30th March 2016

▼ Xofigo®: Change in NIST Standard Reference Material – Information on Implementation

Dear Healthcare Professional,

Bayer Pharma AG in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you about the upcoming change in the numerical value of the radioactive content and patient dose of Xofigo. The change comes into effect once the product released according to the updated NIST 2015-traceable reference material becomes available from April 14th, 2016 onwards.

Summary

- **The National Institute of Standards and Technology (NIST) has revised, in 2015, the primary standardization for radium-223 [1], referred to as the NIST 2015-traceable reference material.**
- **As a result the numerical value of the radioactivity concentration (in Bq/mL) contained in vials of Xofigo and hence the patient dose in Bq/kg body weight will increase by approx. 10%:**
  - **an increase of the nominal value for the radioactivity from 1000 kBq/mL to 1100 kBq/mL at reference date and**
  - **an apparent increase in patient dose, from 50 kBq/kg body weight to 55 kBq/kg body weight.**
- **This does not reflect a real 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-223 dichloride).**
- **Starting from April 14th, 2016, Xofigo product manufactured, tested, and released according to the updated NIST 2015-traceable reference material will be distributed.**
- **Xofigo product released according to the updated reference material will be identifiable by an orange colored sticker "NIST 2015" on each lead container.**
- **The Xofigo product information has been updated to reflect the numerical change of the radioactivity concentration.**
- **Once the first vial manufactured according to NIST 2015 reference material arrives at your facility, the new dial setting on the dose calibrators must be used.**

Further information

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:

- an increase of the nominal value for the radioactivity from 1000 kBq/mL to 1100 kBq/mL at reference date and
- an apparent increase in patient dose, from 50 kBq/kg body weight to 55 kBq/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. A variation regarding the numerical change of the labeled activity of Xofigo has been approved by the respective Health Authority and the product information has been updated accordingly.

Bayer already informed you in a previous Direct to Healthcare Professional Communication in March 2015 about the revision 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 doses. Bayer provided updated reference material (NIST 2015 -traceable reference material) to all treatment sites to allow preparing for this new dial setting.
- Authorized persons in healthcare facilities involved in handling or administering Xofigo were instructed not to use the new dial-setting before the implementation of the Xofigo label change, i.e., prior to receipt of the Xofigo product with the orange sticker stating “NIST 2015”.

Future Actions

Herewith Bayer would like to inform you that starting with deliveries of Xofigo from April 14th, 2016 on, you will receive drug product manufactured, tested, and released according to the updated NIST 2015-traceable reference material.

The label on the vial, on the lead container and on the shipping package 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 product released according to the updated reference material is identified with an **orange colored sticker “NIST 2015”** on each lead container for easy identification.

Once you have received the first vial manufactured according to NIST 2015, authorized persons in your healthcare facilities involved in handling or administering Xofigo must:

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

Please 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.

Call for reporting
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point
For further information, please contact Bayer Ltd, The Atrium, Blackthorn Road, Dublin 18; Tel: +353 1 2999313; Fax: +353 1 2061456; E-mail: info.ireland@bayerhealthcare.com.

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1. 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)