CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203971Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA # Supplement#	203971
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	December 14, 2012
PDUFA Goal Date	August 14, 2013
Proprietary Name / Established (USAN) names	Xofigo/radium Ra 223
Dosage forms / Strength	Single-use vial containing 6000 kBq/6 mL (0.162 mCi/6 mL)
Proposed Indication(s)	The treatment of castration-resistant prostate cancer patients with bone metastases
Recommended:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director Review	Robert Justice
RPM Review	Elleni Alebachew
CDTL Review	Ellen Maher
Medical Officer Review	Paul Kluetz, William Pierce
Statistical Review	Hui Zhang, Shenghui Tang, Rajeshwari Sridhara
Pharmacology Toxicology Review	Wei Chen, Todd Palmby, John Leighton
CMC Review/OBP Review	Martin Haber, Eldon Leutzinger, Denise Miller, Ali Al Hakim
Microbiology Review	N/A
Clinical Pharmacology Review	Pengfei Song, John Christy, Qi Liu, Nitin Mehrotra
OPDP	Michelle Safarik
OSI	Lauren Iacono-Connors, Janice Pohlman, Susan Thompson
OSE/DMEPA	Jibril Abdus-Samad
OSE/DRISK	Bob Pratt
DMIP	Cynthia Welsh, Lucie Yang
SEALD	Jessica Voqui
QT-IRT	Justin Earp, Kevin Krudys, Janice Brodsky, Qianyu Dang, Monica Fiszman, Norman Stockbridge

1. Introduction

On December 14, 2012, Bayer Pharmaceuticals submitted a New Drug Application for radium-223 as a therapeutic alpha particle-emitting pharmaceutical for the treatment of castration-resistant prostate cancer patients with bone metastases.

Radium-223 is a radioactive divalent cation that releases alpha particles during its decay to lead-207. It accumulates in areas of high bone turnover where it can replace calcium in its complex with hydroxyapatite. Alpha particles have a high energy transfer and cause DNA double strand breaks. Despite the high energy transfer, alpha particles have only a short path-length. It is thought that this short path length will minimize damage to surrounding normal tissue such as the bone marrow.

The Phase 3 trial in this application was conducted primarily in Europe between June 2008 and February 2011. As a result, approximately half the patients entering this trial had received docetaxel (approved in the EU in 2005), but none had received cabazitaxel or abiraterone (approved in the EU in 2011). It is unclear whether patients who have received radium-223 will tolerate cabazitaxel and limited information is available on the use of cytotoxic chemotherapy after radium-223. Further, while radium-223 targets only the bone, newer agents like abiraterone and enzalutamide target both visceral and bone metastases making the placement of radium-223 uncertain in the treatment of prostate cancer. The table below provides information on the agents approved for the treatment of metastatic prostate cancer.

Table 1: Prostate Cancer Therapies

Agent	Comparator	Endpoint	Hazard Ratio p-value
Mitoxantrone + Prednisone	Prednisone	2-point decrease 29% vs. 12%[1] Duration of decrease 7.6 vs. 2.1 mos	p = 0.011
Docetaxel + Prednisone	Mitoxantrone + Prednisone	Median Overall Survival 18.9 vs. 16.5 mos	HR = 0.76 p = 0.0094
Sipuleucel-T	PBMC[2]	Median Overall Survival 25.8 vs. 21.7 mos	HR = 0.59 p = 0.01
Cabazitaxel + Prednisone	Mitoxantrone + Prednisone	Median Overall Survival 15.1 vs. 12.7 mos	HR = 0.70 p < 0.0001
Abiraterone + Prednisone	Prednisone	Median Overall Survival 15.8 vs. 11.2 mos	HR = 0.74 p < 0.0001
Enzalutamide	Placebo	Median Overall Survival 18.4 vs. 13.6 mos	HR = 0.63 p < 0.0001

[1]2-point decrease in pain intensity with stable analgesic use

[2]Peripheral blood mononuclear cells

In addition to these agents, 4 products have been approved as bone-targeting therapy. These are shown in the table below. While radium-223 is a bone-targeting agent that it has also shown an improvement in overall survival in patients with prostate cancer.

Table 2: Bone-Targeting Therapies

Agent	Comparator	Endpoint	Hazard Ratio p-value
Zoledronic acid	Placebo	Median time to first SRE[1] Not reached vs. 321 d	HR = 0.67 p = 0.011
		Proportion with a SRE 33% vs. 44%	p = 0.02
Denosumab	Zoledronic acid	Median time to first SRE	HR = 0.82

		20.7 vs. 17.1 mos	p = 0.008
Strontium chloride	Placebo	Reduction in pain score and Stable analgesic use over 6-9 mos	
Samarium-153	Placebo	Reduction in pain score over 4 weeks[2]	

[1]Skeletal-related event

[2]A 0-10 visual analog scale was used

2. CMC/Device

There are no CMC issues that preclude approval. Radium-223 dichloride is generated from (b) (4) (b) (4) . Radionuclide purity and residual solvents are controlled. Compendial excipients are added and the drug product is packaged as 6 mL of radium-223 dichloride at 1000 kBq/mL in a glass vial with a (b) (4) rubber stopper. Three production lots have been manufactured and the shelf-life is 28 days.

