Radium Ra 223 Dichloride (Xofigo)

Medical Policy #: 06.01.36
Original Effective Date: September 2017
Reviewed: September 2022
Revised: September 2022

NOTICE: This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

DESCRIPTION

In 2022 an estimated 268,490 new cases of prostate cancer will be diagnosed with an estimated 34,500 deaths from prostate cancer. The use of prostate specific antigen (PSA) screening and monitoring has allowed prostate cancer to be diagnosed at a localized stage. Despite early detection and appropriate treatment, some individual's progress to metastatic, hormone refractory prostate cancer after the failure of several lines of anti-hormonal therapies, and approximately 85% to 90% of individuals will have radiologic evidence of bone metastases which are a major cause of death, disability and decreased quality of life. Weakened bones due to cancer metastases can lead to fractures and compression of the spinal cord. They necessitate procedures such as surgery and radiation, which are designed to prevent or manage bone complications. The primary goal of treatment for bone metastases is to prevent the occurrence of debilitating bone complications that can affect an individual's quality of life. Radiation treatment has been shown to provide palliative care in patients with advanced prostate cancer.

Radium Ra 223 dichloride (Xofigo®), also known as radium-223, is an alpha particle-emitting radiotherapeutic agent. Radium-223 injection mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover. The high-energy alpha particle radiation causes breaks in the double stranded DNA of the targeted area resulting in an anti-tumor effect on the bone metastases. The short path of the alpha particles limits the damage to the surrounding normal tissue and bone marrow (the radium-223 binds to minerals in the bone to deliver radiation directly to the tumor that has spread to the bones while limiting damage to the surrounding body tissues). The U.S. Food and Drug Administration (FDA) in May 2013, approved radium-223 for the treatment of patients with castration-resistant prostate cancer (CRPC), with symptomatic bone metastases and no known visceral metastatic disease.

The FDA approval was based on clinical data from a multicenter, phase 3, randomized trial (ALSYMPCA) that included 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease. Fifty-seven percent of the patients received prior docetaxel and all patients received best supportive care. Patients were randomized in a 2:1 ratio to 6 monthly radium-223 intravenous injections or placebo. Compared to placebo, radium-223 significantly improved overall survival (medial 14.9 months vs. 11.3 months; HR, 0.70; 95% CI, 0.058-0.83; P < 0001) and prolonged time to first SRE (medial 15.6 months vs. 9.8 months). Preplanned subset analyses showed that survival benefit of radium-223 was maintained regardless of prior docetaxel use. Intention-to-treat analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic skeletal related events (SREs). Grade ¾ hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia and 13% anemia), likely due to the short range of radioactivity. Fecal elimination of the agent led to generally mild non-hematologic side effects, which include nausea, diarrhea, and vomiting. Radium-223 was associated with improved or slower decline of quality of life in ALSYMPCA.

Dosing

The dosing regimen of radium Ra 223 dichloride (Xofigo®) is given at 4-week intervals for a total of 6 injections. It is administered by a slow intravenous injection over 1 minute. Adverse reactions from this therapy include a risk of bone marrow suppression and gastrointestinal symptoms including nausea, vomiting and diarrhea. To monitor for bone marrow suppression a hematologic evaluation of patients must be performed at baseline and prior to every dose of radium-223 (Xofigo®).

According to the FDA approved label, before the first administration the absolute neutrophil count (ANC) should be $\geq$ 1.5 x 10^9/L, the platelet count $\geq$ 100 x 10^9/L and hemoglobin $\geq$10 g/dL. Before subsequent administrations, the ANC should be $\geq$ 1 x 10^9/L and the platelet count $\geq$ 50 x 10^9/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of radium-223 (Xofigo®), despite receiving supportive care, further treatment with radium-223 (Xofigo®) should be discontinued. Additional FDA labeling includes the following: the safety and efficacy beyond 6 injections with radium-223 (Xofigo®) has not been studied; and the safety and efficacy of concomitant chemotherapy with radium-223 (Xofigo®) have not been established.

