VIA EMAIL

December 20, 2017

Important Safety Information on XOFIGO® (radium RA 223 dichloride): Increased incidence of deaths and fractures in a randomized clinical trial with XOFIGO used in combination with abiraterone acetate and prednisone/prednisolone

Dear Health Professional,

Bayer Inc. has consulted with Health Canada and would like to provide important safety information on XOFIGO® (radium Ra 223 dichloride) regarding increased incidence of deaths and fractures in a randomized clinical trial with XOFIGO used in combination with abiraterone acetate and prednisone/prednisolone.

Bayer Inc.
Pharmaceuticals Division
2920 Matheson Blvd. East
Mississauga, ON L4W 5R6

Tel. 905 282-5550
Fax 905 282-5721
www.bayer.com

Summary

- **An increased incidence of deaths and fractures has been identified in a randomised clinical trial in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (CRPC) receiving radium-223 dichloride in combination with abiraterone and prednisone/prednisolone**
- **The ERA-223 study was designed to evaluate the efficacy and safety of radium-223 dichloride or placebo in combination with abiraterone acetate and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic chemotherapy-naïve bone predominant metastatic CRPC. This study was unblinded early based on an Independent Data Monitoring Committee (IDMC) recommendation.**
- **Radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone is not approved or reimbursed for the treatment of metastatic castration-resistant prostate cancer.**
- **The full analysis of the results is not yet complete. Until more information is available, do not treat patients with metastatic castration-resistant prostate cancer with radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone.**
- **Continued monitoring for fractures should be considered for patients who were previously treated with radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone.**
- **The benefit-risk profile of XOFIGO in its approved indication, for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease, remains unchanged.**

Further information

The ERA-223 study was a randomised, double-blind, placebo-controlled, multicenter Phase III study to investigate the efficacy and safety of radium-223 dichloride or placebo 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.

This study was unblinded early based on an IDMC recommendation; however, it will continue per protocol.

Preliminary data showed an increased incidence of fractures (24% vs 7%) and deaths (27% vs 20%) among patients receiving radium-223 dichloride 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). The full analysis of the results is not yet complete. The study is continuing per protocol.

XOFIGO in combination with abiraterone acetate and prednisone/prednisolone is not authorized or reimbursed for the treatment of metastatic castration-resistant prostate cancer.

The benefit-risk profile of XOFIGO in its approved indication, for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease, remains unchanged.

Further actions

The full analysis of the results of ERA-223 is not yet complete. Until more information is available, do not treat patients with metastatic castration-resistant prostate cancer with radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone.

Continued monitoring for fractures should be considered for patients who were previously treated with radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone.

The measures outlined above should be followed while there is further investigation of the implications of these findings. Further information will be communicated as appropriate at the end of the analysis.

The benefit-risk profile of XOFIGO in its approved indication, for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease, remains unchanged.

Reporting Adverse Events

Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any adverse reactions in patients receiving XOFIGO should be reported to Bayer Inc. or Health Canada.

Health care providers and patients are encouraged to report adverse events in patients taking XOFIGO to Bayer Inc. at 1-800-265-7382 or at canada.medinfo@bayer.com.

You can report any adverse reactions associated with the use of health products to Health Canada by calling toll-free at 1-866-234-2345 or visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax.

For additional information, please contact Bayer at 1-800-265-7382.

Sincerely,

BAYER INC.

Shurjeel Choudhri, MD, FRCPC
Senior Vice President & Head, Medical and Scientific Affairs