MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Radiopharmaceuticals for the Treatment of Cancer**
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Product Disclaimer	• *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 or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) 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.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and the lack of peer-reviewed literature, requests for radiopharmaceutical treatments in excess of their U.S. Food and Drug Administration (FDA) approved regimen, will be considered **investigational**.

II. Xofigo injection (Radium Ra 223 Dichloride)

A. Based upon our criteria and assessment of the peer-reviewed literature, **Xofigo** has been medically proven to be effective and, therefore, is considered **medically appropriate** when the following criteria are met:

1. diagnosis of medically or surgically castration-resistant prostate cancer, and
2. presence of symptomatic bone metastases; and
3. no known visceral metastatic disease or bulky regional lymph nodes greater than three (3) cm on imaging performed within the past 30 days.

III. Pluvicto (Lutetium Lu 177 Vipivotide Tetraxetan)

A. Based upon our criteria and assessment of the peer-reviewed literature, **Pluvicto** has been medically proven to be effective and, therefore, is considered **medically appropriate** when the following criteria are met:

1. prostate-specific membrane antigen (PSMA)-positive; and
2. metastatic castration-resistant prostate cancer (mCRPC); and
3. have been treated with one androgen-receptor pathway inhibitors (i.e., enzalutamide and/or abiraterone); and
4. have been treated with one or two taxane-based regimens; and
5. have at least one PSMA-positive metastatic lesion and no PSMA-negative lesions* on 68Ga-PSMA-11 or F-18 piflufolastat PSMA PET/CT scan.

*PSMA negative lesions are defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components ≥ 1.0 cm, lymph nodes ≥ 2.5 cm in short axis, solid organ metastases ≥ 1.0 cm in size.

IV. Samarium Sm 153 Lexidronam

Based upon our criteria and assessment of the peer-reviewed literature, Samarium Sm 153 Lexidronam has been medically proven to be effective and, therefore, is considered **medically appropriate** for the treatment of osteoblastic metastatic bone lesions that enhance on radionuclide bone scan.

V. Strontium-89 Chloride

Based upon our criteria and assessment of the peer-reviewed literature, Strontium-89 Chloride has been medically proven to be effective and, therefore, is considered **medically appropriate** for the treatment of bone pain in patients with confirmed skeletal metastases.

VI. Lutathera (lutetium or Lu 177 dotatate)

A. Based upon our criteria and assessment of the peer-reviewed literature, peptide receptor radionuclide therapy using Lutathera has been medically proven to be effective and, therefore, is considered **medically appropriate** for the treatment of adults with low (G1), intermediate (G2), or high-grade (G3) well-differentiated neuroendocrine tumors in the following settings:
   1. somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETS) of the foregut, midgut and hindgut that are either inoperable or metastatic; or
   2. somatostatin receptor positive tumors of the pancreas that are either inoperable or metastatic; or
   3. somatostatin receptor positive bronchopulmonary or thymic-tumors, which are either inoperable or metastatic; or
   4. pheochromocytomas or paragangliomas;

   when ALL of the following requirements are met:
   5. for well-differentiated G1 or G2 neuroendocrine tumors with a Ki-67 < 20%; OR well-differentiated G3 neuroendocrine tumors with a Ki-67 < 55%; and
   6. positive somatostatin receptor scintigraphy with correlative MRI or CT imaging of metastatic measurable disease or 68-Ga-Dotate PET scan positive for metastatic disease*; and
   7. progression of the disease following treatment with somatastatin-analogs (SSA); and
   8. the absence of the following contraindications:
      a. serum creatinine: 1.7 mg or greater per deciliter or creatinine clearance of 50 ml/minute; and
      b. Hgb. 8.0 g/dl or less; WBC less than 2000/mm^3; platelets less than 75,000 mm^3.

   *In the absence of metastatic disease, documentation should include a surgical or medical consult and the reason for inoperability.