Outside of a clinical trial, concomitant use with chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes or hemibody external radiotherapy are administered during the treatment period, radium-223 (Xofigo®) should be discontinued.

Other Indications

Currently, there are ongoing studies investigating the use of radium-223 for other indications to include breast cancer, osteosarcoma, bone metastases in breast cancer, kidney cancer, lung cancer and paraganglioma and is also being studied in combination with docetaxel for the use in treatment of castration-resistant prostate cancer (CRPC) and bone metastases. Presently, there is insufficient published literature to demonstrate the safety and effectiveness of radium-223 when used for these indications.

Morris et al. (2019) investigated whether combining radium-223 with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase I dose escalation/randomized phase 2a trial. The phase I trial was a dose escalation study to define a recommended phase 2 dose (RP2D) of docetaxel and radium-223. In the phase 2a trial, patients were randomized 2:1 to the recommended combination regimen of docetaxel at a dose of 75 mg/m^2 every 3 weeks (q3w). Patients with bone-predominate metastatic castration-resistant prostate cancer (mCRPC) were eligible. Endpoints were safety, efficacy and treatment related changes in serum and imaging biomarkers. Twenty patients were enrolled in phase 1; 53 patients were randomized in phase 2a: 36 to combination treatment and 17 to docetaxel alone. The RP2D for the combination was radium-223 55 kBq/kg every six weeks × 5 doses, plus docetaxel 60 mg/m^2 q3w × 10 doses. Febrile neutropenia was dose limiting. A higher rate of febrile neutropenia was seen in the docetaxel monotherapy arm (15% versus 0%); the safety profile of the treatment groups was otherwise similar. The combination arm had more durable suppression of prostate-specific antigen (median time to progression, 6.6 versus 4.8 months, respectively), alkaline phosphatase (9 versus 7 months) and osteoblastic bone deposition markers. The authors concluded, radium-223 in combination with docetaxel at the RP2D was well tolerated. Exploratory efficacy data suggested enhanced anti-tumor activity for the combination relative to docetaxel alone. Comparative studies with endpoints of clinical benefit are warranted.

In 2019, Kairemo et al. developed novel criteria in a clinical trial of radium-223 dichloride for response assessment in osteosarcoma, NAFCIST ($Na^{18}F$ PET Response Criteria for Solid Tumors). Patients received one to six cycles of $^{223}RaCl_2$, and cumulative doses varied from 6.84 MBq to 57.81 MBq. Molecular imaging with technetium-99m phosphonate scintigraphy, fluorine-18-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) or sodium fluoride-18 ($Na^{18}F$) PET was used to characterize the disease. Correlation of biomarkers and survival was analyzed with NAFCIST measure from $Na^{18}F$ PET. Of the 18 patients, 17 had bone lesions visible in at least one of the imaging studies. In four of seven patients with multiple skeletal lesions (>5), FDG PET and NaF PET studies could be compared. The skeletal tumor locations varied in our patient population: cranium=2, extremities=7, pelvis=10, spine=12 and

thorax=9. The 18F-FDG PET and $Na^{18}F$ PET studies could be compared in all four patients who had multiple lung lesions (>5). Overall, the Response Evaluation Criteria in Solid Tumors response was seen in one patient, but four patients experienced mixed responses better defined by $Na^{18}F$ PET. Changes in NAFCIST were correlated with changes in bone alkaline phosphatase levels (r=0.54) and negatively with cumulative dose of $^{223}RaCl2$ (r=− 0.53). NAFCIST correlated with overall survival (p value of 0.037) while the PERCIST (PET Response Criteria in Solid Tumors) did not (p value of 0.19). The authors concluded our results indicate that $Na^{18}F$ PET should be further studied in osteosarcoma staging. NAFCIST may be a promising criteria for high-risk osteosarcoma response evaluation and correlates with survival. Further validation studies are needed.

