Xofigo®
radium Ra 223 dichloride
INJECTION

Dose Calibrator Dial Setting Procedure for Xofigo

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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

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

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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Radium Ra 223 dichloride (Ra 223) is primarily an alpha emitter; however, beta particles and photons (gamma and x-rays) are also emitted during decay. The gamma radiation associated with the decay of Ra 223 and its daughters allows for the radioactivity measurement of Xofigo with standard instruments.

The methodology used for measurement of Xofigo dosages to patients as given in this procedure may be used as a standard operating procedure (SOP) for determining the appropriate dial setting for use with Ra 223. An example form is provided with this procedure for recordkeeping.

PROCEDURE FOR RA 223 DOSE CALIBRATOR DIAL SETTING:

STEP 1 A reference standard containing a secondary NIST traceable amount of Ra 223 dichloride solution will be provided in a syringe or vial to the facility from Cardinal Health central radiopharmacy. The reference standard will include paperwork containing the source activity and a decay correction factor table.

STEP 2 Conduct standard quality control and background correction of the dose calibrator according to the manufacturer's instructions and facility SOPs.

STEP 3 Using the paperwork that accompanies the Ra 223 reference standard, enter the following into the form provided:
- Activity at reference date (to 1 decimal place)
- Reference date and time
- Date and time of calibration for this dose calibrator

STEP 4 Using the decay factor correction table included with the Ra 223 reference standard, determine the decay correction factor based on the number of days between the reference date and date/time that this dial setting is being established and record it on the form.

STEP 5 Calculate the decay-corrected activity by multiplying the reference activity by the decay factor and record on the form.

STEP 6 Record the manufacturer, model, and serial number of the dose calibrator on the form.

STEP 7 Record the ID number of the Ra 223 reference standard.

STEP 8 Place the Ra 223 reference standard in the dose calibrator, making sure the sample is centered in the measuring chamber. Adjust the dose calibrator dial setting according to the instrument's operating manual until the dose calibrator reading matches the calculated decay-corrected activity of the reference sample, as determined in Step 5, and record this activity and dial setting on the form. Once the dial setting is determined, it should be used for all subsequent radioactivity measurements of Ra 223.

STEP 9 A total of 3 measurements of the Ra 223 reference standard utilizing the dose calibrator dial setting for Ra 223 should be performed. Record the results on the form. Make sure to allow the dose calibrator time to return to background level between the measurements. All repeat measurements should be essentially the same as determined in Step 8, but must each be within ±5% of the decay-corrected reference standard activity; if not, repeat the measurement.

STEP 10 Record the facility name, name of individual performing calibration, email address, signature, and date completed.

Note: The licensee will not need to perform any geometrical testing.[1]

Dose calibrator requirements may vary by Agreement State regulation.

1. J.T. Cessna and B. E. Zimmerman. Development of secondary standards for ^{223}Ra. *Appl Radiat Isot.* 2010;(68);1367-1370.

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FORM FOR ESTABLISHING A RA 223 DOSE CALIBRATOR DIAL SETTING

Section 1: Decay correction of Ra 223 sample and dose calibrator dial setting				
Activity at reference date [µCi]	Reference date/ time; mm/dd/yy; hh:mm	Date/time of dial setting determination of dose calibrator mm/dd/yy; hh:mm	Decay factor (from decay correction table)	Decay-corrected activity of Ra 223 reference sample [µCi]
(Step 3)	(Step 3)	(Step 3)	(Step 4)	(Step 5)

Dose calibrator: manufacturer, model, serial number			Reference sample ID number	Dial setting (calibration number) for Ra 223
(Step 6)	(Step 6)	(Step 6)	(Step 7)	(Step 8)

Section 2: Measurements (Note: first and second repeat measurements should be essentially the same [ie, within 5% of the decay-corrected reference standard activity as obtained in Step 8])		
Activity measurement at calibrated dial setting [µCi]	First repeat activity measurement [µCi]	Second repeat activity measurement [µCi]
(Step 8)	(Step 9)	(Step 9)

Facility name
(Step 10)

Performed by (print name)	Email address
(Step 10)	(Step 10)

Signature and date	
(Step 10)	(Step 10)

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