Xofigo®
radium Ra 223 dichloride
INJECTION

Administration Guide

Please see Important Safety Information on pages 5 and 6
and click here for full Prescribing Information.

DOSING:

The dose regimen of Xofigo® (radium Ra 223 dichloride) is 55 kBq (1.49 microcurie) per kg body weight, given at 4-week intervals for 6 injections. Safety and efficacy beyond 6 injections with Xofigo have not been studied.

The dose volume to be administered to a given patient should be calculated using the patient's body weight (kg), dosage level 55 kBq (1.49 microcurie)/kg body weight, the radioactive concentration of the product (30 microcurie/mL or 1,100 kBq/mL) at reference date, and the decay correction factor to correct for physical decay of radium 223 (Ra 223). The total volume to be administered to a patient is calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight (kg)} \times (55\ \text{kBq})/\text{kg body weight}}{\text{Decay factor} \times 1{,}100\ \text{kBq/mL}}$$

or:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight (kg)} \times (1.49\ \mu\text{Ci})/\text{kg body weight}}{\text{Decay factor} \times 30\ \mu\text{Ci/mL}}$$

Sites will receive a patient-ready unit dose from the Cardinal Health central radiopharmacy who will verify the above calculation based upon the patient's weight provided.

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

Based on the 2015 standard set by National Institute of Standards and Technology (NIST), the numerical description of the patient dose has been adjusted from 50 kBq/kg to 55 kBq/kg, and the numerical description of the radioactivity in the vial has been changed from 1,000 kBq/mL to 1,100 kBq/mL.[1]

1. US Nuclear Regulatory Commission. Revision to the National Institute of Standards and Technology Standard for Radium-223 and Impact on Dose Calibration for the Medical Use of Radium-223 Dichloride. Washington, DC: US Nuclear Regulatory Commission, Office of Nuclear Materials Safety and Safeguards; 2016.

Please see Important Safety Information on pages 5 and 6 and click here for full Prescribing Information.

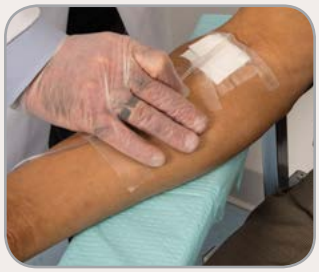
Xofigo® radium Ra 223 dichloride INJECTION

Immediately before and after administration, the net patient dose of administered Xofigo® (radium Ra 223 dichloride) should be determined by measurement in an appropriate radioisotope dose calibrator that has been calibrated with a National Institutes of Standards and Technology (NIST) traceable radium-223 standard (available upon request from Bayer) and corrected for decay using the date and time of calibration. The dose calibrator must be calibrated with nationally recognized standards, carried out at the time of commissioning, after any maintenance procedure that could affect the dosimetry and at intervals not to exceed one year.

STEPS FOR ADMINISTRATION:

Step 1:
Assay the dose immediately before and after administration (see dose calibration procedure flashcard for further instructions on how to determine a dial setting for Ra 223).

Step 2:
Prepare the infusion environment by placing absorbent materials in the immediate area where the injection will take place.



Step 3:
Insert the intravenous cannula or instrument as required per your institution for injection. Connect a 2- or 3-way stopcock to the IV device.

Step 4:
Open the stopcock to allow for flushing of the infusion set-up prior to injection of Xofigo, in order to minimize the risk of extravasal administration. Flush the infusion set to confirm IV patency.

Please see Important Safety Information on pages 5 and 6 and click here for full Prescribing Information.

Xofigo® radium Ra 223 dichloride INJECTION

Step 5:
If IV patency is confirmed, remove the red cap from the syringe containing Xofigo and attach to the open port of the stopcock. Turn the stopcock so that it is closed to the saline syringe and open from the Xofigo syringe to the patient.

Step 6:
Administer Xofigo by slow intravenous injection over 1 minute. When the infusion is complete, turn the stopcock to shut off the Xofigo syringe and open the saline syringe. Flush the infusion system thoroughly with isotonic saline per institutional procedure.

Step 7:
Remove the syringes and injection set-up. Assay for residual activity and dispose of according to institutional policies (please see the Storage and Handling Guide for additional information).

OPTIONAL:

A syringe shield may be utilized according to institutional policy.

Please see Important Safety Information on pages 5 and 6 and click here for full Prescribing Information.

Xofigo® radium Ra 223 dichloride INJECTION

XOFIGO® IS INDICATED for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.

IMPORTANT SAFETY INFORMATION

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 ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 × 10^9/L and the platelet count ≥50 × 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
- **Embryo-Fetal Toxicity:** The safety and efficacy of Xofigo have not been established in females. Xofigo can cause fetal harm when administered to a pregnant female. Advise pregnant females and females of reproductive potential of the potential risk to a fetus. Advise male patients to use condoms and their female partners of reproductive potential to use effective contraception during and for 6 months after completing treatment with Xofigo

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

Please see additional Important Safety Information on page 6 and click here for full Prescribing Information.

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Xofigo® radium Ra 223 dichloride INJECTION

IMPORTANT SAFETY INFORMATION (continued)

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 (≥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 (≥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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Xofigo® radium Ra 223 dichloride INJECTION