09-J2000-01

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Reviewed: 03/13/19

Revised: 04/15/22

Subject: Radium Ra 223 (Xofigo®) Injection

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DESCRIPTION:

Prostate cancer is a leading cause of non-cutaneous cancer in men. Although most will be diagnosed at an early localized stage, up to 30% of cases will recur following curative surgical or radiation therapy. Androgen deprivation therapy with either surgical castration or gonadotropin releasing hormone (GnRH) analogs is commonly initiated to control disease in those who have developed metastases. Unfortunately, nearly all of these cases will continue to progress; when patients recur on androgen deprivation therapy in the setting of "castrate" levels of testosterone, patients are termed "castration-resistant" or "castration-recurrent". Current treatment options for metastatic castration-resistant/recurrent prostate cancer (CRPC) include both systemic and bone-targeted therapies. While systemic therapies (e.g., abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, sipuleucel-T) are not targeted to a specific organ, bone-targeted therapies are active predominately in the bone and leave lymph node and visceral metastases untreated. Available agents include zoledronic acid (Zometa), denosumab (Xgeva), and the radioisotopes strontium 89 (Metastron®) and samarium 153 (Quadramet) – none of which have been shown to possess a survival advantage (zoledronic acid and denosumab were approved based on a delay in time to skeletal related events; radioisotopes were approved for palliation of bone pain).

Radium 223 (Xofigo), an alpha emitting radiopharmaceutical, was approved by the U.S. Food and Drug Administration (FDA) on May 15, 2013 for the treatment of CRPC patients with symptomatic bone metastases and no evidence of visceral metastatic disease. Radium 223 mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover; this leads to a high frequency of double-strand DNA breaks in adjacent cells and results in an anti-tumor effect on bone metastases and ultimately extended patient survival. While radium 223 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 any beneficial effects.

The safety and efficacy of radium 223 were evaluated in subjects with CRPC and symptomatic bone metastases in a randomized, double-blind, placebo-controlled Phase III study. Individuals with visceral metastatic disease were excluded from the study. Subjects were randomized 2:1 to receive radium 223 (dose: 50 kBq/kg IV) every 28 days for six injections plus best supportive care or placebo plus best supportive care. The primary endpoint was overall survival with one predefined interim analysis; a secondary endpoint was time to symptomatic skeletal events. At the predefined interim analysis, the primary endpoint of overall survival met the boundary for statistical significance revealing a decrease in the risk of death in the radium 223 group with a hazard ratio of 0.695 (95% CI: 0.522, 0.875; p=0.00185). The median overall survival was 14 months in the radium 223 group (n=809 patients) compared to 11.2 months in the placebo group (n=268 patients). The time to symptomatic skeletal events was also delayed in the radium 223 arm with a hazard ratio of 0.610 (95% CI: 0.461, 0.807; p=0.00046). The median time to symptomatic skeletal events was 13.5 months compared with 8.4 months for radium 223 and placebo, respectively. The most common adverse reactions (>10%) in patients receiving radium 223 were nausea, diarrhea, vomiting and, peripheral edema. The most common hematologic laboratory abnormalities (> 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia.

In August 2018, the Warnings and Precautions section of package labeling for Xofigo was updated with the result of the ERA-223 trial. An increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) were observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo in combination with abiraterone acetate plus prednisone/ prednisolone. The labeling now states the following, “Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials”, and “Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established.”

The National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer list radium-223 as a category 1 treatment option under “Useful in certain circumstances” (regardless of prior docetaxel or novel hormone therapy) for symptomatic bone metastases in patients with CRPC. The listings include a footnote of “Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT and should not be used in patients with visceral metastases. Concomitant use of denosumab or zoledronic acid is recommended”. Per NCCN, visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases. The guidelines also state that radium 223 alone has not been shown to extend survival in men with visceral metastases or bulky lymph node metastases (>3 to 4 cm). The NCCN notes that radium-223 may increase fracture risk when given concomitantly with abiraterone and thus this combination is not recommended. The NCCN recommends that patients whose disease progresses to CRPC during primary androgen deprivation therapy (ADT) should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL) has been achieved.

POSITION STATEMENT:

Radium Ra 223 (Xofigo) injection **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “6”):

1. Member is diagnosed of metastatic, castration-recurrent prostate cancer (CRPC, a.k.a., castration-resistant or hormone-refractory prostate cancer) – lab documentation of a recent (past 90 days) serum testosterone level at castrate level (<50 ng/dL) must be submitted for members receiving medical castration. A chart note documenting a bilateral orchiectomy must be submitted for members who have received surgical castration.
2. Member has symptomatic bone metastases
3. Member does **NOT** have any known visceral metastatic disease (e.g., brain, liver, lung, adrenal gland, or peritoneum), or bulky lymph node metastases (>3 to 4 cm)
4. Radium 223 will not be used concomitantly with **ANY** of the following:
    a. abiraterone (Zytiga, Yonsa)
    b. apalutamide (Erleada)
    c. cytotoxic chemotherapy agents (e.g., docetaxel, cabazitaxel, mitoxantrone)*
    d. darolutamide (Nubeqa)
    e. enzalutamide (Xtandi)

