HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XOFIGO safely and effectively. See full prescribing information for XOFIGO.

Xofigo (radium Ra 223 dichloride) Injection, for intravenous use

Initial U.S. Approval: 2013

---------- INDICATIONS AND USAGE ----------

Xofigo is an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. (1)

---------- DOSAGE AND ADMINISTRATION ----------

The dose regimen of Xofigo is 50 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------

Single-use vial at a concentration of 1,000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date (3)

---------- CONTRAINDICATIONS ----------

Pregnancy (4, 8.1)

---------- WARNINGS AND PRECAUTIONS ----------

Bone Marrow Suppression: Measure blood counts prior to treatment initiation and before every dose of Xofigo. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after treatment. Monitor patients with compromised bone marrow reserve closely. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care measures. (5.1)

---------- ADVERSE REACTIONS ----------

The most common adverse drug reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema.

The most common hematologic laboratory abnormalities (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

SEE 17 FOR PATIENT COUNSELING INFORMATION
Revised: 05/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The dose regimen of Xofigo is 50 kBq (1.35 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 volume to be administered to a given patient should be calculated using the:

- Patient's body weight (kg)
- Dosage level 50 kBq/kg body weight or 1.35 microcurie/kg body weight
- Radioactivity concentration of the product (1,000 kBq/mL; 27 microcurie/mL) at the reference date
- Decay correction factor to correct for physical decay of radium-223.

The total volume to be administered to a patient is calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 50 \text{ kBq/kg body weight}}{\text{Decay factor} \times 1{,}000 \text{ kBq/mL}}$$

or

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 1.35 \text{ microcurie/kg body weight}}{\text{Decay factor} \times 27 \text{ microcurie/mL}}$$

Table 1: Decay Correction Factor Table

Days from Reference Date	Decay Factor	Days from Reference Date	Decay Factor
-14	2.296	0	0.982
-13	2.161	1	0.925
-12	2.034	2	0.870
-11	1.914	3	0.819
-10	1.802	4	0.771
-9	1.696	5	0.725
-8	1.596	6	0.683
-7	1.502	7	0.643
-6	1.414	8	0.605
-5	1.330	9	0.569
-4	1.252	10	0.536
-3	1.178	11	0.504
-2	1.109	12	0.475
-1	1.044	13	0.447
		14	0.420

The Decay Correction Factor Table is corrected to 12 noon Central Standard Time (CST). To determine the decay correction factor, count the number of days before or after the reference date. The Decay Correction Factor Table includes a correction to account for the 7 hour time difference between 12 noon Central European Time (CET) at the site of manufacture and 12 noon US CST, which is 7 hours earlier than CET.

Immediately before and after administration, the net patient dose of administered Xofigo should be determined by measurement in an appropriate radioisotope dose calibrator that has been calibrated with a National Institute 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.

2.2 Administration

Administer Xofigo by slow intravenous injection over 1 minute.

Flush the intravenous access line or cannula with isotonic saline before and after injection of Xofigo.

2.3 Instructions for Use/Handling

General warning

Xofigo (an alpha particle-emitting pharmaceutical) should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal Xofigo are subject to the regulations and/or appropriate licenses of the competent official organization.

Xofigo should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Radiation protection

The administration of Xofigo is associated with potential risks to other persons (e.g., medical staff, caregivers and patient's household 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.

For drug handling

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. In the event of spillage of Xofigo, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diamine-tetraacetic acid (EDTA) solution is recommended to remove contamination.

For patient care

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.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is expected to be low, because the typical treatment activity will be below 8,000 kBq (216 microcurie). In keeping with the **A**s **L**ow **A**s **R**easonably **A**chievable (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. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of Xofigo and the detection of contamination with standard instruments.

Instructions for preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Xofigo is a ready-to-use solution and should not be diluted or mixed with any solutions. Each vial is for single use only.

Dosimetry

The absorbed radiation doses in major organs were calculated based on clinical biodistribution data in five patients with castration-resistant prostate cancer. Calculations of absorbed radiation doses were performed using OLINDA/EXM (**O**rgan **L**evel **IN**ternal **D**ose **A**ssessment/**EX**ponential **M**odeling), a software program based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For radium-223, which is primarily an alpha particle-emitter, assumptions were made for intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed radiation dose calculations for Xofigo, considering its observed biodistribution and specific characteristics.

The calculated absorbed radiation doses to different organs are listed in Table 2. The organs with highest absorbed radiation doses were bone (osteogenic cells), red marrow, upper large intestine wall, and lower large intestine wall. The calculated absorbed doses to other organs are lower.

Table 2: Calculated Absorbed Radiation Doses to Organs

Target Organ	Mean (Gy/MBq)	Mean (rad/mCi)	Coefficient of Variation (%)
Adrenals	0.00012	0.44	56
Brain	0.00010	0.37	80
Breasts	0.00005	0.18	120
Gallbladder wall	0.00023	0.85	14
LLI[1] Wall	0.04645	171.88	83
Small intestine wall	0.00726	26.87	45
Stomach wall	0.00014	0.51	22
ULI[2] wall	0.03232	119.58	50
Heart wall	0.00173	6.40	42
Kidneys	0.00320	11.86	36
Liver	0.00298	11.01	36
Lungs	0.00007	0.27	90
Muscle	0.00012	0.44	41
Ovaries	0.00049	1.80	40
Pancreas	0.00011	0.41	43
Red marrow	0.13879	513.51	41
Osteogenic cells	1.15206	4262.60	41
Skin	0.00007	0.27	79
Spleen	0.00009	0.33	54
Testes	0.00008	0.31	59
Thymus	0.00006	0.21	109
Thyroid	0.00007	0.26	96
Urinary bladder wall	0.00403	14.90	63
Uterus	0.00026	0.94	28
Whole body	0.02311	85.50	16

[1]LLI: lower large intestine

[2]ULI: upper large intestine

3 DOSAGE FORMS AND STRENGTHS

Xofigo (radium Ra 223 dichloride injection) is available in single-use vials containing 6 mL of solution at a concentration of 1,000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date.

4 CONTRAINDICATIONS

Xofigo is contraindicated in pregnancy.

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Xofigo is not indicated for use in women. Xofigo is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

In the randomized trial, 2% of patients on 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 and 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 on the Xofigo arm and 2% on 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%) were similar for patients treated with Xofigo and placebo. Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Xofigo. In the randomized trial, complete blood counts (CBCs) were obtained every 4 weeks prior to each dose and the nadir CBCs and times of recovery were not well characterized. In a separate single-dose phase 1 study of Xofigo, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Xofigo administration at doses that were up to 1 to 5 times the recommended dose, and most patients recovered approximately 6 to 8 weeks after administration *[see Adverse Reactions (6)]*.

Hematologic evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration of 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. Before subsequent administrations of Xofigo, the ANC should be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of Xofigo, despite receiving supportive care, further treatment with Xofigo should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

The safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use with 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer with bone metastases, 600 patients received intravenous injections of 50 kBq/kg (1.35 microcurie/kg) of Xofigo and best standard of care and 301 patients received placebo and best standard of care once every 4 weeks for up to 6 injections. Prior to randomization, 58% and 57% of patients had received docetaxel in the Xofigo and placebo arms, respectively. The median duration of treatment was 20 weeks (6 cycles) for Xofigo and 18 weeks (5 cycles) for placebo.

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