



Overview of Radionuclide Properties

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INDICATION

Xofigo® is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

IMPORTANT SAFETY INFORMATION

Contraindications: Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman

Warnings and Precautions:

- **Bone Marrow Suppression:** In the phase 3 ALSYMPCA trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was similar for patients treated with Xofigo and placebo. Myelosuppression—notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia—has been reported in patients treated with Xofigo.

Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure

- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9/L$, the platelet count $\geq 100 \times 10^9/L$, and hemoglobin ≥ 10 g/dL. Prior to subsequent administrations, the ANC should be $\geq 1 \times 10^9/L$ and the platelet count $\geq 50 \times 10^9/L$. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care

- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued

- **Increased Fractures and Mortality in Combination With Abiraterone Plus Prednisone/Prednisolone:** Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials. At the primary analysis of the phase 3 ERA-223 study that evaluated concurrent initiation of Xofigo in combination with abiraterone acetate plus prednisone/prednisolone in 806 asymptomatic or mildly symptomatic mCRPC patients, an increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo 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

Administration and Radiation Protection: Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations

Fluid Status: Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting, which may result in dehydration. Monitor patients' oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia

Injection Site Reactions: Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo

Secondary Malignant Neoplasms: Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium -223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs 2%; respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of follow-up for patients on the trial

Subsequent Treatment With Cytotoxic Chemotherapy: In the randomized clinical trial, 16% of patients in the Xofigo group and 18% of patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy

Adverse Reactions: The most common adverse reactions ($\geq 10\%$) in the Xofigo arm vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%). Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in the Xofigo arm ($\geq 10\%$) vs the placebo arm, respectively, were anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%)

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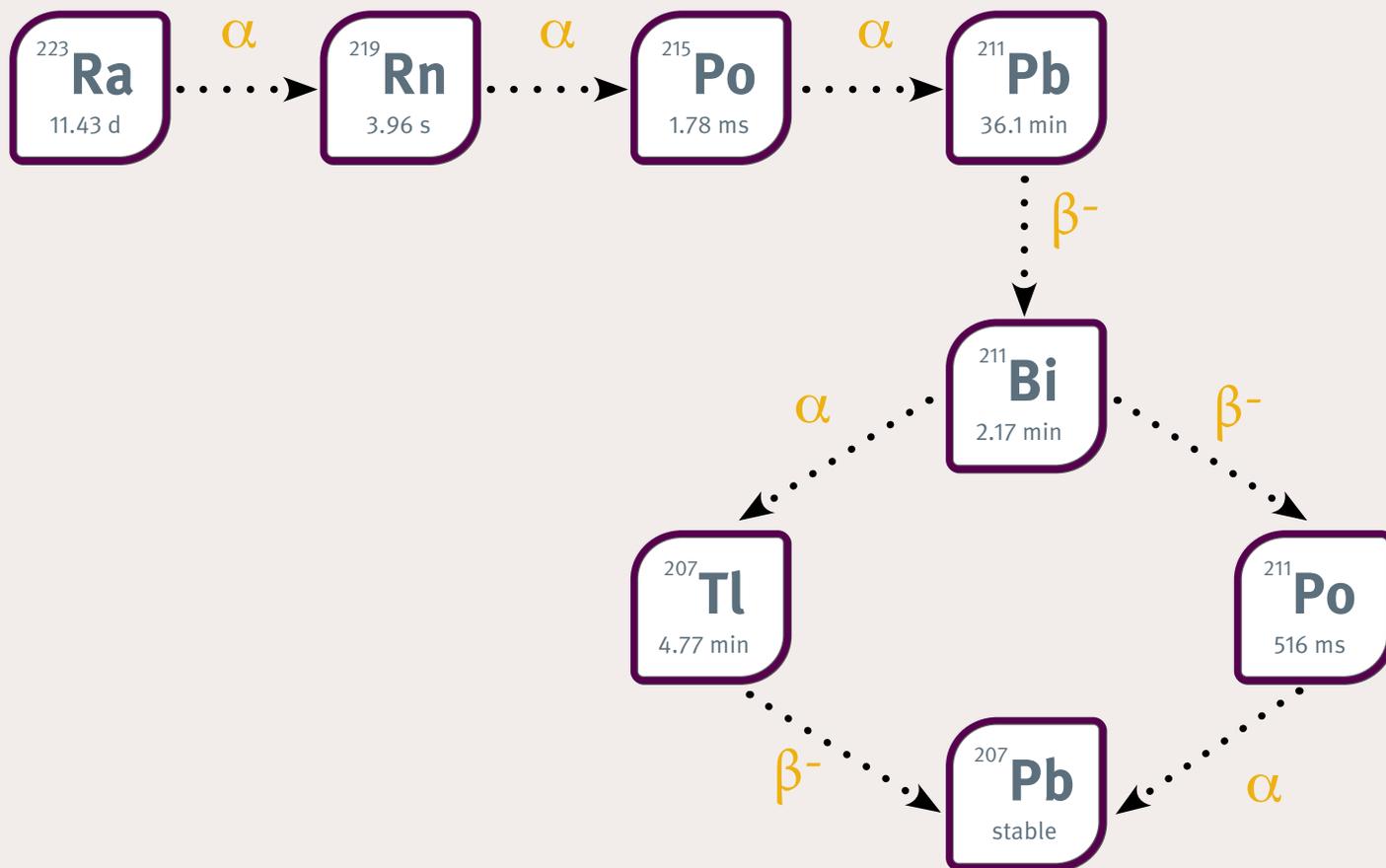
For further information, please visit www.xofigo-us.com



RADIOISOTOPE PROPERTIES

Xofigo, an alpha particle-emitting pharmaceutical, is a radiotherapeutic drug. The six-stage-decay of radium 223 (Ra 223) to stable lead-207 occurs via short-lived daughters and is accompanied predominantly by alpha emissions. There are also beta and gamma emissions with different energies and emission probabilities.

DECAY SCHEME¹



SUMMARY OF PROPERTIES OF XOFIGO¹⁻³

Half-life	11.4 days	Alpha particles	95.3%
Total decay energy	~28 MeV	Beta particles	3.6%
Particle range in tissue	<100 μm	Gamma or X-rays	1.1%

Ra 223 is a by-product material. Although it is primarily an alpha emitter, beta and gamma particles are also emitted during decay, allowing for measurement of radioactivity with standard instruments such as a dose calibrator and standard gamma detector probes. For more information, please see the Xofigo Dose Calibrator Dial Setting Procedure.

- Cheetham P, Petrylak D. Alpha Particles as radiopharmaceuticals in the treatment of bone metastases: mechanism of action of radium-223 chloride (Alpharadin) and radiation. *Oncology*. 2012;26(4):1-13.
- Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals Inc; May 2017.
- Data on file. Bayer HealthCare Pharmaceuticals, Whippany, NJ; 2016.





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