Clinical Policy Title: Radium Ra 223 dichloride injection for prostate cancer

Clinical Policy Number: 05.02.06

Effective Date: July 1 2015
Initial Review Date: March, 18 2015
Most Recent Review Date: March, 15 2017
Next Review Date: March 2018

Policy contains:
- Xofigo® (Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ).
- Metastatic castration-resistant prostate cancer.

Related policies:
- CP# 00.02.06 Infusible pharmaceuticals for bone pain management

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of radium Ra-223 dichloride (radium-223) to be clinically proven and, therefore, medically necessary when the following patient selection criteria are met:

<table>
<thead>
<tr>
<th>Patient Selection Criteria</th>
<th>(ALL criteria must be met)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic (stage IV) castration-resistant prostate cancer (mCRPC).</td>
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<td>Presence of two or more symptomatic bone metastases detected on skeletal scintigraphy.</td>
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<td>No known visceral metastatic disease.</td>
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<td>An absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 10 g/dL prior to the first injection of radium-223.</td>
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</table>

Limitations:
Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of radium-223 are not medically necessary. The use of radium-223 for other malignancies is not currently clinically proven and not medically necessary.

Radium-223 is administered intravenously monthly (every four weeks) for a total of six injections. Administration of radium-223 in excess of six injections is not medically necessary, as its safety and efficacy beyond six injections have not been studied.

Radium-223 is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

Hematologic monitoring during treatment should be performed according to FDA labeling instructions. Prior to subsequent injections of radium-223, the ANC should be \( \geq 1 \times 10^9/L \) and the platelet count \( \geq 50 \times 10^9/L \). Radium-223 should be discontinued if a delay of six to eight weeks does not result in the return of blood counts to these levels.

Radium-223 used with concomitant chemotherapy (e.g., docetaxel) is not medically necessary due to the potential for additive myelosuppression.

Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated.

Radium-223 is contraindicated in: patients with Crohn’s disease, ulcerative colitis, prior hemibody radiation or untreated imminent spinal cord compression, as are patients excluded from the phase III clinical trial; women who are or may become pregnant; and patients who experience life-threatening complications despite supportive care measures.

In patients with bone fractures, orthopedic stabilization should be performed before starting or resuming treatment with radium-223.

Patients must be counseled to stay well hydrated and to monitor oral intake, fluid status, and urine output while being treated with Xofigo. They should be instructed to report signs of dehydration, hypovolemia, urinary retention, or renal failure/insufficiency.

**Alternative covered services:**

Mitoxantrone, bisphosphonates (zoledronate), taxanes (docetaxel, cabazitaxel), external-beam radiotherapy (EBRT), beta-emitting radiotherapy (samarium-153, strontium-89, rhenium 186), osteoclast inhibitors (zoledronic acid, denosumab), androgen antagonists (abiraterone, enzalutamide), and an autologous vaccine (sipuleucel-T).
**Background**

According to the American Cancer Society, prostate cancer is the most frequently diagnosed cancer aside from skin cancer and the second leading cause of death, particularly in older men (ACS 2015). The five-year relative survival rate for men diagnosed in the United States from 2001 to 2007 with local or regional disease was 100 percent, and the rate for distant disease was 28.7 percent (Howlader 2015). The only well-established risk factors for prostate cancer are increasing age, African ancestry, a family history of the disease and certain inherited genetic conditions (ACS 2015).

Most patients are diagnosed with early stage disease through screening detection, for which active surveillance may be a good option. Local treatments such as surgery (open, laparoscopic, or robotic-assisted), external beam radiation, radioactive seed implants (brachytherapy), and hormonal approaches to reduce serum testosterone levels are effective but are associated with adverse effects that impact quality of life (NCI 2015). Age and coexisting morbidity influence the approach to treatment (ACS 2015).

Despite improvements in early diagnosis and aggressive treatment, many patients eventually relapse. Metastatic prostate cancer remains an incurable disease, and there are few reliable biomarkers to monitor disease progression or guide therapeutic decisions (Karantanos 2013). Advanced prostate cancer commonly spreads to the bones, causing significant morbidity and mortality. Clinical manifestations may include pain, hypercalcemia, pathologic fractures, and spinal cord compression.

Prostate cancer cells require androgen hormones such as testosterone to grow and survive. Androgen receptor (AR) signaling is a critical survival pathway for prostate cancer cells (Karantanos 2013). Treatment strategies that inhibit AR signaling, such as androgen-deprivation therapy (ADT), remain the principal treatment for patients with locally advanced and metastatic disease. ADT reduces levels of androgens in circulation, with the goal of improving outcomes in men with prostate cancer. Historically, castrate levels of serum testosterone were defined as less than or equal to 50 ng/dl, but stricter definitions of medical castration of less than 20 ng/dl are being used.