In 2019 Subbiah et al. completed the study NCT01833520 which is an investigator-initiated trial of alpha particle–emitting radium 223 in high-risk osteosarcoma. The study was approved by the MD Anderson Cancer Center institutional review board and the US FDA in accordance with the Declaration of Helsinki. The radioactive isotopes were provided by Bayer HealthCare Pharmaceuticals. Eligible patients were registered in a secure central database, and the study was monitored by the institutional IND office. Eligible patients included those with progressive, locally recurrent, or metastatic osteosarcoma (i.e., high-risk osteosarcoma only) with no standard curative options available and at least one indicator lesion avid on a technetium medronic acid (99mTc-MDP) scan or on a sodium fluoride (NaF) positron emission tomography (PET scan and/ or a fluorodeoxyglucose (FDG) PET scan that could be subjected to further quantitative assessment by these scans. In addition, patients with extremely rare bone-forming osteosarcoma-like tumors that behave like osteosarcoma phenotypically and are clinically treated like osteosarcoma (e.g., malignant fibrous histiocytoma of bone or malignant transformation of giant cell tumor of the bone) were included if the patients satisfied all the other inclusion criteria. Additional key eligibility criteria included an age of ≥15 years, a weight of ≥40 kg, and an Eastern Cooperative Oncology Group performance status of at least 2. Patients or the parents or guardians of patients who were minors provided written informed consent. The required hematology and serum biochemistry screening values were as follows: white blood cell count, $\geq 1{,}500/mm^3$; absolute neutrophil count $\geq 1{,}000/mm^3$; platelet count, $\geq 75 \times 10^3/mm^3$; hemoglobin level, ≥8 g/dL; total bilirubin level, ≤1.5 × institutional upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase levels, ≤2.5 × ULN for each; creatinine level, ≤1.5 × ULN; and albumin level, >25 g/L. A 3+3 phase I, dose-escalation trial of $^{223}RaCl_2$ (50, 75, and 100 kBq/kg) was designed in recurrent or metastatic osteosarcoma patients. Objective measurements including serum alkaline phosphatase and bone turnover markers at baseline, mid-study, and the end of the study were compared with changes in standardized uptake values on PET–computed tomography (CT) (with FDG and/or NaF) and single-photon emission CT (SPECT)-CT (with 99mTc-MDP). The following labs were obtained at baseline and at every cycle: hemoglobin (g/dL), albumin (g/dL), absolute lymphocyte count (k/uL), serum lactate dehydrogenase (IU/L), serum alkaline phosphatase (IU/L), bone alkaline phosphatase (mcg/L), serum carboxy-terminal collagen crosslinks or serum crossLaps (CTX)(pg/mL) and osteocalcin (ng/mL) as exploratory markers of response, or adverse events. $^{223}RaCl_2$ was administered as a slow

bolus IV injection at intervals of every 4 weeks (±6 days) for a total of up to six doses, i.e., six cycles. Patients were assigned to dose levels according to a 3+3 phase I dose escalation schedule. Doses of 50, 75, or 100 kBq/kg were assigned in cohorts of three patients after study registration. Dose 1 was given within 30 days of study registration. At least three patients were required to successfully complete 6 weeks of therapy before the study advanced to the next cohort. Individual patients received the same dose of $^{223}RaCl_2$ as they did at dose 1 for all subsequent doses. Among 18 patients enrolled (including 15 males) aged 15-71 years, tumor locations included spine (n=12, 67%), pelvis (n=10, 56%), ribs (n=9, 50%), extremity (n=7, 39%), and skull (n=2, 11%). Patients received 1-6 cycles of $^{223}RaCl_2$; cumulative doses were 6.84-57.81 MBq. NaF PET revealed more sites of metastases than did FDG PET. One patient showed a metabolic response on FDG PET and NaF PET. Four patients had mixed responses, and one patient had a response in a brain metastasis. Bronchopulmonary hemorrhage from Grade 3 thrombocytopenia (N=1) was a DLT. The median overall survival time was 25 weeks. The authors concluded future studies of $^{223}RaCl_2$ to treat osteosarcoma in an earlier setting and in combination with standard therapies and local control are warranted.

