Important Safety Information on XOFIGO® (radium Ra 223 dichloride) – Increased Incidence of Fractures and Trend for Increased Deaths with XOFIGO used in combination with abiraterone and prednisone/prednisolone

2018-11-08

Audience
Healthcare professionals including genitourinary radiation oncologists, genitourinary medical oncologists, uro-oncologists, heads of genitourinary tumour boards and directors of nuclear medicine at institutions that are certified to receive and administer XOFIGO.

Key messages

- **An increased incidence of fractures and trend for increased deaths has been reported in a clinical trial among patients receiving XOFIGO in combination with abiraterone acetate and prednisone/prednisolone.**
- **Healthcare professionals are reminded that:**
  - **XOFIGO is authorized in Canada for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease.**
  - **XOFIGO is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone.**
- **The Canadian Product Monograph has been updated to include this new safety information.**

What is the issue?

An increased incidence of fractures and a trend for increased deaths was observed in a clinical trial assessing the concurrent initiation of XOFIGO 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.

Products affected
XOFIGO (radium Ra 223 dichloride solution for injection), 1100 kBq/mL (29.7 microcurie/mL)

Background information
XOFIGO is authorized in Canada for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease. This indication of XOFIGO remains unchanged.

This risk communication relates to an investigational study. An increased incidence of fractures and a trend for increased deaths was observed in a randomised, double-blind, placebo-controlled, and multicenter Phase III clinical study (ERA-223 study). This clinical study was conducted to investigate the efficacy and safety of XOFIGO or placebo, concurrently initiated 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. The study was unblinded early following an Independent Data Monitoring Committee (IDMC) review having observed increased fractures and death incidents. In December 2017, Bayer Inc. independently communicated this important safety information to Canadian healthcare professionals.

The primary analysis of the ERA-223 study results has now been completed. An increased incidence of fractures (28.6% vs 11.4%) and a trend for increased deaths (38.5% vs 35.5%) was observed among patients receiving XOFIGO in combination with abiraterone acetate plus prednisone/prednisolone, compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone.

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

Information for consumers
XOFIGO is used in men to treat advanced (castration-resistant) prostate cancer that has spread mainly to the bone and is causing symptoms such as pain.

An increased number of bone fractures and a trend for increased deaths has been seen in a clinical trial involving patients who started treatment with XOFIGO in combination with two other medications (abiraterone acetate and prednisone/prednisolone). Patients should not take XOFIGO in combination with these medications.

Patients and caregivers should discuss any questions or concerns about this information with their healthcare professional.

Patients receiving XOFIGO should also inform their healthcare professional if they experience any side effects.

Information for health care professionals
Healthcare professionals are reminded that:

- XOFIGO is authorized in Canada for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease. This indication of XOFIGO remains unchanged.

- XOFIGO is not recommended for use in combination with abiraterone acetate plus

prednisone/prednisolone.

- Safety and efficacy with the combination of XOFIGO and agents other than gonadotropin-releasing hormone analogues have not been established.

Action taken by Health Canada
Health Canada in collaboration with Bayer Inc. has updated the XOFIGO Canadian Product Monograph. Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site (www.healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php). This communication update will be further distributed through the MedEffect™ e-Notice email notification system.

Report health or safety concerns
Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of fracture or death or other serious or unexpected side effects in patients receiving XOFIGO should be reported to Bayer Inc. or Health Canada.

Bayer Inc.
2920 Matheson Boulevard East
Mississauga, ON
L4W 5R6
Telephone: 1-800-265-7382
Online: Reporting Side Effects (http://www.bayer.ca/en/about-bayer/contact-us/#PH)

To correct your mailing address or fax number, contact Bayer Inc.

You can report any suspected 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate (MHPD)
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Original signed by

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