Although a majority of patients with metastatic prostate cancer initially respond to ADT, most will eventually develop castrate resistance. Prostate cancer that progresses despite castrate serum testosterone levels is referred to as metastatic castration-resistant prostate cancer (mCRPC). In this population, until recently the only treatment showing a survival benefit was docetaxel chemotherapy. For patients progressing on or after docetaxel, there were limited options and prognosis was poor. Numerous new agents such as sipuleucel-T, abiraterone, enzalutamide, cabazitaxel and radium Ra-223 dichloride have been approved since 2010 to treat mCRPC (Karantanos 2013).

Radium-223 is the first alpha-emitting radioactive therapeutic agent that binds with minerals in the bone to deliver radiation directly to bone tumors (FDA 2013). The use of radium-223 for the treatment on bone metastases relies on the chemical similarity to calcium and the ability of the alpha radiation and the short-
lived decay products of radium-223 to kill cancer cells while limiting the damage to the surrounding normal tissues.

In May 2013, the U.S. Food and Drug Administration (FDA) approved radium-223, marketed under the trade name Xofigo® (Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ), under their priority review program as a first-in-class drug to treat men with symptomatic late-stage mCRPC that has spread to bones but not to other organs. It is intended for men whose cancer has spread after receiving medical or surgical therapy to lower serum testosterone.

The dose regimen of radium-223 is 50 kBq (1.35 microcurie) per kg body weight, given at four week intervals for six injections. Radium-223 is administered by slow intravenous injection over one minute. Fecal excretion is the major route of elimination from the body. Treatment is administered on an outpatient basis by a physician, typically a nuclear medicine physician, who is approved and listed on the provider’s Radioactive Materials (RAM) License for therapeutic use of radium-223 with assistance from certified nuclear medicine or radiation oncology staff (FDA 2013).

Searches

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

Searches were conducted on February 8 2017 using the free text terms “xofigo,” or "Radium-223" as well as MeSH terms: "Prostatic Neoplasms, Castration-Resistant/drug therapy" or "Prostatic Neoplasms, Castration-Resistant/radiotherapy" or "Prostatic Neoplasms, Castration-Resistant/therapy".

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings:

Prestige Health Choice identified one systematic review (Hayes 2013 and an update in 2014), one horizon scanning review (Nachternebel 2014), one comprehensive review (Crawford 2015) and three evidence-based
The evidence is sufficient to support the use of radium-223 as treatment for mCRPC in men with metastases to the bone but not to other organs. The ALSYMPCA trial compared radium-223 to placebo plus best standard of care in 921 men with symptomatic CRPC with at least two bone metastases but no visceral metastases. The median age of patients was 71 years, and 57 percent had received prior docetaxel. The majority had a good Eastern Cooperative Oncology Group performance status (ECOG 0 or 1) and at least six metastases. Patients received six monthly injections of 50 kBq/kg of radium-223 or matching placebo. All patients also received optimal usual care, which could include local external beam radiotherapy, glucocorticoids, anti-androgens, ketoconazole, or estrogens. The study was designed to measure overall survival (OS) with a secondary endpoint of time to first skeletal related event. A December 2015 review agrees that radium-223 provides improved overall survival in chemotherapy naïve and chemotherapy treated patients with symptomatic bone metastases (Crawford 2015).

Results from an interim analysis showed that the OS was superior in men receiving radium-223 compared to placebo (median OS: 14 months v. 11.2 months; HR 0.70, 95 percent confidence interval 0.55 - 0.88, \( P = 0.0019 \)), and an improvement in time to first skeletal-related event (Nguyen 2016). The survival benefit was observed in all subgroups, regardless of baseline alkaline phosphatase, previous treatment with docetaxel or use of bisphosphonates. No dose adjustments were needed for patients with mild hepatic impairment or patients with mild/moderate renal impairment. There were insufficient data regarding dose adjustments for patients with moderate/severe hepatic impairment or severe renal impairment.

The most common side effects were nausea, diarrhea, vomiting and swelling of the leg, ankle or foot. The most common blood abnormalities included low levels of red blood cells (anemia), lymphocytes (lymphocytopenia), white blood cells (leukopenia), platelets (thrombocytopenia) and infection-fighting white blood cells (neutropenia). Data from additional regulatory filings and product labeling revealed serious adverse events that did not occur in the published studies, specifically bone marrow failure in 2 percent of patients receiving radium-223 compared with none in the placebo group.

Radium-223 is considered safe and well tolerated, according to results from a 3-year follow-up (Parker 2015). No difference was observed in patients given radium-223 simultaneously with enzalutamide or abiraterone compared with those just given radium-223 (Dan 2015).

Recommendations from evidence-based guidelines are concordant with these findings. There is agreement that radium-223 should be offered to patients with symptomatic bony metastases from mCRPC without known visceral disease regardless of prior docetaxel exposure. Guidelines do not recommend giving radium-223 concordant with chemotherapy (such as docetaxel) outside of a clinical trial because of the potential for additive myelosuppression. There are no restrictions on combining radium-223 with
denosumab or a bisphosphonate. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.

