

19th March 2018



▼ **Radium-223-dichloride (Xofigo) contraindicated in combination with abiraterone acetate and prednisolone/prednisone**

Dear Healthcare professional,

Bayer AG in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of the following while a European review of the benefits and risks of radium-223 dichloride is carried out:

Summary

- Xofigo is now contraindicated in combination with abiraterone acetate and prednisone/prednisolone while the review is ongoing.
- The safety and efficacy of Xofigo in combination with second generation androgens receptor antagonists such as enzalutamide (Xtandi) have not been established.
- You must stop treating patients with the combination of Xofigo with the anti-androgen Zytiga and prednisone/prednisolone, and review patient's treatment.
- Interim analysis of a randomised clinical trial in patients with chemotherapy naïve asymptomatic / mildly symptomatic metastatic castration resistant prostate cancer (CRPC) has shown an increased risk of death and fracture in patients receiving radium 223 dichloride (Xofigo) in combination with abiraterone acetate (Zytiga) and prednisone/prednisolone (15396/ERA study).

Background on the safety concern

Xofigo is approved for the treatment of men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

The clinical efficacy and safety of concurrent initiation of Xofigo, abiraterone acetate and prednisone/prednisolone treatment was assessed in a randomised, double blind, placebo controlled study (ERA-223 trial) in chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee Recommendation. Interim data showed that there was an increased incidence of fractures (26.0% vs 8.1%) and deaths (34.7% vs 28.2%) among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone (n=401) compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone (n=405). In this study concurrent use of bisphosphonates or denosumab reduced the incidence of fractures in both treatment arms.

EMA is further investigating the implication of these findings for the currently authorised use of Xofigo. In the meantime, Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone. The safety and efficacy of Xofigo in combination with second generation androgens receptor antagonists such as Xtandi (enzalutamide) have not been established. Healthcare professionals in the EU must stop treating patients with the combination of Xofigo with the anti-androgen Zytiga and prednisone/prednisolone, and review patient's treatment.

Further advice will be communicated as appropriate at the end of the review.

Call for reporting

Reporting of adverse drug reactions will allow for quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to 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. Reports of suspected adverse reactions can also be made to Bayer Ltd, contact details below.

▼ 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.

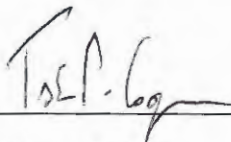
Company contact point

If you have any questions, or if you require any further information, please contact the medical information service of contact Bayer Ltd, The Atrium, Blackthorn Road, Dublin 18; Tel: +353 1 2999313; Fax: +353 1 2061456; E-mail: info.ireland@bayerhealthcare.com.

Annex

Please find the link to the DHPC issued in December 2017: Increased risk of death and fractures in a randomized clinical trial with Xofigo used in combination with abiraterone acetate and prednisolone / prednisone [http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---xofigo-\(radium-223-dichloride\).pdf?sfvrsn=0](http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---xofigo-(radium-223-dichloride).pdf?sfvrsn=0)

With kind regards,



Dr. Tristan P. Cooper
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