Bayer HealthCare

31st March 2015

▼ Xofigo®(radium-223 dichloride): Change in NIST Standard Reference Material

Dear Healthcare Professional,

Bayer Pharma AG in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to provide an early notification of a future change in the way the radioactive content and patient dose of Xofigo are expressed.

Summary

- **The National Institute of Standards and Technology (NIST) recently revised the primary standardisation for radium-223 [1].**
- **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 approximately 10%.**
- **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).**
- **The current reference material (2010 NIST-traceable RM), based on the 2010 standard, must continue to be used for calibration of dose calibrators until further notice.**
- **An additional dial setting for the revised radium-223 standardisation will need to be added to dose calibrators used for verification of Xofigo® doses before the end of 2015. Updated reference material (2015 NIST-traceable RM [2]) needed to allow for this new dial setting will be provided to the treatment sites by Bayer starting in the second quarter of 2015.**
- **The additional dial setting must not be used before further notice by Bayer and before the implementation of the Xofigo® label change, which is expected in early 2016.**

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 (NIST-traceable RM). Activity is defined by the number of nuclear decays per second, the Becquerel.

The NIST Standard Reference Material (NIST SRM), upon which NIST-traceable RM are based, has been re-evaluated after the discovery of a discrepancy in the standard, as described in the recent publication by NIST [1]. The results indicate that an approximate 10% difference exists between activity values obtained using the new standard [1] and those of the former primary standardization published in 2010 [3].

The revision of NIST SRM will result in a numerical change of the labeled activity of Xofigo® (dose and radioactivity in the Xofigo® solution). However, the actual amount of radioactivity administered to the patient will not change. Therefore, there should be no impact to the safety or efficacy of Xofigo® due to this change.

Future Actions
Prior to the end of 2015, an additional dial setting for the revised radium-223 standardisation [2] will need to be added to dose calibrators used for verification of Xofigo® doses. To prepare for the additional dial setting, the updated 2015 NIST-traceable RM will be provided to the treatment sites by Bayer starting in the second quarter of 2015. Bayer will contact the relevant Healthcare Providers involved in the administration of Xofigo®, and Xofigo® clinical investigators directly to provide details about: 1) preparing for the necessary changes in dial settings of the radioisotope dose calibrators and; 2) the ordering procedure for updated NIST-traceable RM.

This additional dial setting based on the 2015 NIST-traceable RM must not be used prior to notification by Bayer and the implementation of the updated Product Information (expected in early 2016). Authorised persons in healthcare facilities involved in handling or administering Xofigo® must continue to use the dial settings on their dose calibrators based on the 2010 NIST traceable RM until further notice from Bayer.

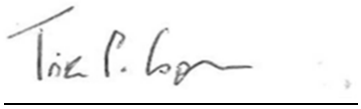
In addition, Bayer is working with the European Medicines Agency to update the Product Information and product labeling for Xofigo® to include the updated nominal values for concentration of radioactivity in the Xofigo® solution and patient dose.

Approximately 2 – 3 weeks prior to implementation of the 2015 NIST-traceable RM and new dial setting, all relevant Healthcare Providers involved in the administration of, or referral for Xofigo® treatment, will be notified via letter of the actual implementation date of the upcoming label change and instructions for initiating the use of the new dial setting for the radioisotope dose calibrator.

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.



Dr. Tristan P. Cooper,
Medical Director

References:

1. B.E. Zimmerman, R. Fitzgerald, J.T. Cessna, D.E. Bergeron, A new primary standard for Ra-223: New experiments and review of 2008 data, Journal of Research of the National Institute of Standards and Technology, Vol.120, Page 37-57- (2015)
2. D.E. Bergeron, J.T. Cessna, B.E. Zimmerman, Secondary standards for ^{223}Ra revised, accepted by Appl. Radiat. Isot.,Volume 101, Page 10-14 (2015)
3. J.T. Cessna and B. E. Zimmerman, Standardization of radium-223 by liquid scintillation counting. Appl. Radiat. Isot., 68, 1523-1528 (2010)