

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203971Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: March 27, 2013

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): radium Ra 223 dichloride (Xofigo[®])

Therapeutic Class: Radiopharmaceutical

Dosage and Route: 50 kBq (0.00135 mCi) per kg body weight every 4 weeks
for 6 cycles; administer by slow intravenous injection

Application Type/Number: NDA 203971

Applicant/sponsor: Bayer HealthCare

OSE RCM #: 2013-40

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity radium Ra 223 dichloride. On December 14, 2012, Bayer HealthCare submitted an original New Drug Application (NDA) for Xofigo[®] (radium Ra 223 dichloride) injection for the treatment of castration-resistant prostate cancer patients with bone metastases. The sponsor did not submit a proposed REMS or risk management plan.

1.1 BACKGROUND

Prostate cancer is the second most common cancer in men worldwide, with an estimated 903,000 new cases and 258,000 deaths in 2008; the American Cancer Society estimates there were 242,000 new cases and 28,000 deaths in the United States in 2012.^{1,2} Although most cases of prostate cancer are diagnosed and treated while the disease is localized, some men have metastatic disease at presentation or develop metastases after standard therapy. Androgen deprivation therapy (ADT) is the primary approach for patients when systemic treatment is indicated for metastatic disease. Patients who experience disease progression while being managed with ADT are considered to have castration-resistant disease.³ Current treatment options for castration-resistant prostate cancer (CRPC) include chemotherapy, such as docetaxel, cabazitaxel, or mitoxantrone; the cancer vaccine sipuleucel-T; and the anti-androgens abiraterone and enzalutamide, as well as other endocrine therapies.

Osteoblastic lesions in bone are the most frequent site of metastasis in men with advanced prostate cancer, and pain is the most common clinical manifestation. Bony metastases can also cause pathologic fractures and spinal cord compression. The treatment of bone metastases is palliative. Treatment options that specifically target bone metastases include osteoclast inhibitors such as bisphosphonates and denosumab (which can help prevent disease progression and the development of skeletal related complications), external beam radiation therapy, and targeted radiopharmaceuticals.⁴

Bone-targeted radiopharmaceuticals are used in men with symptomatic multifocal metastatic prostate cancer to the bone. These agents mimic calcium and target hydroxyapatite in areas of new bone growth in and around metastases. Agents currently approved in the U.S. include strontium-89 chloride (Metastron) and samarium-153 lexidronam pentasodium (Quadramet). Strontium-89 is a pure beta particle (electrons) emitter whereas samarium-153 emits both beta and gamma (electromagnetic waves) energy. The subject of NDA 203971, radium-223, is an alpha particle (2 protons and 2 neutrons) emitter, with only 1% of the emitted energy in the form of gamma energy. A comparison of the physical properties of these radiopharmaceuticals is shown below in Table 1.

¹ Jemal A, et al. Global Cancer Statistics. *CA Cancer J Clin* 2011;61:69-90.

² Siegel R, et al. Cancer Statistics, 2012. *CA Cancer J Clin* 2012;62:10-29.

³ Dawson NA. Overview of the treatment of disseminated prostate cancer. In: UpToDate, Vogelzang N, Lee WR, Richie JP (Eds), UpToDate, Waltham MA, 2013.

⁴ Sartor AO and DiBiase SJ. Management of bone metastases in advanced prostate cancer. In: UpToDate, Vogelzang N, Lee WR, Richie JP (Eds), UpToDate, Waltham MA, 2013.

Table 1. Physical properties of radiopharmaceuticals for patients with bone metastases⁵

| Radiopharmaceutical | Particle | Half-life | Particle energy | Maximum tissue penetration | Standard Dose* |
|---------------------|----------|-----------|--------------------|----------------------------|--|
| Strontium-89 | Beta | 50.5 days | 1.46 MeV | 5.5 mm | 4 mCi/kg (148 MBq/kg) |
| Samarium-153 | Beta | 1.9 days | 0.81 MeV | 2.5 mm | 1 mCi/kg (37 MBq/kg) |
| Radium-223 | Alpha | 11.4 days | 5.64 MeV (mean) | <0.1 mm | 1.35—6.75 μ Ci/kg (50—250 kBq/kg) |

* The Becquerel (Bq) is a derived unit of radioactivity. One Bq is defined as the activity of a quantity of radioactive material in which one nucleus decays per second.

Alpha particles differ from beta particles in that they have much greater mass, less tissue penetration, and high energies transferred over short track lengths. In theory, the shorter alpha track length at sites of osteoblastic metastasis results in less irradiation of healthy bone marrow compared with the longer track length radiation damage produced by beta particles. Another important difference is that beta particle emission produces single-strand DNA breaks, in contrast to the irreparable DNA double-strand breaks caused by alpha particles.^{6,7}

1.2 REGULATORY HISTORY

The sponsor was granted Fast-Track Designation on August 18, 2011 for the investigation of radium-223 dichloride for the treatment of castration-resistant (hormone refractory) prostate cancer in patients with bone metastases. On December 14, 2012, Bayer HealthCare submitted an original New Drug Application (NDA) for the product and indication. The review classification for the application is Priority. The sponsor did not submit a proposed REMS or risk management plan.