Practice Guideline and Position Statements

American Urological Association (AUA)
(In 2013; amended 2018), The AUA issued a guideline for castration resistant prostate cancer, which included the following guideline statements:

- Symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy: Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status and no prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)
- Symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy: Clinicians may offer radium-223 to patients with symptoms from bony metastases from mCRPC with poor performance status and no prior docetaxel chemotherapy and without known visceral disease in select cases, specifically when the performance status is directly related to symptoms related to bone metastases. (Expert Opinion)
- Symptomatic, mCRPC with good performance status and prior docetaxel chemotherapy: Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status who received prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)

(*Accessed September 2022*)

National Comprehensive Cancer Network (NCCN)

- **Bone Cancer Version 1.2023**
  - **Osteosarcoma – Relapsed or Refractory Disease**

- This guideline does not include or indicate the use or Radium Ra-223 Dichloride (Xofigo) in the treatment management of bone cancer. (*Accessed September 2022*)

- **Breast Cancer Version 4.2022**
  - This guideline does not include or indicate the use or Radium Ra-223 Dichloride (Xofigo) in the treatment management of breast cancer. (*Accessed September 2022*)

- **Prostate Cancer Version 4.2022** (*Accessed September 2022*)
  - **Principles of Radiation Therapy – Radiopharmaceutical Therapy**
    - Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in patients who have castration recurrent prostate cancer (CRPC) with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky nodal disease (> 3 to 4 cm). Radium-223 differs from beta-emitting agents, such as samarium 153 and strontium 89, which are palliative and have no survival advantage. Radium-223 causes double strand DNA breaks and has a short radius of activity. Grade 3-4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
    - Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
    - Prior to the initial dose, patients must have absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L, platelet count $\geq$ 100 x 10^9/L, and hemoglobin $\geq$ 10g/dL
    - Prior to subsequent doses, patients must have ANC $\geq$ 1 x 10^9/L and a platelet count $\geq$ 50 x 10^9/L (per label). Radium-223 should be discontinued if a delay of 6-8 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 may occur because radium-223 is eliminated by fecal excretion.
    - Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression, except on a clinical trial.
    - Radium-223 may increase fracture risk when given concomitantly with abiraterone.
    - Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT.
    - Concomitant use of denosumab or zoledroic acid does not interfere with the beneficial effects of radium-223 on survival.

- **Discussion**

  Radium-223 and Other Radiopharmaceuticals

  - In May 2013, the U.S. Food and Drug Administration (FDA) approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of metastatic CRPC in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase 3 randomized trial (ALSYMPCA) that included 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease. Fifty-seven percent of the patients received prior docetaxel and all patients received best supportive care. Patients were randomized in a 2.1 ratio to 6 monthly radium-223 intravenous injections or placebo. Compared to placebo, radium-223 significantly improved OS (median 14.9 months vs 11.3 months); HR, 0.70; 95% CI, 0.058-0.83; P < .001) and prolonged time to first skeletal -related event (SRE) (median 15.6 months vs 9.8 months). Preplanned subset analyses showed that all survival benefit of radium-223 was maintained regardless of prior docetaxel use. Intention to treat analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs. Grade ¾ hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity. Fecal elimination of the agent led to generally mild non-hematologic side effects, which included nausea, diarrhea, and vomiting. Radium-223 was associated with improved or slower decline of QOL in ALSYMPCA.

    The multicenter, international, double-blind, placebo-controlled, phase 3 ERA 223 trial randomized bone-metastatic patients with chemotherapynaïve CRPC to abiraterone with or without radium-223. The patients were asymptomatic or mildly symptomatic. The primary endpoint of symptomatic skeletal event-free survival in the intention-to-treat population was not met. In fact, the addition of radium-223 to abiraterone was associated with an increased frequency of bone fractures compared with placebo. The Panel therefore does not recommend this combination.

