MEDICAL POLICY

Capital BLUE

POLICY TITLE	RADIUM RA223 DICHLORIDE (XOFIGO®)
POLICY NUMBER	MP-2.180

Original Issue Date (Created):	**September 28, 2013**
Most Recent Review Date (Revised):	**September 28, 2013**
Effective Date:	**January 01, 2014**

I. POLICY

Radium RA223 dichloride (Xofigo)® may be considered **medically necess**ary for treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Policy Guidelines

- Prior to the initial dose, patients must have an absolute neutrophil count ≥1.5 X10(9) /L , platelet count ≥100X 10 (9) , and hemoglobin ≥10g/dL.
- Prior to subsequent doses, patients must have absolute neutrophil count ≥1 X 10 (9)/L and platelet count ≥50 X 10 (9) per label.
- Radium RA223dichloride (Xofigo) should be discontinued if a delay of 6-8 weeks does not result in return of blood counts to these levels.
- At the present time, except on a clinical trial, radium-223 (Xofigo) is not intended to be used in combination with chemotherapy due to potential for additive myelosuppression.

Cross-reference:

MP-2.237 Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer
MP-2.151 Cellular Immunotherapy for Prostate Cancer
MP-2.158 Cabazitaxel (Jevtana®)
MP-2.043 Brachytherapy
MP-2.152 Denosumab (Prolia® and Xgeva®)
MP-2.143 Zolendric acid (Reclast® and Zometa®)

II. PRODUCT VARIATIONS

Key:
[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO (see note)
[N] SeniorBlue PPO (see note)
[N] Indemnity
[N] SpecialCare
[N] POS
[N] FEP PPO

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Note: "FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if determined that the use is medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice." Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2-Unlabeled Use of Drug)." *http://www.cms.gov/manuals/Downloads/bp102c15.pdf*

III. DESCRIPTION/BACKGROUND

Prostate cancer forms in a gland in the male reproductive system found below the bladder and in front of the rectum. The male sex hormone testosterone stimulates the prostate tumors to grow. According to the National Cancer Institute, an estimated 238,590 men will be diagnosed with prostate cancer and 29,720 will die from the disease in 2013.

Radium-223 chloride (Xofigo, formerly called Alpharadin) is a radiopharmaceutical to improve survival in patients with bone metastases from advanced cancer. It has been developed by the Norwegian company Algeta ASA, in a partnership with Bayer. Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. "Castrate resistant" means the cancer is still growing despite the fact that hormone therapy (either an orchiectomy or an LHRH agonist or antagonist) is keeping the testosterone in the body at very low, "castrate" levels.

The dose regimen of Xofigo is 50 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections (intravenously). Safety and efficacy beyond 6 injections with Xofigo have not been studied. Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. Xofigo is usually administered by 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 in accordance with national and local regulations.

Prior to the initial dose, patients must have an absolute neutrophil count ≥1/5 X10(9) /L , platelet count ≥100X 10 (9) , and hemoglobin ≥10g/dL. Prior to subsequent doses, 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.

The most common adverse drug reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema. The most common hematologic laboratory abnormalities (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman. The safety and efficacy of Xofigo in pediatric patients have not been established.

At the present time, except on a clinical trial, radium-223 (Xofigo) is not intended to be used in combination with chemotherapy due to potential for additive myelosuppression. Concomittent use of denosumab or zolendronic acid does not interfere with the beneficial effects of radium -223 on survivial.

IV. RATIONALE

The efficacy and safety of Xofigo were evaluated in a double-blind, randomized, placebo-controlled phase 3 clinical trial of patients with castration-resistant prostate cancer with symptomatic bone metastases. Patients with visceral metastases and malignant lymphadenopathy exceeding 3 cm were excluded. The primary efficacy endpoint was overall survival. A key secondary efficacy endpoint was time to first symptomatic skeletal event (SSE) defined as external beam radiationtherapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention. There were no scheduled radiographic assessments performed on study. All patients were to continue androgen deprivation therapy. At the cut-off date of the pre-planned interim analysis, a total of 809 patients had been randomized 2:1 to receive Xofigo 50 kBq (1.35 microcurie)/kg intravenously every 4 weeks for 6 cycles (n = 541) plus best standard of care or matching placebo plus best standard of care (n = 268). Best standard of care included local EBRT, corticosteroids, antiandrogens, estrogens, estramustine orketoconazole. Therapy was continued until unacceptable toxicity or initiation of cytotoxic chemotherapy, other systemic radioisotope, hemi-body EBRT or other investigational drug. Patients with Crohn's disease, ulcerative colitis, prior hemibody radiation or untreated imminent spinal cord compression were excluded from the study. In patients with bone fractures, orthopedic stabilization was performed before starting or resuming treatment with Xofigo.

The following patient demographics and baseline disease characteristics were balanced between the arms. The median age was 71 (range 44-94) with a racial distribution of 94% Caucasian, 4% Asian, 2% Black and <1% Other. Patients were enrolled predominantly from Europe (85%) with 4% of patients enrolled from North America. ECOG performance status was 0-1 in 86% of patients. Eighty-five percent of patients had 6 or more bone scan lesions and of those 40% had > 20 lesions or a superscan. Opiate pain medications were used for cancer-related pain in 54% of patients, non-opiate pain medications in 44% of patients and no pain medications in 2% of patients. Patients were stratified by baseline ALP, bisphosphonate use, and prior docetaxel exposure. Prior

bisphosphonates were used by 41% of patients and 58% had received prior docetaxel. During the treatment period, 83% of Xofigo patients and 82% of placebo patients received gonadotropin-releasing hormone agonists and 21% of Xofigo patients and 34% of placebo patients received concomitant antiandrogens. Use of systemic steroids (41%) and bisphosphonates (40%) was balanced between the arms.