VII. Azedra (iobenguane I 131)

A. Based upon our criteria and assessment of the peer-reviewed literature, Azedra (iobenguane I 131) has been medically proven to be effective and therefore, is considered **medically appropriate** when the following criteria are met:
   1. inoperable locally advanced or metastatic pheochromocytoma or paraganglioma requiring systemic treatment; and
   2. individual is 12 years of age or older; and
   3. iodine meta-iodobenzylguanidine scan (MIBG, Iobenguane scan) positive; and
   4. the absence of the following contraindications:
      a. creatinine clearance <30mL/min; and
      b. platelet count of 80,000mcL or less; and
      c. absolute neutrophil count of 1,200/mcL or less

VIII. HICON (sodium iodide I 131 solution/ capsules)

A. Based upon our criteria and assessment of the peer-reviewed literature, HICON (sodium iodide I 131 solution/ capsules) have been medically proven to be effective and therefore, are considered **medically appropriate** for the treatment of thyroid carcinoma (i.e., follicular, papillary, Hürthle cell) when one of the following criteria are met:
   1. remnant ablation after surgery in T1b/T2 localized disease when there are no other adverse pathologic, laboratory, or imaging features; or
   2. adjuvant therapy under the following circumstances:

a. gross extrathyroidal extension; or
b. a primary tumor greater than 4 cm; or
c. postoperative unstimulated thyroglobulin (Tg) greater than 10ng/mL; or
d. six or more positive lymph nodes or bulky lymph nodes; or
e. for follicular or Hürthle cell/Oncocytic, extensive vascular invasion (≥4 foci); or

3. presence of proven and documented unresectable or metastatic disease based on pathology or pretherapy radioiodine scan.

IX. Zevalin (ibritumomab tiuxetan)

A. Based upon our criteria and assessment of the peer-reviewed literature, Zevalin (ibritumomab tiuxetan) has been medically proven to be effective, and therefore, is considered **medically appropriate** for adults with:
1. relapsed low grade B-cell CD20-positive follicular non-Hodgkin lymphomas (NHLs); or
2. refractory low grade B-cell CD20-positive follicular NHLs; or
3. newly diagnosed (consolidation after chemotherapy) low grade B-cell CD20-positive NHLs after at least a partial response (PR) to therapy; or
4. newly diagnosed (initial treatment) low grade B-cell CD20-positive follicular NHLs for the elderly or infirm when no other option is expected to be tolerated; or
5. transformed B-cell follicular NHLs that are CD20-positive; AND
6. bone marrow biopsy demonstrating <25% involvement with lymphoma; AND
7. the absence of the following contraindications:
a. platelet count of 100,000/mm^3 or less; and
b. neutrophil count (ANC) ≤1,500, bone marrow cellularity < 15%; and
c. high tumor burden in the bone marrow (lymphoma bone marrow involvement >25%); and
d. previous radiation to >25% of active marrow sites.

This policy does not address the use of radiotracers for advanced diagnostic procedures. Please refer to CMP #6.01.29 Positron Emission Tomography (PET) Oncologic Applications

POLICY GUIDELINES

I. The dose regimen of Xofigo is 55 kBq (1.49 mCi) per kg body weight, given in six injections at four-week intervals.

II. The dose regimen of Pluvicto is 7.4 GBq (200 mCi) given by intravenous injection or infusion every six weeks for up to six doses. The frequency depends on how the cancer responds and how the patient tolerates therapy.

III. The dose regimen of Samarium Sm 153 Lexidronam is 1 mCi/kg given IV over 1 minute followed by saline flush and then 500 ml of fluid (either IV or PO).

IV. The recommended dose of Strontium-89 Chloride is 148 MBq, 4 mCi, administered IV over one to two minutes or a dose of 1.5- 2.3 MBq/kg, 40-60 uCi/kg body weight. Repeated administration of Strontium-89 Chloride should be based on an individual patient's response to therapy, current symptoms, and hematologic status, and are generally not recommended at intervals of less than 90 days.

V. The recommended dose of Lutathera is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses.

VI. The recommended dose regimen of Azedra is based on body weight. The dosimetric dose for patients weighing greater than 50 kg is 185 to 222MBq (5 or 6 mCi). The dosimetric dose for patients weighing 50 kg or less is 3.7 MBq/kg (0.1 mCi/kg)

VII. The recommended dose regimen of HICON is based on thyroid gland size and uptake. The dose for the treatment of thyroid carcinoma is 1,110 MBq to 3,700 MBq (30 mCi to 100 mCi) administered orally. The National Comprehensive Cancer Network (NCCN) recommends 30-50mCi for remnant ablation, 50-150mCi for adjuvant therapy and 100-200 mCi for the treatment of known disease.

