Xofigo®
radium Ra 223 dichloride
INJECTION

Storage and Handling Guide

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.

Please see additional Important Safety Information on page 2 and click here for full Prescribing Information.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued):

- **Bone Marrow Suppression (continued):** 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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For further information, please visit www.hcp.xofigo-us.com.

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RADIATION SAFETY PRACTICES

Xofigo should be received, used, and administered only by persons authorized to handle radiopharmaceuticals in designated clinical settings. The receipt, storage, use, transfer, and disposal of the drug are subject to regulation by the Nuclear Regulatory Commission or applicable Agreement State authorities, as well as specific facility license requirements. Xofigo should be handled by the user in a manner that satisfies both radiation safety and pharmaceutical quality requirements. In accordance with facility policies, appropriate aseptic precautions should be taken.

HOW DISTRIBUTED

Treatment sites will receive a unit dosage in a syringe prepared by Cardinal Health central radiopharmacy.

Xofigo is a ready-to-use solution and should not be diluted or mixed with any solutions. The drug is supplied in a Type A-certified package containing:

- Shielding container
- Decay correction table according to physical decay of Ra 223

STABILITY AND STORAGE

When a unit dose syringe is provided by Cardinal Health central radiopharmacy, the shelf life of the Xofigo dose in the syringe is 96 hours from time of draw at room temperature.[1]

Store Xofigo at room temperature, below 40°C (104°F) in the original container or equivalent radiation shielding.[2]

MEASUREMENT OF RADIOACTIVITY USING STANDARD INSTRUMENTS

The gamma radiation associated with the decay of Ra 223 and its daughters allows for the radioactivity measurement of Xofigo and the detection of contamination with standard instruments, such as a dose calibrator and standard gamma detectors.

RADIATION PROTECTION

The administration of Xofigo is associated with potential risks to other persons (eg, medical staff, caregivers, and patient's family members) 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.

Follow the normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids to avoid contamination. In case of contact with skin or eyes, the affected area should be flushed immediately with water.

The external radiation exposure associated with the handling of patient doses is expected to be low, because the typical treatment activity will be below 8,000 kBq (216 µCi). The administered activity of Xofigo will be 104 µCi (3.8 MBq) for an average patient who weighs 70 kg.[1]

In keeping with the As Low As Reasonably Achievable (ALARA) principle, for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding.

EXPOSURE FROM A TREATED PATIENT TO OTHERS

In accordance with 10 CFR 35.75, treatment with Xofigo can be done on an outpatient basis. For example, the average patient (70 kg) receiving 104 µCi (3.8 MBq) would have a dose rate at 1 m <0.016 mrem/hr.[1]

There are no restrictions regarding contact with other people after receiving Xofigo. Patients should be advised to follow good hygiene practices while receiving Xofigo and for at least 4 weeks after the last injection in order to minimize radiation exposure from bodily fluids to household members and caregivers.

Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with Xofigo or patient fecal matter or urine should be washed promptly and separately from other clothing.

DISPOSAL

In accordance with 10 CFR 35.92, any unused product or materials used in connection with the preparation or administration of Xofigo are to be treated as radioactive waste and should be disposed of in accordance with local and/or federal regulations. All Ra 223 waste should be stored in a secure area. Decay to background according to site-specific radiation safety policies and procedures.

1. Data on file. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2016.
2. Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; December, 2019.

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