    Radium-223 is category 1 option to treat symptomatic bone metastases without visceral metastases. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose. Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial as the potential for additive myelosuppression. It is not recommended for use in combination with docetaxel or any other systemic therapy except ADT. It should not be used in patients with visceral metastases, and it should be given with concomitant denosumab or zoledronic acid.

Beta-emitting radiopharmaceuticals are an effective and appropriate option for patients with widespread metastatic disease, particularly if they are no longer candidates for effective chemotherapy. Because many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Unlike the alpha-emitting agent radium-223, beta emitters confer no survival advantage and are palliative. Beta-emitting radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include strontium-89 (89Sr) or samarium-153 (153Sm). The risk of bone marrow suppression, which might influence the ability to provide additional systemic chemotherapy, should be considered before this therapy is initiated.

- **Progression to and Management of CRPC**
  - Most patients with advanced disease eventually stop responding to traditional ADT and are categorized as castration-resistant (also known as castration-recurrent). CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL).710 Patients whose disease progresses to CRPC during primary ADT should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL; <1.7 nmol/L). Imaging tests may be indicated to monitor for signs of distant metastases. Factors affecting the frequency of imaging include individual risk, age, overall patient health, PSA velocity, and Gleason grade.

    For patients who develop CRPC, ADT with an LHRH agonist or antagonist should be continued to maintain castrate serum levels of testosterone (<50 ng/dL).

    Patients with CRPC and no signs of distant metastasis on conventional imaging studies (M0) can consider observation with continued ADT if PSADT is greater than 10 months (preferred), because these patients will have a relatively indolent disease history. Secondary hormone therapy with continued ADT is an option mainly for patients with shorter PSADT (≤10 months) as described below, because the androgen receptor may remain active.

    For patients who develop metastatic CRPC, metastatic lesion biopsy is recommended, as is MSI/MMR testing, if not previously performed. If MSIH or dMMR is found, referral to genetic counseling should be made to assess for the possibility of Lynch syndrome
    e. These patients should also have germline and tumor testing to check for mutations in homologous recombination genes (ie, BRCA1, BRCA2, ATM, PALB2, FANCA) if not done previously. This information may be

used for genetic counseling, early use of platinum chemotherapy, use of PARP inhibitors, or eligibility for clinical trials.

TMB testing should also be considered for patients with metastatic CRPC to inform possible use of pembrolizumab in later lines of therapy (see Pembrolizumab, below). ADT is continued in patients with metastatic CRPC while additional therapies, including secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies, are sequentially applied, as discussed in the sections that follow; all patients should receive best supportive care. The Panel defined treatment options for patients with metastatic CRPC based on previous exposure to docetaxel and to a novel hormone therapy. Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide received for metastatic castration-naïve disease, M0 CRPC, or previous lines of therapy for M1 CRPC.

The Panel notes that relugolix has not been adequately studied in combination with potent androgen receptor inhibitors such as enzalutamide, apalutamide, darolutamide, or abiraterone acetate, nor has it been studied in combination with docetaxel or cabazitaxel chemotherapy. Potential drug interactions include induction of cytochrome P450 enzymes and reduced concentration and efficacy of relugolix with enzalutamide or apalutamide and cardiac QTc interactions with abiraterone. Further studies of relugolix dosing and drug interactions with commonly used agents in advanced prostate cancer are needed to ensure patient safety and proper dosing. Therefore, relugolix is not recommended in combination with other therapies at this time.

The decision to initiate therapy in the CRPC setting after disease progression on one or more treatments should be based on the available high-level evidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. Prior exposures to therapeutic agents should be considered. There are not much data to inform the optimal sequence for delivery of these agents in patients with metastatic CRPC (see Sequencing of Therapy in CRPC, below). Choice of therapy is based largely on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, symptoms, and potential side effects.