VIII. The recommended dose regimen of Zevalin is administered in two steps and is based on body weight; 0.4mCi/kg if platelet count is ≥ 150,000; 0.3 mCi/kg (11.1MBq per kg) if platelet count is 100,000-149,000/mm^3.

DESCRIPTION

Radiopharmaceuticals deliver radiation to the cancer cells within their microenvironment, providing a more targeted approach. This is done either by using delivery vehicles that bind preferentially to a specific target or may be taken up by a tumor based on its environment. Radiopharmaceuticals have different emission properties which deliver radiation using either alpha or beta particles. Response to treatment with radiopharmaceuticals is much quicker than chemotherapy which may occur after many months or cycles and may occur after one single injection or up to five injections. Adverse events from treatment may also be less.

Xofigo

On May 15, 2013, the FDA approved radium-223 marketed under the name Xofigo injection (Bayer HealthCare Pharmaceuticals Inc). Xofigo is an alpha-emitting agent for treatment of patients with symptomatic, bone-metastatic, castration resistant prostate cancer (CRPC). Xofigo has a half-life of 11.4 days, and releases 94% of its energy as alpha-particles with very little beta or gamma-emission. Xofigo mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. Alpha-emission consists of particles with high energy and a short range, causing non-repairable breakage of double-strand DNA in adjacent cells, which results in a highly localized cytotoxic effect in the target areas, and causes an anti-tumor effect on bone metastases. The alpha particle range from Xofigo is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue and reduces marrow toxicity.

Xofigo is administered intravenously, given once per month for six months, by an appropriately licensed facility, usually in nuclear medicine or radiation therapy departments. Hematologic evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Prior to the initial dose, patients must have absolute neutrophil count (ANC) greater than or equal to 1.5 x 10^9/L, platelet count greater than or equal to 100 x 10^9/L, and hemoglobin greater than or equal to 10 g/dL. Before subsequent administrations of Xofigo, the ANC should be greater than or equal to 1 x 10^9/L and the platelet count greater than or equal to 50 x 10^9/L. Xofigo should be discontinued if a delay of six to eight weeks does not result in the return of blood counts to these levels. Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms are likely related to the fact that Xofigo is predominantly eliminated by fecal excretion. Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. Clothing soiled with Xofigo or patient fecal matter or urine should be washed promptly and separately from other clothing. Caregivers should use universal precautions, such as washing hands, wearing gloves and barrier gowns when handling patients' bodily fluids to avoid contamination.

Pluvicto

Formally known as ^{177}Lu-PSMA-617, Pluvicto (Novartis) was approved by the FDA on March 23, 2022 for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

Pluvicto is the first targeted radioligand therapy. The half-life is 6.647 days by emitting beta-particle radiation. Pluvicto emits beta-particle radiation selectively to PSMA-positive cells surrounding microenvironment. In early-phase studies in previously treated patients with metastatic castration resistant prostate cancer, Pluvicto has shown biochemical and radiographic response rates, reduced pain, and low toxicity.

Samarium Sm-153 Lexidronam

Samarium Sm-153 Lexidronam is a beta-emitting radionuclide that was approved by the FDA in March 1997. Samarium Sm-153 Lexidronam emits both medium-energy beta particles and a gamma photon and is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan. The half-life is 46.3 hours and it has a maximum range in the tissue of three mm. After complexing with EDTMP, Sm-153 binds to sites of active bone turnover, accumulating in osteoblastic lesions more than in normal bone. The dose regimen of Samarium Sm-153 Lexidronam is 1 mCi/kg given IV over 1 minute followed by saline flush and then 500 ml of fluid (either IV or PO). The patient should void as soon as possible after injection to minimize radiation exposure to the bladder. Samarium Sm-

153 Lexidronam should be used with caution in patients with compromised bone marrow reserves and low platelet counts. Pain relief may occur within one week after administration and a transient increase in bone pain may occur within 72 hours of injection.

