaceuticals used in treatment of prostate cancer are Pluvicto and Xofigo. Pluvicto and Xofigo are typically second line therapies, yet have proven to be efficacious. The PSMAfore trial (NCT04689828) demonstrated a significant improvement in radiographic progression-free survival (rPFS) in patients treated with Pluvicto [HR 0.41 (0.29, 0.56); p < 0.0001]. Xofigo also proved to decrease the number of deaths and increase median survival in patients when compared to placebo [HR 0.695 (0.552, 0.875); p = 0.00185].

Prostate-specific membrane antigen (PSMA) is a transmembrane carboxypeptidase that is highly expressed in prostate cancer. Radioligand therapy (RLT) with 177Lu-labeled compounds has shown clinical benefit, and the U.S. Food and Drug Administration (FDA) approved Pluvicto for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) after progressing on taxane-based chemotherapy and at least 1 line of androgen receptor pathway inhibitors (ARPIs).

There have been 2 significant randomized prospective trials that evaluated Pluvicto in the treatment of patients with mCRPC: VISION and TheraP. TheraP was a randomized phase 2 trial involving 200 patients in which Pluvicto was randomized against cabazitaxel and a primary endpoint of the percentage of patients with a 50% decline in PSA (PSA50). In TheraP, a large percentage of patients had a PSA50 response with Pluvicto compared with cabazitaxel (66% vs. 37%, respectively; P = 0.0016). VISION was a randomized phase 3 study of 831 patients who were randomized to protocol-defined standard treatments with or without Pluvicto. The trial had 2 primary endpoints: OS and radiographic progression-free survival as defined by the Prostate Cancer Working Group 3. In VISION, 1 Pluvicto demonstrated improved OS (15.3 vs. 11.3 mo, P < 0.001) and radiographic progression-free survival (8.7 vs. 3.4 mo, P < 0.001) compared with the best standard of care, and this trial was the basis of regulatory approval of Pluvicto in the United States.

In addition to the VISION and TheraP trials, 2 prospective phase 2 studies have been published. The first was a 50-patient cohort at the Peter MacCallum Centre and demonstrated a PSA50 in 64% of patients. The second was the RESIST-PC study, which reported results from a 64-patient cohort from UCLA and the Excel Diagnostics & Nuclear Oncology Center. The primary endpoint of RESIST-PC was the percentage of patients with a PSA50 response after 2 cycles. In the cohort reported, 28% of patients had a PSA50 response after 2 cycles. Given the small sample size and nonrandomized design, conclusions from these studies are limited.

Skeletal metastases, commonly referred to as bone metastases, is typically a result of cancers like prostate and breast cancer. Osteoblastic metastatic bone lesions are a subtype of bone metastases in which there is deposition of new bone. If a patient has this condition, they may experience deep pain, that typically isn't localized, worsens at night, and isn't relieved by sleep or lying down. Bone metastases itself is treated with stabilization and then radiotherapy, but the pain is primarily treated with radiotherapy itself. Sometimes bisphosphonates and calcium with vitamin D can also help. Quadramet and Strontium Chloride Sr-89 are both treatment options for skeletal metastases bone pain, but Quadramet is specifically for osteoblastic metastatic bone lesions. Quadramet has proven to reduce pain scores when compared to placebo in two seperate studies. Strontium Chloride Sr-89 also proved to reduce pain scores, reduce analgesia intake, and reduce the number of new pain sites in patients as well.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of therapeutic radiopharmaceuticals are considered experimental/investigational and therefore, will follow Molina's Off- Label policy.
Contraindications to Azedra (iobenguane I-131) include: a platelet count less than 80,000/mcL or absolute neutrophil count less than 1,200/mcL.
Contraindications to Lutathera (lutetium Lu 177 dotatate) include: No labeled contraindications.
Contraindications to Pluvicto (lutetium Lu 177 vipivotide tetraxetan) include: No labeled contraindications.
Contraindications to Strontium Chloride Sr-89 (strontium chloride Sr-89) include: a platelet count less than 60,000/mcL or white cell count less than 2,400/mcL.
Contraindications to Quadramet (samarium Sm 153 lexidronam) include: known hypersensitivity to EDTMP or similar phosphate compounds.
Contraindications to Xofigo (radium Ra 223 dichloride) include: an absolute neutrophil count less than 1,500/mcL, a platelet count <100,000/mcL, and a hemoglobin <10 g/dL.
Contraindications to Zevalin Y-90 (ibritumomab tiuxetan for Yttrium-90) include: ≥25% lymphoma marrow involvement or impaired bone marrow reserve.

OTHER SPECIAL CONSIDERATIONS:
For detailed instructions on pre-medication, proper use, handling, and preparation of each medication, refer to their respective FDA medication labels.

Lutathera: Administer long-acting octreotide 30 mg intramuscularly 4 to 24 hours after each Lutathera dose and short-acting octreotide for symptomatic management. Continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing LUTATHERA until disease progression or for 18 months following treatment initiation.

Zevalin: Day 1: Administer rituximab 250 mg/m2 intravenous infusion. Day 7, 8, or 9: Administer rituximab 250 mg/m2 intravenous infusion. If platelets at least 150,000/mm3: Within 4 hours after rituximab infusion, administer 0.4 mCi/kg (14.8 MBq per kg) Y-90 Zevalin intravenous infusion. If platelets 100,000 to 149,000/mm3 in relapsed or refractory patients: Within 4 hours after rituximab infusion, administer 0.3 mCi/kg (11.1 MBq per kg) Y-90 Zevalin intravenous infusion.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be allinclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American*

Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industrystandard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCPCS CODE	DESCRIPTION
A9513	Lutetium lu 177, dotatate, therapeutic, 1 millicurie
A9543	Yttrium y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 millicuries
A9590	Iodine i-131, iobenguane, 1 millicurie
A9600	Strontium sr-89 chloride, therapeutic, per millicurie
A9604	Samarium sm-153 lexidronam, therapeutic, per treatment dose, up to 150 millicuries
A9606	Radium ra-223 dichloride, therapeutic, per microcurie
A9607	Lutetium lu 177, vipivotide tetraxetan, therapeutic, 1 millicurie

AVAILABLE DOSAGE FORMS:
Azedra Dosimetric SOLN 15MCI/ML
Azedra Therapeutic SOLN 15MCI/ML
Lutathera SOLN 370MBQ/ML
Pluvicto SOLN 1000MBQ/ML
Quadramet SOLN 1850MBQ/ML
Strontium Chloride Sr-89 SOLN 1MCI/ML
Xofigo SOLN 30MCCI/ML
Zevalin Y-90 KIT 3.2MG/2ML

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SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q2 2025