NCCN recommends that patients being treated for CRPC be closely monitored with radiologic imaging (ie, CT, bone imaging), PSA tests, and clinical exams for evidence of progression. Therapy should be continued until clinical progression or intolerability in cases where PSA or bone imaging changes may indicate flare rather than true clinical progression. The sequential use of these agents is reasonable in a patient who remains a

candidate for further systemic therapy. Clinical trial and best supportive care are additional options.

Regulatory Status
Radium Ra 223 dichloride (Xofigo®) injection was approved by the FDA on May 15, 2013, for the treatment of individuals with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease.

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary
Radium Ra 223 dichloride (Xofigo®), also known as radium-223 is considered **medically necessary** and, therefore, covered for a maximum of **six injections** for the treatment of prostate cancer when **ALL** of the following criteria are met:

- The individual is ≥ 18 years old
- The individual has been diagnosed with castration-resistant prostate cancer (CRPC); **and**
- The individual has symptomatic skeletal (bone) metastases; **and**
- The individual has no evidence of bulky nodal disease > 3 or visceral metastases on imaging; **and**
- Will not be used concurrently with other chemotherapy or biologic therapy
    - *Note: the individual may be kept on ablative hormonal treatment to maintain a castrate level in accordance with the National Comprehensive Cancer Network (NCCN) guidelines which is defined as serum testosterone level <50 ng/dL.*

Investigational
Radium Ra 223 dichloride (Xofigo®), also known as radium-223 is considered **investigational** when the above criteria is not met, including but not limited to the any of the following:

- All other indications
- When used in combination with chemotherapy or biologic therapy
- Has received a previous course of Radium Ra 223 dichloride (Xofigo®)
- Beyond six injections (due to exceeding the FDA approved dosing)

Based on the peer reviewed medical literature the safety and effectiveness for indications other than the medically necessary indication listed above has not been established. Additional studies are needed to further investigate the safety and efficacy of radium-223 (Xofigo®) for the patient populations other than castration-resistant prostate cancer (CRPC). Also, the FDA approved label indication state the safety and efficacy beyond 6 injections with radium-223 (Xofigo®) has not been studied; and the safety and efficacy

of concomitant chemotherapy with radium-223 (Xofigo®) have not been established. The evidence is insufficient to demonstrate the effects on net health outcomes for the indications listed above.

Policy Guidelines

- Prior to the initial dose of radium-223, patients must have an absolute neutrophil count ≥1.5 X 10^9/L, platelet count ≥100 X 10^9, and hemoglobin ≥ 10g/dL.
- Prior to subsequent doses of radium-223, patients must have absolute neutrophil count ≥1 X 10^9/L and platelet count ≥50 X 10^9 per label.
- Radium-223 should be discontinued if a delay of 6-8 weeks does not result in return of blood counts to these levels.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- A9606 Radium RA-223 dichloride, therapeutic per microcurie

SELECTED REFERENCES

- Cookson M, Roth B, Dahm P, et. al. Castration-Resistant Prostate Cancer: American Urological Association Guideline. May 2013 (Amended April 2015). J Urol 2015 Feb;193(2):491-9. PMID 25444753
- National Comprehensive Cancer Network (NCCN) Prostate Cancer Version 4.2022. Also available at https://www.nccn.org
- National Comprehensive Cancer Network (NCCN) Bone Cancer Version 1.2023. Available at https://www.nccn.org
- National Comprehensive Cancer Network (NCCN) Breast Cancer Version 4.2022. Available at https://www.nccn.org
- UpToDate. Radium-223 Drug Information Lexicomp. Also available at https://www.uptodate.com
- UpToDate. Bone Metastases in Advanced Prostate Cancer: Management. A Oliver Sartor M.D., Steven J. DiBiase M.D., Topic last updated July 16, 2019. Also available at https://www.uptodate.com
- UpToDate. Overview of the Treatment of Castration-Resistant Prostate Cancer (CRPC). Nancy A. Dawson M.D., Topic last updated September 10, 2018. Also available at https://www.uptodate.com
- UpToDate. Radiation Therapy for the Management of Painful Bone Metastases. Lisa A. Kachinic M.D., Steven J. DiBiase M.D., Topic last updated May 30, 2019. Also available at https://www.uptodate.com
- UpToDate. Cancer Pain Management: Adjuvant Analgesics (Coanalgesics). Russell K. Portenoy M.D., Ebtesam Ahmed, PharmD, MS, Yair Y. Keilson M.D., Topic last updated September 4, 2018. Also available at https://www.uptodate.com