Strontium-89 Chloride

On July 11, 2013, the FDA approved Strontium-89 chloride for relief of bone pain in patients with painful skeletal metastases. Strontium-89 Chloride acts similarly to calcium, localizing in bone mineral and is absorbed in sites of osteogenesis, especially at sites of metastases, compared to normal healthy bone. Strontium-89 Chloride is a beta-emitter with a maximum range in tissue of ~ 8 mm and has a half-life of 50.5 days. The recommended dose of Strontium-89 Chloride is 148 MBq, 4 mCi, administered IV over one to two minutes or a dose of 1.5- 2.3 MBq/kg, 40-60 uCi/kg body weight. Repeated administration of Strontium-89 Chloride should be based on an individual patient's response to therapy, current symptoms, and hematologic status, and are generally not recommended at intervals of less than 90 days. Bone marrow toxicity in the white blood cells and platelets is variable from patient to patient and must be monitored following administration of Strontium-89 Chloride. Relief of pain may not occur for seven to 20 days post injection and some patients have experienced a transient increase in pain at 36 to 72 hours after injection. Strontium-89 Chloride is excreted by the kidney and should be administered with caution in patients with renal dysfunction.

Lutathera (lutetium or Lu 177 dotatate)

Lutathera (lutetium or Lu 177 dotatate) (Novartis, formerly Advanced Accelerator Applications) was approved by the FDA on January 26th, 2018. It is also commonly referred to as "Lu 177". It is classified as a peptide receptor radionuclide. It is a radiolabeled-somatostatin analogue that binds to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors such as neuroendocrine tumors. It is then internalized and beta particle emission from Lutathera induces cellular damage by formation of free radicals in somatostatin receptor-positive cells and adjacent cells. It is considered as an alternative treatment option to first-line somatostatin analogues.

Azedra (Iobenguane I 131)

Azedra (Iobenguane I 131) (Progenics Pharmaceuticals, Inc.) was approved by the FDA on July 30th, 2018 and is a radioactive therapeutic agent with a structure similar to norepinephrine. Due to its structure, it is taken up by the norepinephrine transporter where it accumulates in adrenergically innervated tissues including pheochromocytoma and paraganglioma cells. The beta and gamma radiation resulting from the radioactive decay causes an anti-tumor affect. It is indicated for the treatment of adult and pediatric patients 12 years of age and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic therapy.

HICON (Sodium iodide I 131)

The primary treatment of choice for differentiated thyroid carcinoma is surgery, followed by radioactive iodine (RAI) ablation for select patients. HICON (Sodium iodide I 131) also referred to as ^{131}I, is a radioactive therapeutic agent, when given orally, (via capsule or solution) is naturally taken up through the blood by the thyroid, causing decay via beta emission and associated gamma emission. RAI has been in use since the 1940's, but the high concentration version of the drug received FDA approval on January 24th, 2003 (DraxImage). Serum thyroglobulin (Tg) levels can indicate the existence of distant metastases. RAI is given after total thyroidectomy to eliminate the normal thyroid remnant, ensure that Tg levels are undetectable after surgery, to reduce the risk of recurrence (adjuvant treatment), and to treat persistent or recurrent disease (treatment of known disease). Tumors that do not take up iodine, i.e., anaplastic (undifferentiated) and medullary thyroid carcinomas cannot be treated with RAI.

Zevalin (ibritumomab tiuxetan)

Zevalin (ibritumomab tiuxetan) (Biogen Idec) is a combination of a CD20-directed monoclonal antibody and the radioisotope yttrium-90. It has also been referred to as ^{90}Y ibritumomab tiuxetan. Zevalin was FDA approved on February 19, 2002 for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell Non-Hodgkin lymphomas (NHL), including patients with Rituximab refractory follicular NHL. The regimen includes the unlabeled antibody rituximab, which is given prior to Zevalin to saturate CD20 binding sites on B-cells in the peripheral blood and spleen, to improve Zevalin's biodistribution. Zevalin is seen as an effective treatment alternative for eligible patients but is not commonly used because the administration is seen as highly complex.

RATIONALE

The National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer (v1.2023) principles of radiopharmaceutical therapy states that Xofigo is an alpha-emitting radiopharmaceutical that has been shown to extend survival in patients who have castration-resistant prostate cancer (CRPC) with symptomatic bone metastases, but no visceral metastases. Xofigo alone has not been shown to extend survival in patients who have visceral metastases or bulky nodal disease greater than three to four cm. Xofigo differs from beta-emitting agents, such as samarium-153 and strontium-89, which are palliative and have no survival advantage. Xofigo causes double-strand DNA breaks and has a short radius of activity. Grade 3-4 hematologic toxicity (2 percent neutropenia, 3 percent thrombocytopenia, 6 percent anemia) occurs at a low frequency. At the present time, except on a clinical trial, Xofigo is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression. Concomitant use of denosumab or zoledronic acid does not interfere with the beneficial effects of Xofigo on survival.