The bone-targeted radiopharmaceuticals Metastron (approved 1993) and Quadramet (approved 1997) are administered under the guidelines of the Nuclear Regulatory Commission (NRC), Title 10 CFR 35.300 or Agreement State Institutional License. Institutional licenses must specifically list individuals licensed to use Section 35.300 materials.⁸ Radium-223 has the potential to be the first therapeutic radiopharmaceutical being administered primarily for its alpha emissions. In a decisional letter dated January 10, 2013, the NRC notified all Agreement States that medical use of radium-223 dichloride will be regulated under Title 10 Part 35 Subpart E, “Unsealed Byproduct Material – Written Directive Required”.⁹ The NRC determined that physicians who are approved for the use of any beta emitter or gamma-

⁵ Goyal G and Antonarakis ES. Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases. *Cancer Letters* 2012;323:135-146.

⁶ Cheetham PJ and Petrylak DP. Alpha particles as radiopharmaceuticals in the treatment of bone metastases: mechanism of action of radium-223 chloride (Alpharadin) and radiation protection. *Oncology* 2012;26:330-341.

⁷ Silberstein EB. An alpha edge? *Oncology* 2012;26:345-348.

⁸ Silberstein EB, et al. Society of Nuclear Medicine Procedure Guidelines for Palliative Treatment of Painful Bone Metastases; version 3.0, approved January 25, 2003 (accessible at http://interactive.snm.org/docs/pg_ch25_0403.pdf).

⁹ U.S. Nuclear Regulatory Agency Notice of Licensing Decision on Radium-223 Dichloride (FSME-13-002), January 10, 2013 (accessible at <http://nrc-stp.ornl.gov/asletters/program/sp13002.pdf>).

emitting radionuclide under § 35.390 or § 35.396 already have the requisite education, training, and experience to safely and effectively use radium Ra 223 dichloride.

2 MATERIALS REVIEWED

- December 14, 2012, Original NDA 203971 submission. Sections reviewed include:
 - Section 2.5, Clinical Overview
 - Section 2.7.4, Summary of Clinical Safety
- January 4, 2013, slides from Bayer HealthCare Xofigo NDA orientation meeting
- January 10, 2013, U.S. Nuclear Regulatory Agency Notice of Licensing Decision on Radium-223 Dichloride (FSME-13-002)⁹
- February 14, 2013, slides from NDA 203971 Mid-Cycle Meeting
- March 1, 2013, Response to FDA Request for Information
- March 5, 2013, Response to FDA Request for Information

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The sponsor completed a single Phase-3 clinical trial in support of the proposed indication. Study BC1-06 was a randomized, double-blind, placebo-controlled international study in 809 patients with symptomatic CRPC that metastasized to the bone. Subjects were randomized 2:1 to receive radium-223 dichloride (50 kBq/kg) plus best standard of care (BSoC) or placebo plus BSoC. Subjects received six intravenous doses, each separated by an interval of four weeks. The primary efficacy endpoint was overall survival. The main secondary endpoints included changes and time to progression of alkaline phosphatase and prostate specific antigen, and time to occurrence of skeletal-related events. Compared with placebo, treatment with radium-223 dichloride increased median overall survival from 11.3 months to 14.9 months, with a Hazard ratio (95% CI) of 0.695 (0.581, 0.832). The median times to progression of alkaline phosphatase and prostate specific antigen, and time to occurrence of the first skeletal-related event, were prolonged in favor of radium-223 dichloride compared with placebo, with hazard ratios that favored the treatment arm for each endpoint.

3.2 SAFETY CONCERNS

3.2.1 Radiation Safety

The administration of radiopharmaceuticals falls under the jurisdiction of radiation safety regulations and various national and local radiation safety programs apply. Radiopharmaceuticals can only be supplied to institutions with a radioactive materials license, which specifies the healthcare professionals who are qualified to handle these products.

The alpha particle emission from radium-223 dichloride is readily blocked (e.g., by a sheet of paper) and has an extremely short penetration; there is very little gamma emission from the product. These properties make radium-223 relatively easy to handle and safe as long as universal precautions are adhered to and internalization is avoided. Radiation exposure and shielding requirements are no different than those routinely used for diagnostic radiopharmaceuticals, and patients may be treated on an outpatient basis. After treatment,

radiation exposure to household members and caregivers can be minimized by good hygiene practices and avoidance of internalization of the patient's bodily fluids; fecal excretion is the major route of radium-223 elimination, with up to 5% excreted in urine.

