INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee's specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
POLICY DESCRIPTION:

This policy provides information about Xofigo® (Radium 223) and its recommended use. Xofigo® (Radium 223) is a radioactive therapeutic agent indicated for the treatment of men with symptomatic, castration-resistant prostate cancer that has spread to bones but not to other organs.

Xofigo® is usually administered on an outpatient basis by a physician in an approved licensed facility, usually in nuclear medicine or radiation therapy departments. The administration of Xofigo® is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken.

The goal is to improve overall survival (OS), alleviates pain, slows disease progression, and improves quality of life in these patients.

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

The use of Radium (RA)-223 dichloride (Xofigo®) may be considered MEDICALLY NECESSARY for the treatment of men with symptomatic, metastatic, castration-resistant prostate cancer that has spread to bones but not to other organs.

Note: Castration-resistant prostate cancer (CRPC) is defined by rising levels of prostate-specific antigen (PSA) in spite of androgen deprivation therapy and castrate levels of serum testosterone.

The use of Radium (RA)-223 dichloride (Xofigo®) for breast cancer and for use in combination with docetaxel or any other chemotherapy is considered EXPERIMENTAL AND INVESTIGATIONAL because its effectiveness for indications other than the one listed above has not been established.

Clinical Considerations:

- Ra-223 is not approved for use in combination with docetaxel or any other chemotherapy.
- Ra-223 is administered intravenously once monthly for 6 months by an appropriately licensed facility, usually in nuclear medicine or radiation therapy departments.
- Prior to the initial dose, patients must have absolute neutrophil count greater than or equal to 1.5 x 10(9)/L, platelet count greater than or equal to 100 x 10(9)/L, and hemoglobin greater than or equal to 10 g/dL.
- Prior to subsequent doses, patients must have absolute neutrophil count greater than or equal to 1.0 x 10(9)/L, and platelet count greater than or equal to 50 x 10(9)/L (per label, although this may be too low in practice). Ra-223 should be discontinued if a delay of 6 to 8 weeks does not result in the return of blood counts to these levels.
- Grade 3-4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at a low risk.
- Non-hematological side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms are likely related to the fact that Ra-223 is predominantly eliminated by fecal excretion.
- At the present time, except on a clinical trial, Ra-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 the beneficial effects of Ra-223 on survival.

- 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.

Contraindications:
- Radium-223 dichloride is contraindicated in women who are or may become pregnant.
- Concomitant chemotherapy is not recommended due to the potential for additional myelosuppression.
- Radium-223 dichloride should be discontinued in patients who experience life-threatening complications despite supportive care measures.

**BACKGROUND:**

Prostate cancer is the most common cancer in men and the second leading cause of cancer death in men. The annual incidence of prostate cancer in the United States is approximately 242,000. Approximately 85% to 90% of patients with castration-resistant prostate cancer (CRPC) have radiological evidence of bone metastases, which are a major cause of decreased quality-of-life, disability, and death. To-date, however, treatments for bone metastases have been primarily palliative. Castration-resistant prostate cancer (CRPC) is defined by rising levels of prostate-specific antigen (PSA) in spite of androgen deprivation therapy and castrate levels of serum testosterone. The overall survival (OS) of men with CRPC is approximately 18 months after treatment with the first-line agent, Taxotere (docetaxel; Sanofi-Aventis). Prostate cancer most commonly metastasizes to the bone in its advanced stages. The most common sites of bony metastases are the vertebrae, pelvis, ribs, and skull. These metastases can structurally compromise bones and lead to skeletal-related events (SREs) such as fractures, pain, hypercalcemia, and a reduced quality of life. Vertebral fractures are associated with spinal cord compression and other neurologic symptoms. Patients with SREs may require orthopedic surgical intervention, analgesics including strong opioids, and radiotherapy with its attendant pancytopenia. Without treatment, up to 22% of men with metastatic prostate cancer of the bone experience fractures. Increases in PSA and markers of bone turnover such as alkaline phosphatase (ALP) correlate with SREs and OS. Available agents for treating bony metastases include bisphosphonates, Prolia (denosumab; Amgen), and beta-emitting radioisotopes. These may relieve pain or delay SREs, but have not been shown to prolong OS.

Xofigo® (radium-223 dichloride) injection (Bayer HealthCare Pharmaceuticals Inc.), initially called Alpharadin, is indicated for the treatment of patients with CRPC who have symptomatic bone metastases but no visceral metastases. It is a radioactive therapeutic agent that mimics calcium and selectively binds to areas of bone-repairing activity, forming complexes with bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. Radium-223 dichloride emits alpha particles (subatomic particles consisting of 2 protons and 2 neutrons) that deliver high energy over a short range. Radium-223 dichloride causes irreparable, double-stranded breaks in DNA, but due to the short range of effect of alpha particles, the radiated zone is restricted to a 2- to 10-cell diameter, minimizing the effect on adjacent, healthy tissue. The dose lethal to 50% of animals was not reached in preclinical studies, suggesting high tolerance, probably due to surviving pockets of bone marrow unaffected by alpha
The half-life of radium-223 is 11.4 days. Gamma scintigraphy following administration reveals a concentration of the isotope in bone and intestine. The majority of intestinal radium-223 is located in the contents of the intestine rather than the wall, and harm to intestinal tissue is considered minimal and reversible. Fecal excretion is the major route of elimination.