The 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. An exploratory updated overall survival analysis performed before patient crossover with an additional 214 events resulted in findings consistent with the interim analysis (Table 5).

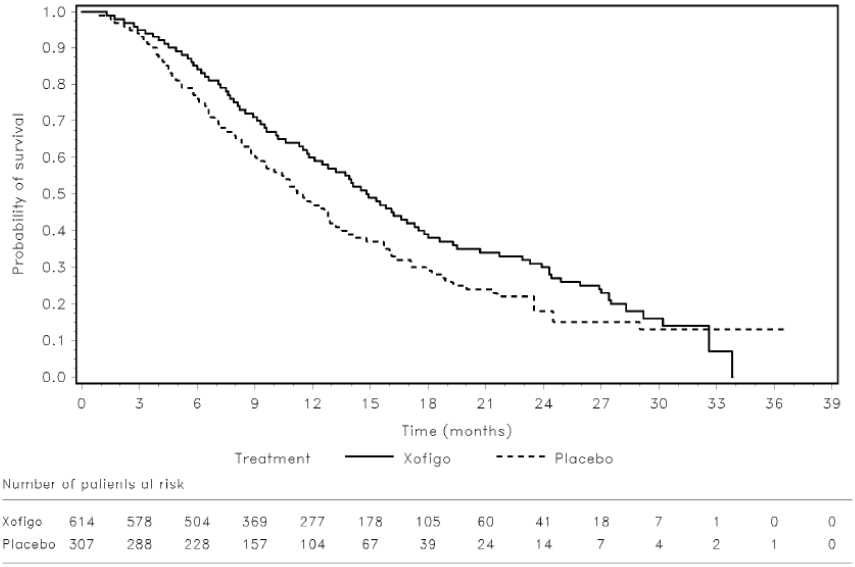
V.

Table 5: Overall Survival Results from the Phase 3 Clinical Trial

	Xofigo		Placebo
Interim Analysis			
Subjects randomized	541		268
Number of deaths	191 (35.3%)		123 (45.9%)
Censored	350 (64.7%)		145 (54.1%)
Median survival (months) [a] (95% CI)	14.0 (12.1, 15.8)		11.2 (9.0, 13.2)
p-value[b]		0.00185	
Hazard ratio (95% CI)[c]		0.695 (0.552, 0.875)	
Updated Analysis			
Subjects randomized	614		307
Number of deaths	333 (54.2%)		195 (63.5%)
Censored	281 (45.8%)		112 (36.5%)
Median survival (months) [a] (95% CI)	14.9 (13.9, 16.1)		11.3 (10.4, 12.8)
Hazard ratio (95% CI)[c]		0.695 (0.581, 0.832)	

a Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.
b p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior use of docetaxel.
c Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel. Hazard ratio < 1 favors radium-223 dichloride.

Figure 1: Kaplan-Meier Overall Survival Curves from the Phase 3 Clinical Trial



VI. DEFINITIONS

N/A

VII. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VIII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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IX. REFERENCES

American Cancer Society. Prostate Cancer. Revised 05/13/13. [Website]: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-hormone-therapy Accessed August 2, 2013.

Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual. Publication 100-02. Chapter 15. Section 50.4.2. Unlabeled Use of Drug. Effective 06/05/08 [Website]: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf. Accessed August 2, 2013.

Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual. Publication 100-02. Chapter 15. Sections 50, 50.4.1, 50.4.3. Drugs and Biologicals. Effective 06/08/12. [Website]: http://www.cms.gov/manuals/Downloads/bp102c15.pdf. Accessed August 2, 2013.

FDA News Release. FDA approves new drug for advanced prostate cancer. May 15, 2013. [Website]: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm352363.htm Accessed July 31, 2013.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Prostate Cancer (V.4.2013). [Website]: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf Accessed August 2, 2013.

Xofigo prescribing information. May 2013. [Website]: http://labeling.bayerhealthcare.com/html/products/pi/Xofigo_PI.pdf Accessed July 31, 2013.

X. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

HCPCS Code	Description
J3590	Unclassified biologics

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ICD-9-CM Diagnosis Code*	Description
170.0-170.1	Malignant neoplasm of bones of skull and face
170.4	Malignant neoplasm of scapula and long bones of upper limb
170.5	Malignant neoplasm of short bones of upper limb
170.6	Malignant neoplasm of pelvic bones, sacrum, and coccyx
170.7	Malignant neoplasm of long bones of lower limb
170.8	Malignant neoplasm of short bones of lower limb
170.9	Malignant neoplasm of bone and articular cartilage, site unspecified
185	Malignant neoplasm of prostate

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2014:

ICD-10-CM Diagnosis Code*	Description
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones of unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C41.0	Malignant neoplasm of bones of skull and face
C41.1	Malignant neoplasm of mandible
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C61	Malignant neoplasm of prostate

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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XI. POLICY HISTORY

MP- 2.180	**CAC 9/24/13** New policy. Radium Ra 223 dichloride (Xofigo®) was FDA approved in May 2013 for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. Policy coded.