6 August 2018

▼Xofigo (radium-223-dichloride): new restrictions on use due to increased risk of fracture and trend for increased mortality

Dear Healthcare Professional,

Bayer AG in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- The use of Xofigo is associated with an increased risk of fractures. A possible increased risk of death was also observed in a clinical trial investigating radium-223 dichloride (Xofigo) in combination with abiraterone acetate and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic castration resistant prostate cancer.
- Radium-223 should only be used as monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), and symptomatic bone metastases, and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.
- Radium-223 is contraindicated in combination with abiraterone acetate and prednisone/prednisolone.
- Radium-223 is not recommended in patients with a low level of osteoblastic bone metastases, in patients with only asymptomatic bone metastases and in combination with other systemic cancer therapies other than LHRH analogues. In patients with mildly symptomatic bone metastases, the benefit of treatment should be carefully assessed to outweigh the risks
- Bone health status and baseline risk of fractures should be assessed prior to treatment initiation and closely monitored for at least 24 months. The use of bisphosphonates or denosumab should be considered.

Background on the safety concern

Data from a randomised, double blind, placebo controlled phase III trial (ERA-223), showed that there was an increased incidence of fractures (28.6% vs 11.4%), a reduction in overall median survival (30.7 months vs 33.3 months, HR 1.195, 95% Confidence Interval (CI) 0.950 - 1.505, p=0.13) and an increased risk of radiological non-bone progression (HR 1.376 [95% CIs 0.972, 1.948], p=0.07) among patients receiving radium-223 in combination with abiraterone acetate plus prednisone/prednisolone (n=401) compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone (n=405). An increased fracture risk has been found, especially in patients with a medical history of osteoporosis and in patients with fewer than 6 bone metastases. A statistically significant overall survival benefit of treatment could not be demonstrated in the subgroups of patients with fewer than 6 metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 - 1.466], p=0.674) or a baseline total alkaline phosphatase (ALP) <220 U/L (HR 0.823 95% CI 0.633-1.068, p=0.142), in a randomised, double blind, placebo controlled phase III trial (ALSYMPCA); the use of radium-223 is not recommended, in patients with a low level of osteoblastic bone metastases.

In view of the newly identified fracture risk, the uncertainties regarding a trend for increased mortality and the concerns on imbalances regarding non-bone progression, the indication of radium-223 is restricted as stated above.

In mildly symptomatic patients, the benefit of treatment should be carefully assessed to outweigh the risks considering that high osteoblastic activity is likely to be required for treatment benefit.

Radium-223 is believed to accumulate at sites of high bone turnover such as sites of degenerative bone disease (osteoporosis) or recent (micro-)fracture, increasing the risk of fractures. Other factors such as concomitant use of steroids may further increase the risk of fracture. Therefore, patients with these risk factors may have a higher risk of experiencing fractures.

Prior, during and after treatment with radium-223, bone status (e.g. by scintigraphy, bone mineral density measurement) and risk of fractures of patients (e.g. osteoporosis, less than 6 bone metastases, medication increasing fracture risk, low body mass index) should be carefully monitored. Concurrent use of bisphosphonates or denosumab has been found to reduce the incidence of fractures in patients treated with radium-223. Therefore such preventive measures should be considered before starting or resuming treatment with radium-223. In patients with a high baseline risk of fracture, carefully consider the benefit of treatment against the risks.

Because of the increased risk of fracture and possible increased mortality observed when combining radium-223 with abiraterone and prednisone/prednisolone, this triple combination remains contraindicated. In addition, radium-223 is not recommended to be initiated in the first 5 days following the last dose of abiraterone and prednisone/prednisolone. Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of Xofigo.

Further studies will be conducted to further characterise the efficacy and safety of radium-223, and in particular, the mechanisms responsible for the increased risk of fractures and possible increased mortality reported in the ERA-223 study.

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

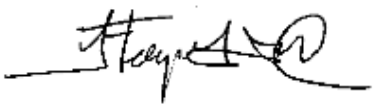
You can also report suspected adverse drug reactions to Bayer via email: pvuk@bayer.com

▼ 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