19 March 2018

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

Dear Healthcare professional,

Bayer AG in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) 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 (Zytiga) and prednisone/prednisolone while the review is ongoing.
- The safety and efficacy of Xofigo in combination with second generation androgen receptor antagonists such as enzalutamide (Xtandi) have not been established.
- You must stop treating patients with the combination of Xofigo with the anti-androgen abiraterone acetate (Zytiga) and prednisone/prednisolone, and review the patient's treatment.
- Interim analysis of a randomised clinical trial (15396/ERA study) 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.

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.

The 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 androgen receptor antagonists such as enzalutamide (Xtandi) have not been established. Healthcare professionals in the EU must stop treating patients with the combination of Xofigo with the anti-androgen abiraterone acetate (Zytiga) and prednisone/prednisolone, and review the patient's treatment.

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

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. It is easiest and quickest to report ADRs online via the Yellow Cards website https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Yellow Card Information Service free phone line: 0800-731-6789
- or by downloading and printing a form from the Yellow Card section of the MHRA website

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, product brand name and batch number

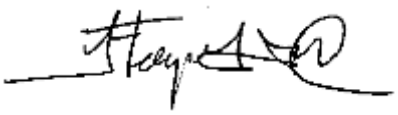
You can also report suspected adverse drug reactions to Bayer via email: pvuk@bayer.com

▼ 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. See section 4.8 of the SmPC, for how to report adverse reactions.

Company contact point

Contact point details for further information are given in the product information of the medicinal products (SmPC and PL) at: http://www.ema.europa.eu/ema/ or contact Bayer plc Medical Information directly (telephone: 0118 206 3116, e-mail: medical.information@bayer.co.uk).

Yours faithfully,



Dr Luis Felipe Graterol
Medical Director
Bayer plc

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s) / active substance(s)	Xofigo / radium Ra223 dichloride
Marketing authorisation holder(s)	Bayer AG
Safety concern and purpose of the communication	Radium-223-dichloride (Xofigo) contraindication in combination with abiraterone acetate and prednisolone/prednisone
DHPC recipients	Urologists in radium treatment target centres. Prescribers or referrers of patients for radium-223: Clinical oncologists, medical oncologists, nuclear medicine clinicians; chief hospital pharmacists; professional societies-Chair of British Nuclear Medicine Society (BNMS) and Chair of British Uro-oncology group (BUG)
Method of dissemination of the DHPC	DHPC by e-mail (where email addresses are available) and post on 19 March 2018.
Member States where the DHPC will be distributed	All Member states where the product is used or likely to be used before the final commission decision on the Article 20 for Xofigo / radium Ra223 dichloride.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	8 March 2018
Submission of translated DHPCs to the national competent authorities for review	12 March 2018
Agreement of translations by national competent authorities	14 March 2018
Dissemination of DHPC	19 March 2018