The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial was a phase 3, randomized, double-blind, placebo-controlled study that randomized 921 patients with symptomatic bone-metastatic CRPC to six injections every week of either radium-223(50 kBq/kg) or placebo. Patients were symptomatic with two or more bone metastases, without visceral metastases and had received docetaxel or were ineligible for docetaxel treatment. Median overall survival in the Xofigo arm was 14.9 months compared to 11.2 months in the placebo arm. Median time-to-first skeletal related event was significantly improved in the treatment arm (13.6 months) compared to placebo (8.4 months). Time-to-alkaline-phosphatase-progression and time-to-PSA-progression was also improved in the treatment group. More adverse events were observed in the Xofigo group, with discontinuation of treatment due to adverse events occurring in 13 percent of the patients in the Xofigo and 20 percent of the patients in the placebo arm. The significantly improved overall survival in the treatment group met the predetermined boundary for discontinuing the study early and the trial was terminated due to evidence of significant treatment benefit of Xofigo.

The ERA 223 was a randomized, double-blind, placebo-controlled phase 3 trial. It included 165 oncology and urology centers in 19 countries, which assessed the efficacy and safety of combination therapy with abiraterone acetate plus prednisone or prednisolone and Xofigo in patients with asymptomatic or mildly symptomatic, chemotherapy-naïve, castration-resistant prostate cancer and bone metastases. A total of 806 patients with a minimum of two bone metastases and no known visceral or brain metastases were randomized 1:1 to either Xofigo combination therapy or placebo combination therapy. The primary end-point was occurrence of a symptomatic skeletal event, defined as use of external beam radiotherapy to relieve skeletal symptoms, a new symptomatic pathological bone fracture, spinal cord compression, or tumor-related orthopedic surgical intervention. The study showed that the combination of abiraterone acetate plus prednisone or prednisolone and Xofigo did not improve symptomatic skeletal event-free survival or overall survival and was associated with an increased frequency of fractures. Based on the results of this study, the manufacturer, Bayer HealthCare Pharmaceuticals Inc, does not recommend Xofigo for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials.

The National Comprehensive Cancer Network (NCCN) Guidelines for Bone Cancer (v3.2023) state that Sm 153 Lexidronam is a beta-particle-emitting, bone-seeking radiopharmaceutical, and has been evaluated in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases. Studies have reported that Samarium Sm 153 Lexidronam with peripheral blood progenitor cell support had low non-hematologic toxicity and provide pain palliation for patients with osteosarcoma local recurrence or osteoblastic bone metastases. Results of dose-finding studies have also demonstrated that Samarium Sm 153 Lexidronam can be effective in the treatment of patients with high-risk osteosarcoma.

In early-phase studies in previously treated patients with metastatic castration resistant prostate cancer, Lutetium Lu 177 vipivotide tetraxetan (Pluvicto) has shown biochemical and radiographic response rates, reduced pain, and low toxicity.

The VISION trial, an international multi-center phase 3 trial compared treatment with Pluvicto and standard care to standard care alone in patients with metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regiments (Sartor et al., 2021). A total of 891 patients with a PSMA-positive gallium-68-labeled PSMA PET scan and who had progressed on androgen-receptor-pathway inhibitors and taxane therapy were randomized 2:1 to Pluvicto and standard care or standard care alone. Imaging-based progression

free survival (PFS), overall survival, objective response, disease control, and time to symptomatic skeletal events were evaluated. Both PFS and overall survival were longer in the Pluvicto and standard care group (median 8.8 months and 15.3 months, respectively) compared to standard care alone (3.4 months and 11.3 months, respectively). Pluvicto and standard care group experienced more grade 3 and 4 adverse events (52.7%) than the standard care group (38.0%) but quality of life was not adversely affected. The authors concluded that Pluvicto along with standard care prolongs PFS and overall survival when compared to standard care alone in patients with metastatic castration – resistant prostate cancer.