- UpToDate. Overview of Therapeutic Approaches for Adult Patients with Bone Metastasis from Solid Tumors. H. Michael Yu, M.D.,ScM, Sarah E. Hoffe M.D., Topic last updated May 10, 2019. Also available at https://www.uptodate.com
- UpToDate. Radiation Therapy Techniques in Cancer Treatment. Topic last updated August 1, 2017. Also available at https://www.uptodate.com
- Anderson PM, Subbiah V, Rohren E. Bone seeking radiopharmaceuticals as targeted agents of osteosarcoma: samarium-153-EDTMP and radium-223. Adv Exp Med Biol 2014;804:291-304. PMID 24924191
- Cheetam PJ, Petrylak DP. Alpha particles as radiopharmaceuticals in the treatment of bone metastases: mechanism of action of radium-223 chloride (Alpharadin) and radiation protection. Oncology (Williston Park) 2012 Apr;26(4):330-7. PMID 22655525
- Harrison MR, Wong TZ, Armstrong AJ, et. al. Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease. Cancer Manag Res 2013;5:1-14. PMID 23326203
- Nilsson S, Strang P, Aksnes AK, et. al. A randomized, dose response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer 2012 Mar;48(5):578-86. PMID 22341993
- Nilsson S, Franzen L, Parker C, et. al. Two-year survival follow-up of the randomized, double-blind placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. Clin Genitourin Cancer 2013 Mar;11(1):20-6. PMID 23021204
- Parker CC, Pascoe S, Chodacki A, et. al. A randomized double-blind, dose-finding, multicenter, phase 2 study of radium chloride (RA 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol 2013 Feb;63(2):189-97. PMID 23000088
- Parker C, Nilsson S, Heinrich D, et. al. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. The New England Journal of Medicine July 18, 2013 Vol. 369 No. 3
- Vapiwala N, Glatstein E. Fighting prostate cancer with radium-223 not your Madame's isotope. N Engl J Med 2013 Jul 18;369(3):276-8. PMID 23863055
- MacVicar GR, Hussain MH. Emerging therapies in metastatic castration-sensitive and castration-resistant prostate cancer. Curr Opin Oncol 2013 May;25(3):252-60. PMID 23511665
- Takalkar A, Adams S, Subbiah V. Radium-223 dichloride bone-targeted alpha particle therapy for hormone refractory breast cancer metastatic to bone. Exp Hematol Oncol 2014 Sep 8;3:23. PMID 25243101
- Colman R, Aksnes AK, Naume B, et. al. A phase IIa, nonrandomized study of radium-223 dichloride in advanced breast cancer patients with bone-dominant disease. Breast Cancer Res Treat 2014 Jun;145(2):411-8. PMID 2472861
- Subbiah V, Anderson P, Rohren E. Alpha-emitter radium 223 in high risk osteosarcoma: first clinical evidence of response and blood-brain barrier penetration. JAMA Oncol 2015 May;1(2):253-5. PMID 26181034

