MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Radiopharmaceuticals**
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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 assessment of the peer-reviewed literature, **Xofigo** injection (Radium Ra 223 Dichloride) has been medically proven to be effective and, therefore, is considered **medically appropriate** for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

II. Based upon our criteria and assessment of the peer-reviewed literature, **Pluvicto** (Lutetium Lu 177 Vipivotide Tetraxetan) has been medically proven to be effective and, therefore, is considered **medically appropriate** for the treatment of patients with prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC) and who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

III. 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.

IV. Based upon our criteria and assessment of the peer-reviewed literature, **Metastron** (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 painful confirmed skeletal metastases.

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. The safety and efficacy of Xofigo beyond six injections have not been determined.

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 Metastron 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 Metastron 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.

DESCRIPTION

Bone metastases is a common complication that occurs more frequently in prostate, breast, thyroid, kidney, and lung cancers. Bone metastases can cause pain refractory to non-steroidal anti-inflammatory drugs or opioids, pathological fractures, compression of the spinal cord or nerve roots, and life-threatening hypercalcemia. These complications may limit the ADL's, thus reducing a persona's quality of life. Radiopharmaceutical therapy (RPT) may be used to alleviate pain caused from bone metastases.

RPT is radiation delivery 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 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 1.5×10^9/L, platelet count greater than or equal to 100×10^9/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 1×10^9/L and the platelet count greater than or equal to 50×10^9/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 (lutetium Lu 177 vipivotide tetraxetan) 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 (Quadramet) 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 Quadramet is 1 mCi/kg given IV over one 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. Quadramet 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.

Metastron 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. Sr-89 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 Metastron 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 Metastron 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 Metastron. 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. Metastron is excreted by the kidney and should be administered with caution in patients with renal dysfunction.

RATIONALE

Quadramet (Samarium (Sm-153) lexidronam) is a beta-emitting radionuclide that was approved by the FDA in March 1997.

On May 15, 2013, the FDA approved radium-223 marketed under the name Xofigo injection (Bayer HealthCare Pharmaceuticals Inc).

On July 11, 2013, the FDA approved Metastron (Sr-89 chloride) for relief of bone pain in patients with painful skeletal metastases.

Pluvicto (lutetium Lu 177 vipivotide tetraxetan) 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.

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 (two percent neutropenia, three percent thrombocytopenia, six 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 weeks 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 doxcetaxel 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) states 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.

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.

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
79101	Radiopharmaceutical therapy, by intravenous administration

HCPCS Codes

Code	Description
A9600	Strontium Sr-89 chloride, therapeutic, per mCi
A9604	Samarium Sm-153 lexidronam, therapeutic, per treatment dose, up to 150 mCi
A9606	Radium Ra 223 dichloride, therapeutic, per UCI

Code	Description
A9607	Lutetium lu 177 vipivotide tetraxetan, therapeutic, 1 millicurie (*effective 10/01/2022*) (Pluvicto)
A9699	Radiopharmaceutical, therapeutic, not otherwise classified
C9399	Unclassified drugs or biologicals

ICD10 Codes

Code	Description
C61	Malignant neoplasm of prostate
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
D40.0	Neoplasm of uncertain behavior of prostate
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, Quadramet, Strontium-89 Chloride, radiopharmaceutical, Samarium, Strontium, radiotherapeutic

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.