The NCCN Guidelines for Bone Cancer (v2.2022) state that samarium-153 ethylene diamine tetramethylene phosphonate (Sm-153-EDTMP) is a beta-particle-emitting, bone-seeking radiopharmaceutical, and has been evaluated in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases. Studies have reported that Sm-153-EDTMP with peripheral blood progenitor cell support had low non-hematologic toxicity and provide pain palliation for patients with osteosarcoma local recurrence or osteoblastic bone metastases. Results of dose-finding studies have also demonstrated that Sm-153-EDTMP can be effective in the treatment of patients with high-risk osteosarcoma.

The FDA approval for the use of Lutathera is based on the results of two published studies. The NETTER 1 study 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 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 eight 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 Lutathera arm vs 10.8% in the control group. The response rate was 18% in the Lutathera group vs 3% in the control group. In an updated analysis, progressive disease was seen in 23% of the Lutathera 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 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%.

The MIP-1B12B study (NCT00874614) was a multicenter, open-label, single-arm prospective study of the radiopharmaceutical Azedra, that included 74 intention-to-treat participants, 12 years of age or older with a diagnosis of pheochromocytoma or paraganglioma. To be eligible, participants had to be appropriate for curative treatment and had failed a prior treatment. The primary outcome was the number of patients with 50% or greater reduction in antihypertensive medication(s) lasting for at least six months after administering the last therapeutic dose of Azedra. The primary endpoint was met by 25% of patients (95% CI, 16.2% to 36.5%). Antitumor activity was demonstrated with 22.1% (95% CI, 13.6% to 32.7%) of patients maintaining a response for at least 6 months. Given the severity and rarity of the condition and its association with a high degree of morbidity and mortality, the results of the study represent a clinically meaningful outcome.

In 2019, the American Thyroid Association (ATA), the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association issued a joint statement for the use of ^{131}I therapy for the treatment of differentiated thyroid cancer. The societies defined terminology that should be used to communicate the goals of ^{131}I therapy. Adapted from the joint statement:

	^{131}I		
Goal	**Remnant Ablation**	**Adjuvant Treatment**	**Treatment of Known Disease**

Initial staging	✓	✓	✓
Facilitate follow-up	✓	✓	✓
Improve disease-specific survival	-	✓	✓
Decrease recurrence	-	✓	-
Improve progression-free survival	-	✓	✓
Curative intent	-	✓	✓
Palliative intent	-	-	✓

The categories for thyroid cancer staging by the American Thyroid Association are low, intermediate, and high risk, which provides risk for recurrence. Preoperative staging and risk of recurrence determine the need for radiotherapy after surgery and following surveillance. The evidence for the use of ^{131}I in the post operative setting of differentiated thyroid carcinoma is limited to retrospective studies. Although numerous have been published, findings are inconsistent regarding improvement in outcomes. The joint consensus states that, "Even though most guidelines make recommendations with regard to the postoperative use of ^{131}I based primarily on staging systems that predict risk of recurrence or disease specific mortality, the actual goal of ^{131}I therapy can only be determined once the postoperative disease status has been assessed. Regardless of initial risk stratification, patients with biochemical, structural, or functional evidence of persistent disease can only be candidates for "treatment of known disease." Patients demonstrating no histological, biochemical, or imaging evidence of persistent disease after appropriate initial surgery may be candidates for observation, remnant ablation, or adjuvant treatment."

NCCN, in the v.2.2023 Guidelines for Thyroid Carcinoma, recommends postoperative RAI when a number of clinical factors predict a significant risk of recurrence, distant metastases, or disease-specific mortality, including carcinoma type, size of primary tumor, post operative Tg level, vascular invasion, presence of metastases, etc. RAI is not typically indicated for patients considered to have a low risk of recurrence, or after lobectomy, or for patients that have metastatic disease that is not amenable to RAI therapy, meaning iodine refractory disease. NCCN states that RAI may be used for patients without gross residual disease, but that data is conflicting.

Witzig et al., in a 2007 post-hoc analysis, aimed to assess the durability of four clinical trials-a Phase I-II dose-finding trial in patients with indolent and aggressive NHL, a Phase II trial of reduced-dose ^{90} Y ibritumomab tiuxetan in patients with mild thrombocytopenia, a randomized Phase III trial that compared the ibritumomab tiuxetan regimen with rituximab mono-therapy, and a Phase III trial in patients with rituximab-refractory NHL. The trials represented a total of 211 patients from 30 centers across the United States. The analysis revealed that 37% of patients treated with ^{90} Y ibritumomab tiuxetan had a long-term response to the treatment (defined as time to progression of 12 months or longer). With a median follow- up of 53.5 months, the median duration of response was 28.1 months. The median overall survival in the 211 patients was 49.3 months. Overall survival was 52 months or longer in 82% of those individuals with a long-term response, compared to 34.6 months in patients without a long term response. The estimated overall survival at 5 years was 53% for all patients treated with ^{90} Y ibritumomab tiuxetan.

