



NDA 203971

NDA APPROVAL

Bayer HealthCare Pharmaceuticals
Attention: Deepika Jalota, Pharm.D.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Dr. Jalota:

Please refer to your New Drug Application (NDA) dated December 14, 2012, received December 14, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xofigo[®] (radium Ra 223 dichloride) Injection, 1000 kBq/mL (0.027 microcurie/mL) at reference date.

We acknowledge receipt of your amendments dated December 18, 21, 2012, January 9, 10, 16, 22, 24, 25, 29, 31, February 4, 5, 7, 8, 13, 19, 25, 26, 28, March 5, 6, 7, 8, 13, 14, 18, 19, 21, 22, 25, 26, 27, 28, April 1, 2, 5, 23, 26, 30, May 2, 10, 13, 2013.

This new drug application provides for the use of Xofigo[®] (radium Ra 223 dichloride) Injection for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry SPL Standard for Content of Labeling Technical Qs and As, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels and/or carton, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “Final Printed Carton and Container Labels for approved NDA 203971.” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRY DATING AND STORAGE CONDITIONS

The drug product is granted a shelf-life of 28 days stored below 40 °C.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Elleni Alebachew, M.S. RAC
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2183
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Xofigo[®] (radium Ra 223 dichloride) Injection was not referred to an FDA advisory committee because the application showed improvement in overall survival and did not raise significant safety or efficacy issues.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable as this indication does not occur in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of long-term bone marrow suppression and to identify an unexpected serious risk of developing secondary malignancies.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2041-1 An observational study (N = 1200) to assess the long-term safety of radium Ra 223 dichloride 50 kBq/kg every 4 weeks for 6 doses in patients with castration-resistant prostate cancer with bone metastases.

The timetable you submitted on April 26, 2013 and on May 2, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
First Interim Report Submission:	09/2017
Second Interim Report Submission:	09/2019
Study Completion:	12/2023
Final Report Submission:	09/2024

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of bone marrow suppression and identify an unexpected serious risk of developing secondary malignancies.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2041-2 A randomized clinical trial to assess the safety of radium Ra 223 dichloride in patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

The timetable you submitted on April 26, 2013 and on May 2, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2013
Trial Completion:	12/2017
Interim Report Submission:	09/2018
Final Report Submission:	03/2025

2041-3 A trial of the short and long-term safety of re-treatment of patients with castration-resistant prostate cancer with bone metastases with radium Ra 223 dichloride.

The timetable you submitted on April 26, 2013 and on May 2, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2013
Trial Completion:	09/2016
Interim Report	03/2017
Final Report Submission:	01/2024

Submit the protocol(s) to your (b) (4), with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

2041-4 Optimize the dosing regimen of Xofigo by conducting a randomized Phase 2 clinical trial to evaluate the efficacy and safety of Xofigo at a dose higher than 50 kBq/kg in patients with castration-resistant prostate cancer with bone metastases.

Depending on the results of the Phase 2 trial, a randomized Phase 3 trial may be needed to further confirm the appropriateness of the dosing regimen determined in the Phase 2 trial.

The timetable you submitted on May 2, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	09/2018
Final Report Submission:	03/2019

Submit clinical protocols to your IND 067521 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more

information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

You will be contacted by ERG to schedule the interview following this action on your application; ERG will provide specifics about the interview process at that time. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While

your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Elleni Alebachew, Regulatory Health Project Manager, at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
05/15/2013