    Androgen deprivation therapy (e.g., leuprolide, degarelix), denosumab, or zoledronic acid are not considered cytotoxic chemotherapy; concomitant use is permitted.
5. The dosage does not exceed 1 injection of 55 kBq/kg (1.49 microcurie) every 28 days for 6 total injections
6. The member has not received more than 5 doses of radium 223 treatment in their lifetime

Duration of approval: 12 months to allow for a total of 6 injections (and not to exceed 6 life-time doses)

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.
- The dose regimen is 55 kBq (1.49 microcurie) per kg body weight, given at 4 week intervals for 6 injections. Safety and efficacy beyond 6 injections have not been studied. Immediately before and after administration, the net patient dose of administered Xofigo should be determined by measurement in an appropriate radioisotope dose calibrator that has been calibrated with a National Institute of Standards and Technology (NIST) traceable radium-223 standard (available upon request from Bayer) and corrected for decay using the date and time of calibration. Refer to the product label for the decay correction factor table.

Dose Adjustments

None

Drug Availability

Single-use vial containing 6 mL of solution at a concentration of 1,100 kBq/mL (30 microcurie/mL) at the reference date with a total radioactivity of 6,600 kBq/vial (178 microcurie/vial) at the reference date

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Pregnancy

Precautions/Warnings

- **Bone Marrow Suppression**: In the randomized trial, 2% of patients on the radium-223 arm (n=13) experienced bone marrow failure or ongoing pancytopenia compared to no patients treated with placebo. There were two deaths due to bone marrow failure and for 7 of 13 patients treated with radium-223, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the radium-223 arm and 2% on the placebo arm permanently discontinued therapy due to bone marrow suppression. Hematologic evaluation of patients must be performed at baseline and prior to every dose of radium-223. Before the first administration, the absolute neutrophil count (ANC) should be ≥1.5x109/L, the platelet count ≥100x109/L and hemoglobin ≥10 g/dL. Before subsequent administrations of Xofigo, the ANC should be ≥1x109/L and the platelet count ≥50x109/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of radium-223 arm, despite receiving supportive care, further treatment should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue radium-223 arm in patients who experience life-threatening complications despite supportive care for bone marrow failure. The safety and efficacy of concomitant chemotherapy with radium-223 arm 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 arm should be discontinued.
- **Increased Fractures and Mortality in Combination with Abiraterone plus Prednisone/Prednisolone:** Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials. The clinical efficacy and safety of concurrent initiation of Xofigo treatment and abiraterone acetate plus prednisone/prednisolone treatment was assessed in a randomized, placebo-controlled multicenter phase 3 study (ERA-223 trial) in 806 patients with asymptomatic or mildly symptomatic castration resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee recommendation. At the primary analysis, an increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo in combination with abiraterone acetate plus prednisone/prednisolone. Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

A9606	Radium ra-223 dichloride, therapeutic, per microcurie

ICD-10 Diagnosis Codes That Support Medical Necessity

C61	Malignant neoplasm of prostate

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Castrate-resistant/recurrent prostate cancer (CRPC): disease progression despite androgen deprivation therapy (ADT) with either medication or surgery (i.e., removal/destruction of testicles, and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

RELATED GUIDELINES:

Abiraterone acetate (Zytiga), 09-J1000-36
Cabazitaxel (Jevtana), 09-J1000-77
Cryosurgical Ablation of the Prostate (CSAP), 02-54000-14
Docetaxel (Taxotere) IV, 09-J0000-95
Gonadotropin Releasing Hormone Analogs and Antagonists, 09-J0000-48
Oral Oncology Medications, 09-J3000-65
Sipuleucel-T (Provenge), 09-J1000-29

OTHER:

None

REFERENCES:

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4. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 3/10/22.
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6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2022 [cited 2022 Mar 10]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
7. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013 Jul 18;369(3):213-23.
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9. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Feb 6. pii: S1470-2045(18)30860-X.
10. Xofigo (radium chloride ra-223) [package insert]. Bayer HealthCare. Wayne (NJ): December 2019.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Coverage Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

09/15/13	New Medical Coverage Guideline.
04/15/14	Review and revision to guideline; consisting of description, position statement, references.
04/15/15	Review and revision to guideline; consisting of description, dosage/administration, HCPCS coding, and references.
11/01/15	Revision: ICD-9 Codes deleted.
04/15/16	Review and revision to guideline consisting of description section, dosage/administration, definitions, and references.
09/15/16	Revision to guideline consisting of position statement, dosage/administration, and references.
11/15/16	Revision to guideline consisting of updating position statement to allow 6 total doses during a 6-month approval period
04/15/17	Review and revision to guideline consisting of description section, position statement, related guidelines, and references.

04/15/18	Review and revision to guideline consisting of description section, position statement, dosage/administration section, precautions section, and references.
04/15/19	Review and revision to guideline consisting of updating the description section, position statement, precautions/warnings, related guidelines, and references.
01/01/20	Revision to guideline consisting of updating the position statement.
04/15/22	Revision to guideline consisting of updating the description section, related guidelines, and references.