



# Arkansas Department of Health

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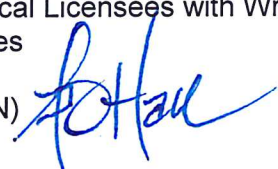
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**Governor Asa Hutchinson**

**Nathaniel Smith, MD, MPH, Director and State Health Officer**

## **ARKANSAS INFORMATION NOTICE 16-03**

**To:** Nuclear Pharmacy Licensees and Medical Licensees with Written Directives  
Arkansas Radioactive Material Licensees

**From:** Angie D. Hall, MA, BS, CNMT, ARRT (N)   
Health Physicist  
Radioactive Materials Program

**Subject:** **Important Drug Information Update for Xofigo Radium-223 Dichloride Therapies for Intravenous Uses**

**Date:** April 12, 2016

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This Arkansas Information Notice (IN) is to advise nuclear pharmacy licensees and medical licensees with written directives of the upcoming changes in the Xofigo Radium-223 Dichloride Therapy preparations and uses.

The Department is distributing the Bayer HealthCare Pharmaceuticals letter, dated March 14, 2016 and received April 11, 2016, as an enclosure to this IN. Bayer HealthCare's letter addresses the specific changes, new requirements, and other important drug information updates.

Some of the key points are the changes in the patient dose calculation, radioactivity concentration per vial, implementation and use of the updated National Institute of Standards and Technology (NIST) 2015 – Traceable Reference Material, the new dial setting for the dose calibrator, and the use of orange color stickers labeled "NIST 2015."

Nuclear pharmacy licensees and medical licensees may contact Bayer HealthCare with questions at telephone number (888) 842 – 2937 or with their local Bayer Radiotherapy Specialist.

The expected effective date is April 25, 2016.

No response to this IN is required.



**IMPORTANT  
DRUG  
INFORMATION  
UPDATE**

REC'D APR 11 2016

March 14, 2016

**SUBJECT: Xofigo® (radium Ra 223 dichloride) Injection, for intravenous use  
Implementation of NIST Standard Reference Material change for quantifying the  
radioactivity of radium-223, and updated corresponding label information.**

Dear Healthcare Professional,

Bayer Healthcare Pharmaceuticals would like to inform you about the upcoming change in the numerical value of the radioactive content and patient dose of Xofigo® (radium Ra 223 dichloride) Injection. This does not reflect a change in the actual product radioactivity or in the amount of radioactivity given to the patient and therefore will not impact the safety and efficacy of Xofigo® (radium Ra 223 dichloride).

The change comes into effect once product released according to the updated NIST 2015-traceable reference material becomes available which is expected from April 25, 2016 onwards.

**Summary**

- The National Institute of Standards and Technology (NIST) revised the primary standardization for radium-223 [1], referred to as the NIST 2015-traceable reference material (notification in Mar 2015).
- The numerical value of the radioactivity concentration (in Bq/mL) contained in vials of Xofigo® (radium Ra 223 dichloride) and hence the patient dose in Bq/kg body weight will increase by approx. 10%:
  - this results in an increase of the nominal value for the radioactivity from 1000 kBq/mL to 1100 kBq/mL at the reference date and



- a corresponding increase in patient dose, from 50 kBq/kg body weight to 55 kBq/kg body weight (or an increase from 1.35 uCi (microcurie)/kg body weight to 1.49 uCi (microcurie)/kg body weight).
- This does not reflect a change in the actual product radioactivity or in the amount of radioactivity given to the patient and therefore will not impact the safety and efficacy of Xofigo<sup>®</sup> (radium Ra 223 dichloride).
- Xofigo<sup>®</sup> (radium Ra 223 dichloride) will be manufactured, tested, released and distributed according to the updated NIST 2015-traceable reference material. It will become available from April 25, 2016 onwards.
- Xofigo<sup>®</sup> (radium Ra 223 dichloride) product released from the manufacturing site in accordance to the updated reference material will be identifiable by an orange colored sticker on the lead container and labelled “NIST 2015”.
- Each patient ready dose shipped to your facility will also be identifiable by an orange colored sticker on the syringe pig and labelled “NIST 2015”.
- Once the first patient ready dose (manufactured according to NIST 2015 reference material) arrives at your facility, you must use the new dial setting on the dose calibrators.
- Xofigo<sup>®</sup> (radium Ra 223 dichloride) product information has been updated to reflect the numerical change of the radioactivity concentration.

### **Background**

The active moiety of Xofigo<sup>®</sup> is radium-223, an alpha particle-emitting radioisotope. The activity of radium-223 can be measured in an appropriate radioisotope dose calibrator that has been calibrated with a National Institute of Standards and Technology (NIST)-traceable radium-223 reference material.

The NIST standard reference material, upon which NIST-traceable reference material is based, has been re-evaluated in 2015. The results indicate that an approx. 10% difference exists between activity values obtained using the new standard (NIST 2015) and those obtained based on the former primary standardization published in 2010. The use of the updated NIST 2015-traceable reference material results in a numerical change of the labeled radioactivity of Xofigo<sup>®</sup> (radium Ra 223 dichloride):

- an increase of the nominal value for the radioactivity from 1000 kBq/mL to 1100 kBq/mL at reference date and



- a corresponding increase in patient dose, from 50 kBq/kg body weight to 55 kBq/kg body weight (or an increase from 1.35 uCi (microcurie)/kg body weight to 1.49 uCi (microcurie)/kg body weight)

However, the change does not reflect a change in the actual product radioactivity or in the amount of radioactivity given to the patient. The labeling supplement regarding the numerical change of the labeled activity of Xofigo<sup>®</sup> (radium Ra 223 dichloride) has been approved by the FDA and the product information has been updated accordingly.

Bayer previously provided information in a Direct to Healthcare Professional Communication that was released in March 2015 about the revision to the NIST standardization and the upcoming consequences:

- An additional dial setting for the revised radium-223 standardization needed to be added to dose calibrators used for verification of Xofigo<sup>®</sup> (radium Ra 223 dichloride) doses.
- Bayer is working to provide updated reference material (NIST 2015 -traceable reference material) to all remaining treatment sites in preparation for this new dial setting.
- Authorized persons in healthcare facilities involved in handling or administering Xofigo<sup>®</sup> (radium Ra 223 dichloride) have been instructed not to use the new dial-setting before the implementation of the Xofigo<sup>®</sup> (radium Ra 223 dichloride) label change.

### **Future Actions**

Bayer would like to inform you that starting with distribution of Xofigo<sup>®</sup> (radium Ra 223 dichloride) on April 25, 2016 you will receive drug product manufactured, tested, and released according to the updated NIST 2015-traceable reference material. The label on the lead container and on syringe pig as well as the updated product information inserted in each package will display the changed activity values.

For the first six months following the implementation of the updated NIST 2015-traceable<sup>4</sup> reference material (April – September 2016), Xofigo<sup>®</sup> (radium Ra 223 dichloride) product released according to the updated reference material will be identified with an **orange colored sticker “NIST 2015”** on each lead container and syringe pig for easy identification.



Once you have received the first patient ready dose (manufactured according to NIST 2015), authorized persons in your healthcare facilities involved in handling or administering Xofigo<sup>®</sup> (radium Ra 223 dichloride) must:

- i) **discontinue using the former dial setting based on the NIST standard published in 2010;**
- ii) **ONLY use the NEW dial setting on the dose calibrators based on the NIST 2015-traceable reference material.**

Ensure appropriate documentation of old and new dial-setting and the change for all dose calibrators in use. Only one dial-setting should be active in the dose calibrator at one point in time to avoid any confusion and error in measurement.

**Company contact point**

Healthcare providers with any questions about the information contained in this letter or the safe and effective use of Xofigo<sup>®</sup> (radium Ra 223 dichloride) should contact the Bayer Call center at:

US: 1-888-84-Bayer, or 1-888-842-2937

**Reporting Adverse Events**

Healthcare providers and patients are encouraged to report adverse events in patients taking Xofigo<sup>®</sup> (radium Ra 223 dichloride) to Bayer HealthCare Pharmaceuticals at 1-888-842-2937.

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's Med Watch Adverse Event Reporting program either online, by regular mail or by fax.

- Complete and submit report **Online:**  
[www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)
- Regular Mail or Fax: Download form [www.fda.gov/MedWatch/getforms.htm](http://www.fda.gov/MedWatch/getforms.htm) or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

# Bayer HealthCare Pharmaceuticals



This letter is not intended to provide a complete description of the benefits and risks related to the use of Xofigo® (radium Ra 223 dichloride). Please refer to the enclosed full prescribing information.

For additional information, please contact Bayer at 1-888-842-2937 or visit [www.Xofigo-us.com](http://www.Xofigo-us.com)

Sincerely,

A handwritten signature in black ink, appearing to read "Dario Mirski, MD". The signature is written over a faint, circular stamp or watermark.

Dario Mirski, MD

Senior Vice President and Head Medical Affairs Americas  
Bayer HealthCare Pharmaceuticals, Inc.

## References:

1. Xofigo® (radium Ra 223 dichloride) Prescribing Information
2. B.E. Zimmerman, D.E. Bergeron, J.T. Cessna, R. Fitzgerald, and L. Pibida, Revision of the NIST Standard for 223 Ra: New Measurements and Review of 2008 data, Journal of Research of the National Institute of Standards and Technology, Vol 120, Page 37-57 (2015)