Xofigo® (radium Ra 223 dichloride injection) is supplied in single-use vials containing 6 milliliters (mL) of solution at a concentration of 1000 kilobecquerels per mL (kBq/mL) (27 microcurie/mL) with a total radioactivity of 6000 kBq/vial (162 microcurie/vial). Radium-223 dichloride is a ready-to-use solution and should not be diluted or mixed with any solutions. The drug is administered by slow intravenous injection over 1 minute. The dose is 6 injections of 50 kBq per kilogram (kg) of body weight given at 4-week intervals. Safety and efficacy beyond this number of injections has not been established; however, the Food and Drug Administration (FDA) has required an additional postmarketing study to further evaluate and optimize the dose. The dose of radiation to members of the patient’s family is low so patients may be discharged immediately after administration although radiation protection precautions must be used.

### REGULATORY STATUS:

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**
   
   The Center for Drug Evaluation Research (CDER) approved the radium-223 dichloride (Xofigo®) injection (Bayer HealthCare Pharmaceuticals Inc.) on May 15, 2013 (New Drug Application [NDA] 203971) for treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease. Over the next several years, the sponsor is required to conduct:
   
   - An observational study to assess the long-term safety of the 50-kBq/kg dose in patients with CRPC with bone metastases.
   - A randomized trial to assess safety in patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease.
   - A trial of the short- and long-term safety of retreatment of patients with CRPC and bone metastases with radium-223 dichloride.
   - A phase 2 trial to evaluate the efficacy and safety of radium-223 dichloride at a dose higher than 50 kBq/kg in patients with CRPC with bone metastases; depending on the result, this trial may need to be further confirmed by a randomized phase 3 trial.

2. **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):**

   The Centers for Medicare & Medicaid Services (CMS) does not have a National Coverage Determination (NCD) addressing Xofigo® (Radium-223).

   Because there are no specific HCPCS codes for this drug, the use of an unlisted or unclassified HCPCS code is required. HCPCS code C9399 must be used for Radium 223 submitted on a UB 04 facility claim and HCPCS code A9699 must be used for Radium 223 when submitted on a UB 1500.

Correct Reporting of Xofigo®

Because there are no specific HCPCS codes for this drug, the use of an unlisted or unclassified HCPCS code is required. The official HCPCS code description for C9399 is “unclassified drugs or biologicals.” One dose of Xofigo® may provide as much as 162 uci/6ml or 27uci/ml. Do not bill units based on the way the drug is packaged, stored, or stocked.

Xofigo® is currently billed with HCPCS code C9399. The number of units reported in FL 46 of the UB-04 claim form, or electronic equivalent, must equal one (1) unit for one administration of Xofigo® providing up to 162 uci/6ml or 27uci/ml.

When HCPCS code C9399 is billed for Xofigo®, the claim must include specific information in the remarks section to allow correct claims processing. Specifically, the “Remarks” (FL 80, or electronic equivalent) section of the claim must include the:

- Name of the drug
- NDC number in the proper 5-4-2 format including the dashes
- Route of administration
- Date of administration
- Total amount of the drug (in units) the beneficiary received

Note: If any of the required information is missing or incorrect, the claim must be returned to the provider (RTP) for correction.

Report Xofigo® with:

- Revenue code 0636, Drugs requiring detailed coding
- HCPCS code C9399, Unclassified drugs or biologicals
- Remarks Section of the Claim must include:
  - Xofigo®
  - 50419-0208-01 (NDC for Xofigo®)
  - IV (intravenous)
  - Date of administration
  - 1 unit

3. MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS): Minnesota DHS does not have a policy statement regarding Xofigo® (Radium-223) for castrate-resistant prostate cancer (CRPC) with symptomatic bone metastases in its Provider Manual or other specific provider references.

CLINICAL EVIDENCE:

SUMMARY:

While the published studies suggest that the efficacy of Xofigo® for reducing symptoms and improving survival in patients with metastatic CRPC outweighs the risks of AEs such as myelosuppression, additional studies are needed to fully evaluate the safety of this treatment.

Nevertheless, the available evidence supports the use of radium-223 as a first-line or second-line therapeutic option for men with symptomatic, metastatic, castration-resistant prostate cancer that has
spread to bones but not to other organs. Few, well-designed studies consistently have shown that
treatment with 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. Pre-specified interim analysis of overall survival revealed a statistically significant improvement
in patients receiving XOFIGO® plus best standard of care compared with patients receiving placebo plus
best standard of care.

APPLICABLE CODES:

The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only.
Listing of a service or device code in this policy does not imply that the service described by this code is a covered or
non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims
payment. Other medical policies and coverage determination guidelines may apply.

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<td>Radiopharmaceutical therapy, by intravenous administration</td>
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CPT® is a registered trademark of the American Medical Association.

REFERENCES:

1. American College of Radiology (ACR). ACR–ASTRO Practice Guideline for the Performance of Therapy
   with Unsealed Radiopharmaceutical Source. Revised 2010. Available at:
2. Bayer HealthCare Pharmaceuticals Inc. Xofigo® (radium Ra 223 dichloride) Injection, for intravenous
   use [prescribing information]. Revised May 2013a. Available at:
3. Bayer Healthcare Pharmaceuticals Inc. Xofigo® (radium Ra 223 dichloride injection). Therapeutic Use of
   Xofigo® Procedure Checklist. Revised May 2013b. Available at:
4. Bayer HealthCare Pharmaceuticals Inc. Information on Licensure of Xofigo®. Xofigo® (radium Ra 223
   dichloride injection). Revised May 2013c. Available at:


**POLICY HISTORY:**

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<td>New policy 2012M0063A. Approved by the Medical Policy Committee.</td>
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<td>05/22/2014</td>
<td>Reviewed and approved by the Quality Improvement Advisory and Credentialing Committee (QIACC).</td>
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