Establishment inspections were acceptable.

3. Nonclinical Pharmacology/Toxicology

There are no nonclinical issues that preclude approval. Radium-223 emits alpha particles causing double strand DNA breaks. Given its mechanism of action, it is thought to be carcinogenic, genotoxic, and teratogenic. Formal studies were not required. Radium-223 is calcium-mimetic and it lodges in the bone. In repeat dose toxicology studies, radium-223 affected growing areas of the bone and teeth and caused bone marrow suppression. In animals, osteosarcoma, breast cancer, and lymphoma were seen 6 months after initial administration.

4. Clinical Pharmacology/Biopharmaceutics

There are no clinical pharmacology issues that preclude approval. Radium-223 is administered as 50 kBq/kg intravenously over approximately 1 minute. It is rapidly cleared from the blood with 20% of the administered dose remaining in the blood at 15 minutes. It is distributed to the bone and intestine. It is secreted into the feces like other divalent cations. At 7 days, ~ 63% of the administered dose has been excreted in the feces. However, fecal excretion does vary markedly with intestinal transit time. The half-life of radium-223 is 11.4 days and dosing must be corrected for product decay. In the body, radium-223 decays into lead-207, a stable isotope. The amount of lead retained by the body is 3.2 ng per 6 mL vial of radium-223.

There is no entero-hepatic circulation and little urinary excretion. Dose adjustment is not needed for mild hepatic impairment or for mild/moderate renal impairment. Use of calcium channel blockers or bisphosphonates did not affect the safety or the efficacy profile of radium-223. No large changes in mean QTc intervals (i.e., > 20 ms) were detected at up to 4 hours post-injection at the proposed dose.

In exploratory analyses, the clinical pharmacology group found an improvement in overall survival with increasing body weight quartile and increasing dose. During drug development, the radium-223 dose was not extensively explored. Dose will be further explored as a post-marketing commitment.

5. Clinical Microbiology

N/A.

6. Clinical/Statistical- Efficacy

This application was primarily supported by a double-blind, randomized, placebo-controlled trial in patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease. Patients were allocated 2:1 to Xofigo, 50 kBq (1.35 microcurie)/kg, intravenously every 4 weeks for 6 cycles plus best standard of care (N=541) or to matching placebo plus best standard of care (N=268). Best standard of care included local radiotherapy, corticosteroids, anti-androgens, estrogens, estramustine or ketoconazole. All patients were to continue androgen deprivation therapy. The median age was 71 years, 94% were Caucasian, 86% had an ECOG performance status of 0-1, and 58% had received prior docetaxel. Fifty-four percent of patients used opiate and 44% used non-opiate pain medications. Overall survival (OS) was the primary endpoint.

At the pre-specified interim analysis, a statistically significant improvement in OS was demonstrated [HR 0.70 (95% CI: 0.55, 0.88), p = 0.00185]. The median OS was 14.0 and 11.2 months in the Xofigo and placebo arms, respectively. The improvement in OS was supported by a delay in time-to- first symptomatic skeletal event favoring the Xofigo arm.

Table 3: Primary Analysis		
	Radium-223 N = 541	Placebo N = 268
Events	35%	46%
Censored	65%	54%
Median OS (95% CI)	14.0 mos (12.1, 15.8)	11.2 mos (9.0, 13.2)
Hazard Ratio	0.70 (0.55, 0.88)	
p-value (2-sided)	0.00185	

Data Cutoff 10-14-10

Secondary Endpoints

Analysis of the time to the first symptomatic skeletal event shown in the table below differs from the pre-specified analysis in the statistical plan. The pre-specified analysis did not account for informative censoring due to patient deaths prior to the development of a skeletal event. In this analysis, patient deaths are included as events. The most prominent component of this endpoint is the number of patients who required radiation therapy to the bone. Note that this endpoint differs from skeletal-related events in that routine X-rays were not performed.

Table 4: Time to the First Symptomatic Skeletal Event		
	Radium-223 N = 541 (%)	Placebo N = 268 (%)
Event	262 (48)	160 (60)
Median Time to Event (95% CI)	8.2 mos (7.5, 9.4)	6.1 mos (5.1, 7.1)
Hazard Ratio (95% CI)	0.66 (0.54, 0.80)	
p-value	< 0.0001	

Data Cutoff 10-14-10

An additional secondary endpoint was the time to PSA progression. The median time to PSA progression was 3.6 and 3.4 months in the radium-223 and placebo arms, respectively. An exploratory analysis found that 6% of radium-223 and 1% of placebo-treated patients had a confirmed $\geq$ 50% decrease in PSA.