**Unanswered questions.** Despite lack of significant toxicity and gains in OS, several questions remain regarding optimal dosage and precisely where to incorporate the radioisotope in the therapeutic pathway of mCRPC. Moreover, different modes of administration of available treatment regimens have to be taken into account and may determine patients’ preferences. Results of phase II trials suggest dose-dependent improvements with no increase in toxicity, implying that the optimal dose of radium-223 could be higher than the 50 kBq/kg used in the phase III study. The safety and efficacy of using radium-223 in earlier stages of disease, in combination with other systemic therapies, or compared to other already licensed agents is unknown, but several phase I and II clinical trials are underway.

**The evidence is insufficient to support the use of radium-223 as treatment for other cancers.** Several phase I and phase II studies are ongoing in patients with sarcoma (Clinicaltrials.gov identifier NCT01833520), breast-cancer with a bone-dominant disease (NCT02258464, NCT02258451) and non-small cell lung cancer with bone metastases (NCT02283749).

The administration of radium-223 is associated with potential risks to other persons (e.g. medical staff, caregivers and patient’s household members) from radiation or contamination from spills of bodily fluids such as urine, feces or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

A systematic review of economic studies found that the cost of radium-223 for prostate cancer per quality adjusted life years was 80,000 to 94,000 Euros (about $84,786 to $99,624), but was unable to make an ultimate statement about their use (Norum 2015).

**Policy updates:**
A total of five peer-reviewed references were added to this policy.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayes (2013, updated 2014)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Phase I and II studies for Xofigo</td>
<td>• Systematic review of 5 RCTs (n = 64 to 921), including one multinational, phase III, Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial and substudies and several phase I and II studies; unpublished safety data provided to FDA by manufacturer; a radiation safety study; FDA NDA 203971 Summary Review with follow-up data; an NCCN guideline update; and two reviews. All trials sponsored by manufacturer.</td>
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<tr>
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<td>• Overall quality: moderate.</td>
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<tr>
<td></td>
<td>• Xofigo improves overall survival (OS), alleviates pain, slows disease progression, and improves quality of life in patients with metastatic CRPC, and may be a reasonable treatment option for this group.</td>
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<td>• Xofigo associated with fewer adverse events (AE) than best care, but unpublished results.</td>
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revealed additional safety issues, e.g., bone marrow failure.

- Additional studies needed to confirm findings and further evaluate safety, particularly the risk of bone marrow suppression; establish optimum dose; determine how Xofigo may be combined or sequenced with other agents, and evaluate the safety and efficacy of retreatment.

Nachtnebel (2014) Review of radium-223 for adverse effects, survival

Key points:

- Horizon scanning review of one phase III trial and four phase II trials.
- OS was extended by 3.6 months in the radium-223 group; secondary outcomes favoured treatment with radium-223.
- Bone pain (50%), nausea (36%) and anemia (31%) were the most common treatment-related AEs of all grades.
- At two-year survival follow-up, 10 patients (30%) of the radium-223 group were alive compared with four patients (13%) in the control group. The most frequent cause of death for both groups was progression of disease. Treatment-related AEs or long-term hematological toxicity during the follow-up were not reported.
- Dosage of radium-223 is unclear and may have to be higher than examined in phase III study.
- Trials needed to examine the best combination of radium-223 with other already licensed agents such as enzalutamide, abiraterone acetate, cabazitaxel or docetaxel.
- Authors’ conclusions: radium-223 expands the treatment scope for CRPC with lower radiation toxicity, less negative impact on surrounding tissue than beta/gamma emitters, but questions on dosage and best combination remain.

CMS policies:

<table>
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<tr>
<th>Organization</th>
<th>Policy</th>
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<tbody>
<tr>
<td>CMS</td>
<td>Radium Ra 223 dichloride (XOFIGO) (A9606) Coverage is for the FDA approved indication: the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. It is administered at 4 week intervals for a total of 6 doses. Use diagnosis codes 185 and 198.5. Coverage is effective 05/15/2013 — FDA approval date. Off label use is not covered. Do not use both diagnosis codes if the indications have not been met.</td>
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<tr>
<td>No NCD found</td>
<td>LCD L28576 Chemotherapy Drugs and their Adjuncts (05901) Louisiana, South Carolina</td>
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</table>

References

FDA filings:


**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National coverage determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local coverage determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.
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<thead>
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<th>CPT Code</th>
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<th>ICD-10 Code</th>
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<td>C61</td>
<td>Malignant neoplasm prostate</td>
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<tr>
<td>C79.31</td>
<td>Brain metastasis</td>
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<tr>
<td>C79.51</td>
<td>Bone metastasis</td>
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<th>HCPCS Level II</th>
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<tbody>
<tr>
<td>A9606</td>
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