Bayer HealthCare

News Release

Intended for U.S. Media Only

Bayer Receives U.S. FDA Approval for Xofigo® (radium Ra 223 dichloride) Injection as a New Treatment for Castration-Resistant Prostate Cancer with Bone Metastases

Wayne, NJ, May 15, 2013 – Bayer HealthCare announced today that the U.S. Food and Drug Administration (FDA) approved Xofigo® (radium Ra 223 dichloride) for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease. Xofigo is the first and only alpha particle-emitting radioactive therapeutic agent approved by the FDA that has demonstrated improvement in overall survival (OS) and delay in time to first symptomatic skeletal event (SSE) compared to placebo, as shown in the pivotal Phase III ALSYMPCA trial.[1]

The commercial production of Xofigo is underway, and first doses are expected to be ready for patient treatment within a few weeks. Bayer has worldwide exclusive marketing rights for Xofigo. Algeta US, LLC and Bayer Healthcare will co-promote the product in the U.S.

“Most men with castration-resistant prostate cancer develop bone metastases, which can decrease overall survival,” said Oliver Sartor, MD, North American Principal Investigator for the pivotal trial and medical director of the Tulane Cancer Center. “Xofigo has demonstrated an anti-tumor effect on bone metastases and will be an important addition to the treatment of this cancer.”

Bone is the most common site in the body to be affected by metastatic cancer, and bone metastases are particularly prevalent in patients with prostate cancer.[3] Approximately 90% of patients with metastatic prostate cancer show evidence of bone metastases.[4, 5, 6, 7] Bone metastases can lead to an increase in frequency of skeletal events and are shown to be the main cause of morbidity and death in patients with CRPC.[2, 8]

“At Bayer, we remain committed to our mission of delivering innovative ways to help patients and physicians, and to bring new treatment options in cancer,” said Pamela A. Cyrus, MD, Vice

President and Head of U.S. Medical Affairs, Bayer HealthCare Pharmaceuticals. “We are pleased to add Xofigo to our oncology franchise for the treatment of castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases.”

Jan Manarite, senior educational facilitator for the Prostate Cancer Research Institute also added, “It is encouraging to have a new treatment for men with castration-resistant prostate cancer who are dealing with bone metastases. Xofigo provides another new option to treat this cancer using a different approach.”

Efficacy and Safety Data Supporting Xofigo® (radium Ra 223 dichloride) Approval

The approval of Xofigo is based on data from the pivotal Phase III ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial. At the interim analysis, Xofigo significantly improved overall survival (OS) [HR=0.695 (95% CI 0.552-0.875), p=0.00185]; median OS was 14.0 months with Xofigo plus best standard of care vs. 11.2 months with placebo plus best standard of care.[1] Additionally, at the interim analysis there was a delay in time to first symptomatic skeletal event (SSE) for patients treated with Xofigo vs. placebo.

An updated analysis, conducted after the study was unblinded, showed improvement in overall survival (OS), with a median OS of 14.9 months vs. 11.3 months; HR=0.695 (95% CI 0.581-0.832).[1]

The most common adverse reactions (greater than or equal to 10%) in patients receiving Xofigo in the ALSYMPCA trial were nausea, diarrhea, vomiting and peripheral edema. The most common hematologic laboratory abnormalities (greater than or equal to 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia and neutropenia.[1]

About Xofigo® (radium Ra 223 dichloride) Injection

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

Xofigo is an alpha particle-emitting radioactive therapeutic agent with an anti-tumor effect on bone metastases. The active ingredient in Xofigo is the alpha particle-emitting isotope radium-223, which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. The high linear energy transfer of Xofigo may

cause double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium-223 dichloride is less than 100 micrometers which may limit the damage to the surrounding normal tissue.[1]

In September 2009, Bayer signed an agreement with Algeta ASA (Oslo, