



**IMPORTANT
DRUG
INFORMATION
UPDATE**

March 21, 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[®] (radium Ra 223 dichloride).
- Xofigo[®] (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[®] (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[®] (radium Ra 223 dichloride) product information has been updated to reflect the numerical change of the radioactivity concentration.

Background

The active moiety of Xofigo[®] 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[®] (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[®] (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[®] (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[®] (radium Ra 223 dichloride) have been instructed not to use the new dial-setting before the implementation of the Xofigo[®] (radium Ra 223 dichloride) label change.

Future Actions

Bayer would like to inform you that starting with distribution of Xofigo[®] (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 reference material (April – September 2016), Xofigo[®] (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[®] (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[®] (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[®] (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
- Regular Mail or Fax: Download form <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



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 [full prescribing information](#).

For additional information, please contact Bayer at 1-888-842-2937 or visit www.Xofigo-us.com

Sincerely,

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)