Supportive Studies

Six small supportive studies using a variety of doses and schedules were submitted. This includes 3 Phase 2 studies described below.

- BC1-02: This study randomized 64 patients with castration-resistant prostate cancer and bone metastases to radium-223 50 kBq/kg q 4 weeks x 4 or placebo. All patients had received radiation therapy in the 7 days prior to entry. For both arms, the median field size of the irradiated regions was 202 cm^2 (range 29-450 cm^2) and the median dose was 16 Gy (range 8-30 Gy). The primary endpoints were time to a composite endpoint and change in alkaline phosphatase. The composite endpoint was complex and included an increase in pain and analgesic use as well as the need for radiation therapy or surgical intervention for bone disease. The median time to this composite endpoint was 15.0 weeks in the radium-223 and 13.6 weeks in the placebo arm. The median change in bone-ALP 4 weeks after the last dose was -66% in the radium-223 and +9% in the placebo arm. At 24 months, the hazard ratio for OS was 0.48 in favor of radium-223.

- BC1-03: This study randomized 100 patients with castration-resistant prostate cancer, bone metastases, and a pain score $\geq$ 2 on the Brief Pain Inventory to 5, 25, 50, or 100 kBq/kg of radium-223 x 1 dose. The primary endpoint was a pain index that included both bone pain and analgesic use. Scores were assessed at multiple time points and were not adjusted for multiplicity. In the per protocol population (patients with a pain index $\geq$ 2 at baseline), a test for trends found a decrease in the pain index with increasing dose at week 2. This analysis was not significant in the ITT population.

- BC1-04: This study randomized 122 patients with metastatic castration-resistant prostate cancer to 25, 50, or 80 kBq/kg q 6 wks x 3. The primary endpoint was the percentage of patients with a confirmed $\geq$ 50% decrease in PSA. This was 0 in the 25, 2/36 (5.6%) in the 50 and 5/39 (12.8%) in the 80 kBq/kg groups.

7. Safety

Using a data cutoff of July 15, 2011, 600 patients on the Phase 3 trial received 50 kBq/kg radium-223 and 301 patients received placebo. Dose reductions were not permitted and dose delays were seen in a small percentage of patients on the Phase 3 study. In addition to the 600 patients in the Phase 3 trial, an additional 103 patients from the Phase 1-2 trials received 50 kBq/kg radium-223.

Table 5: Patient Exposure on the Phase 3 Trial

	Radium-223 N = 600	Placebo N = 301
Median Duration of Exposure (range)	20 weeks (0.1-28)	18 weeks (0.1-27)
Percentage Completing 6 Injections	64%	47%
Median Cumulative Activity (range)	21,726 kBq (2,700-41,985)	NA
Dose Delay due to Adverse Event	15%	18%

Data Cutoff July 15, 2011

Overall, 904 patients received radium-223 at doses ranging from 46-250 kBq as a single injection and from 80 kBq/kg every 6 weeks x 3 to 50 kBq/kg every 4 weeks x 6 doses as repeat injections. The highest cumulative dose of radium-223 was 41,985 kBq. The Safety Update (data cutoff December 1, 2012) included 25 patients who crossed over from placebo to radium-223 on the Phase 3 trial and line listings of safety reports in ongoing studies.

The most common ($\geq$ 10%) adverse reactions in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema. The most common ($\geq$ 10%) hematologic laboratory abnormalities were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Two percent of patients on the Xofigo arm experienced bone marrow failure or ongoing pancytopenia. No patients on the placebo arm experienced bone marrow failure or pancytopenia.

8. Advisory Committee Meeting

This application was not referred to an ODAC because the application showed improvement in overall survival and did not raise significant safety or efficacy issues.

9. Pediatrics

The pediatric study requirement for this application was waived because necessary studies are impossible or highly impracticable as this indication does not occur in children.

10. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment

Despite the availability of an increasing number of therapeutic options, metastatic castration-resistant prostate cancer remains a serious and life-threatening disease. Radium-223 provides an additional option, but is limited to patients with bone-only disease. It is likely that radium-223 can be added to other therapeutic options which are not cytotoxic.

Radium-223 improved overall survival with a hazard ratio of 0.70, p = 0.0012. Radium-223 lengthened the time to the development of a symptomatic skeletal event. Adverse drug reactions in $\geq$ 10% of patients included nausea, diarrhea, vomiting and peripheral edema. Hematologic laboratory abnormalities in $\geq$ 10% of patients included anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Whether late toxicities such as the development of bone marrow suppression and second primary malignancies will occur with radium-223 remains unknown. Post-marketing requirements will assess the late toxicities associated with radium-223.

The risk-benefit profile was also discussed in Drs. Justice, Maher, Kluetz and Pierce's reviews. In addition, the review team recommends approval of this application, and I concur.

- Recommendation for Postmarketing Risk Management Activities: None.
- Recommendation for other Postmarketing Study Commitments: See action letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMY E KIM
05/15/2013

RICHARD PAZDUR
05/15/2013