3.2.2 Hematologic toxicity

In Study BC1-06, Grade 3-4 thrombocytopenia was observed at a higher rate in patients treated with radium-223 dichloride compared with placebo (6.3% vs. 2%); 11.5% of patients in the radium-223 arm experienced thrombocytopenia of any grade. Grade 3-4 adverse events of neutropenia and leukopenia also occurred at higher rates in the radium-223 arm (2.2% vs. 0.7%, and 1.3% vs. 0.3%, respectively); neutropenia of any grade occurred in 5% of the radium-223 treated patients. Pancytopenia occurred in 2% of the radium-223 treated patients, whereas there were no cases in the placebo arm. The higher frequencies of these hematologic events did not result in an increased rate of fatal bleeding or fatal infections, but slightly higher rates of serious adverse events of bleeding or infection were reported in the patients who received radium-223 dichloride.

3.2.3 Gastrointestinal toxicity

Gastrointestinal (GI) adverse events were the most common adverse events observed in each arm of Study BC1-06. Vomiting occurred more frequently in the radium-223 dichloride group compared with placebo (18.5% vs. 13.6%), as did the occurrence of diarrhea (25.2% vs. 15.0%). Most of these GI events were Grade 1-2 toxicities.

3.2.4 Secondary malignancies

Ten second primary malignancies have been observed following treatment with radium-223 dichloride in all clinical studies. No cases of osteosarcoma, myelodysplastic syndrome, or acute myeloid leukemia have been reported. One case of multiple myeloma was diagnosed one month after the third injection; the latency period for the other second primary malignancies reported ranged from an estimated one to 24 months after initial exposure to radium-223. The calculated absorbed radiation doses from radium-223 dichloride are highest for bone, red marrow, and large intestine, with low absorption by other organs.

3.2.5 Administered dose of radiation activity

Radium-223 dichloride is distributed directly to the authorized user in a glass vial with an activity concentration of 1,000 kBq/ml at the reference date. The user calculates the patient-specific volume needed to provide a dose of 50 kBq/kg at the time of administration using the patient's body weight and a fractional decay correction factor supplied by the manufacturer. To confirm that the actual pre-administration radiation activity is consistent with the prescribed activity, assay and verification of the radiation activity can be determined at the clinical site using a dose calibrator and radium-223 reference standards, using a procedure to be specified in the labeling.

3.2.6 Proposed Postmarketing Studies

Although safety-related postmarketing requirements have not been determined at the time of this review, discussions regarding dose optimization as well as a long-term evaluation of the risk of secondary malignancy are ongoing.

4 DISCUSSION

Radium-223 dichloride is an alpha emitting radiopharmaceutical that targets bone metastases. In the Phase-3 clinical trial of patients with CRPC, the drug significantly prolonged overall survival and other secondary efficacy endpoints compared with placebo. Although the safety profile demonstrated higher rates of GI adverse events associated with radium-223 treatment, most of the adverse events were not severe. The frequency of events associated with bone marrow suppression and radium-223 treatment is comparatively less than that seen with the beta emitting radiopharmaceuticals Metastron and Quadramet. Approximately 5% of radium-223 treated patients experienced leukopenia or neutropenia and 10% thrombocytopenia in the Phase-3 study, whereas leukopenia and thrombocytopenia are observed in up to 80% of patients treated with Metastron and 95% of those who receive Quadramet.^{5,10}

The risk of secondary hematologic or solid malignancies associated with radium-223 appears low based on the clinical experience in patients with CRPC to date, though the development of these cancers likely takes longer than the duration of survival for these patients. The secondary malignancy risk could be higher for prostate cancer patients with minimal metastatic burden as well as for patients with other metastatic malignancies associated with a longer life expectancy.

A radioactive materials license addresses the training and experience requirements for personnel to be authorized to safely and effectively use radium-223. The labeling should advise authorized users to assay the radiation activity of radium-223 prior to its administration. Use of an appropriate system—such as a dose calibrator with a reference standard— and procedures to assay these activities can confirm activity at the treatment site independent of the manufacturer’s calibration.

DRISK does not recommend a REMS for the management of the risks associated with radium-223 dichloride. Men with a diagnosis of CRPC and bone metastases have an advanced, life-threatening disease with limited treatment options. Radium-223 significantly prolonged overall survival and other secondary efficacy endpoints compared with placebo in the pivotal clinical study. The safety profile of radium-223 is favorable compared with radiopharmaceuticals already approved for the treatment of skeletal metastases, including Metastron and Quadramet, neither of which have a REMS. The use and handling of radium-223 presents minimal radiation protection concerns to authorized users, caregivers, and household members.

5 CONCLUSION

DRISK concurs with the Division of Oncology Products-1 that, based on the available data and the potential benefits and risks of treatment, a REMS is not required for radium-223 dichloride and the risks associated with the drug can be managed through labeling. If new safety information becomes available this decision can be re-evaluated.

¹⁰ Quadramet labeling (accessible at <http://dailymed.nlm.nih.gov>).

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