November 30, 2017

Xefigo® (radium Ra 223 dichloride): Important safety information update regarding increased incidence of deaths and fractures in an investigational Phase III clinical trial with Xefigo used in combination with abiraterone acetate and prednisolone/prednisone

Dear Healthcare Professional,

Bayer, in discussion with the Food and Drug Administration, would like to inform you of the following information concerning the Bayer-sponsored investigational study 15396 / ERA-223 (NCT 02043678)

Summary

An increased incidence of deaths and fractures has been identified in a randomized clinical trial in asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone predominant metastatic castration-resistant prostate cancer (CRPC) receiving radium Ra 223 dichloride in combination with abiraterone acetate and prednisolone/prednisone (15396/ERA-223 study).

- This study is being un-blinded early based on an Independent Data Monitoring Committee (IDMC) recommendation.
- The full analysis of the results is not yet completed. Until more information is available, do not treat patients with metastatic castration-resistant prostate cancer with radium Ra 223 dichloride in combination with abiraterone acetate and prednisolone/prednisone.
- Continued monitoring for fractures should be considered for patients who were previously treated with radium Ra 223 dichloride in combination with abiraterone acetate and prednisolone/prednisolone.
- Preliminary evidence from this clinical trial indicates that use of bone health agents such as bisphosphonates or denosumab may minimize the risk of fractures.
- Xefigo is approved for the treatment of men with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.
- Since its approval more than 18,000 patients¹ have been treated with Xefigo in the US and there are more than 4,700 patients² globally enrolled in ongoing clinical trials. The benefit-risk profile of Xefigo in its approved indication remains positive.

² Bayer Data on File. November 2017
Further information

- The ERA-223 study was a randomized, double-blind, placebo-controlled, multi-center phase III study to investigate the efficacy and safety of radium Ra 223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone predominant metastatic castration-resistant prostate cancer.
- Preliminary data from an independent ad-hoc analysis showed an increased incidence of fractures (24% vs 7%) and deaths (27% vs 20%) 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). This study is being un-blinded early based on an Independent Data Monitoring Committee recommendation; however, data collection and patient monitoring will continue per protocol.
- The measures outlined in this letter should be followed while the implications of these findings are being fully investigated. Further information will be communicated once the analysis has been finalized.

Reporting adverse drug reactions

Health care providers and patients are encouraged to report adverse events in patients taking Xofigo (radium Ra 223 dichloride) to Bayer at 1-888-842-2937. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

This letter is not intended as a complete description of the benefits and risks related to the use of Xofigo. Please refer to the Xofigo full Prescribing Information

If you have any questions, or if you require any further information, please contact Bayer medical information services at 1-888-842-2937.

With kind regards,

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