- Nilsson S. Alpha-emitter radium-223 in the management of solid tumors: current status and future directions. Am Soc Clin Oncol Educ Book 2014:e132-9. PMID 24857093
- Silva SC, Wilson C, Woll PJ. Bone Targeted agents in the treatment of lung cancer. Ther Adv Med Oncol 2015 Vol. 7(4) 219-228
- Saad F, Carles J, Gillessen S, et. al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open label, single arm phase 3b trial. Lancet Oncol 2016 Sep;17(9):1306-16. PMID 27473888
- Joung JY, Ha YS, Kim IY, Radium Ra 223 dichloride in castration-resistant prostate cancer. Drugs Today (Barc) 2013 Aug;49(8):483-90. PMID 23977665
- Xofigo-Radium Ra 223 Dichloride. Also available at https;//www.xofigo-us.com
- Doyle CM, Mills M, Damgaci S, et. al. Integration of Radium-223 Dichloride (Xofigo) into Clinical Practice for the Treatment of Castration-Resistant Prostate Cancer. Journal of Clinical Oncology 2019 37;7 suppl 312-312
- American Cancer Society. What's New in Osteosarcoma Research? Also available at https://www.cancer.org
- Deshayes E, Roumiguie M, Thibault C, et. al. Radium 223 dichloride for prostate treatment. Drug Des Devel Ther 2017;11:2643-2651. PMID 28919714
- Morris MJ, Loriot Y, Sweeney CJ, et. al. Radium-223 in combination with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase 1 dose escalation/randomized phase 2a trial. Eur J Cancer 2019 Jun;114:107-116. PMID 31082669
- Subbiah V, Anderson PM, Keriemo K, et. al. Alpha particle radium 223 dichloride in high risk osteosarcoma: a phase I dose escalation trial. Clin Cancer Res 2019 Jul 1;25(13):3802-3810. PMID 30733229
- Taber AM, Riley D, Adam J, et. al. Radium-223 following front line chemotherapy for patients with non-small cell lung cancer and bone metastases. Journal of Clinical Oncology 2018 36:15 suppl e21211-e21211
- Geva R, Lopez J, Danson S, Joensuu H, et. al. Radium-223 in combination with pacilataxel in cancer patients with bone metastases: safety results from an open label, multicenter phase Ib study. Eur J Nucl Med Mol Imaging 2019 May;46(5):1092-1101. PMID 30547207
- Sullivan J, Carles J, Cathomas R, et. al. Radium-223 within the evolving treatment options for metastatic castration-resistant prostate cancer: recommendations from a European Expert Working Group. Also available at https://doi.org/10.1016/j.euo.2019.02.007
- Silva S, Wilson C, Woll P. Bone-targeted agents in the treatment of lung cancer. Ther Adv Med Oncol 2015 Jul;7(4):219-228. PMID 26136853
- Kairemo K, Rohren E, Anderson P, et. al. Development of sodium fluoride PET response criteria for solid tumors (NAFCIST) in a clinical trial of radium-223 in osteosarcoma: from RECIST to PERCIST to NAFCIST. ESMO Open 2019; 4(1): e00439. PMID 30962954

- Subbiah V, Anderson P, Kairemo K. et. al. Alpha particle Radium 223 dichloride in high-risk osteosarcoma: a phase I dose escalation trial. Clinc Cancer Res. 2019 Jul 1;25(13):3802-3810. PMID 30733229
- Alibhai SMH, Breunis H, Feng G, et al. Association of Chemotherapy, Enzalutamide, Abiraterone, and Radium 223 With Cognitive Function in Older Men With Metastatic Castration-Resistant Prostate Cancer. JAMA Netw Open. 2021;4(7):e2114694. doi:10.1001/jamanetworkopen.2021.14694
- American Cancer Society. Cancer Facts & Figures 2022. Atlanta: American Cancer Society; 2022.

POLICY HISTORY

Date	Reason	Action
September 2022	Annual Review	Policy Revised
September 2021	Annual Review	Policy Renewed
September 2020	Annual Review	Policy Renewed
September 2019	Annual Review	Policy Renewed
September 2018	Annual Review	Policy Revised
September 2017		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.