CODES

- *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.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
77750	Infusion or instillation of radioelement solution (includes 3-month follow-up care (*effective 01/01/06*)
78800	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, single area (e.g., head, neck, chest, pelvis), single day imaging (*effective 01/01/20*).
78801	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, 2 or more areas (e.g., abdomen and pelvis, head and chest), 1 or more days imaging or single area imaging over 2 or more days (*effective 01/01/20*).
78802	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, whole body, single day imaging (*effective 01/01/20*).
78803	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), single area (e.g., head, neck, chest, pelvis), single day imaging (*effective 01/01/23*).
78804	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, whole body, requiring 2 or more days imaging (*effective 01/01/20*).
79101	Radiopharmaceutical therapy, by intravenous administration
79005	Radiopharmaceutical therapy, by oral administration (*effective 01/01/05)*
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug (*effective 01/01/09*)
96375	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug (list separately in addition to code for primary procedure) (*effective 01/01/09*)
96409	Chemotherapy administration,; intravenous, push technique, single or initial substance/drug *(effective 01/01/06)*

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HCPCS Codes

Code	Description
A4641	Radiopharmaceutical, diagnostic, not otherwise classified (*effective 01/01/06*)
A9513	Lutetium lu 177, dotatate injection, therapeutic, 1mCi (Lutathera) (*effective 01/01/19*)
A9517	Iodine I-131 sodium iodide capsule(s), therapeutic, per mCi (HICON) (*effective 01/01/06*)
A9530	Iodine I-131 sodium iodide solution, therapeutic, per mCi (HICON) (*effective 01/01/06*)

Code	Description
A9543	Yttrium Y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 mCi (Zevalin) (*effective 01/01/06)*
A9590	Iodine I-131, Iobenguane, 1mCi (Azedra) (*effective 01/01/20*)
A9600	Strontium sr-89 chloride, therapeutic, per mCi (*effective 01/01/06*)
A9604	Samarium sm-153 lexidronam, therapeutic, per treatment dose, up to 150 mCi
A9699	Radiopharmaceutical, therapeutic, not otherwise classified
A9606	Radium RA-223 dichloride, therapeutic, per UCI (Xofigo) (*effective 01/01/15*)
A9607	Lutetium lu 177 vipivotide tetraxetan, therapeutic, 1 millicurie (*effective 10/01/22*) (Pluvicto)
A9699	Radiopharmaceutical, therapeutic, not otherwise classified (*effective 01/01/06*)
C9399	Unclassified drugs or biologicals

ICD10 Codes

Code	Description
C61	Malignant neoplasm of prostate
C7A.010-C7A.019	Malignant carcinoid tumors of the small intestine code range
C7A.020-C7A.025	Malignant carcinoid tumors of the appendix, large intestine, and rectum code range
C71.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.092	Malignant carcinoid tumor of the stomach
C7A.094-C7A.096	Malignant carcinoid tumor of the foregut, midgut, and hindgut, unspecified code range
C7B.00-C7B.09	Secondary neuroendocrine tumor code range
C7B.8	Other secondary neuroendocrine tumors
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
D40.0	Neoplasm of uncertain behavior of prostate
V58.0	Radiotherapy
Z85.46	Personal history of malignant neoplasm of prostate

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*Key Article

KEY WORDS

XoFigo, Ra-223, radium-223, Radium Ra 223 Dichloride, Lutetium Lu 177 Vipivotide Tetraxetan, Pluvicto, Strontium-89 Chloride, radiopharmaceutical, Samarium, Strontium, radiotherapeutic, Lutathera, Peptide receptor radionuclide therapy, PRRT, PRRNT, Receptor-mediated radiotherapy, Radiolabeled nuclide therapy, somatostatin analog, ^{90}Y-DOTATOC, 177Lu-DOTA0, Tyr3, 90Y-DOTA0.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based on our review, radiopharmaceuticals for the treatment of cancer are not addressed in National or Regional Medicare coverage determinations or policies.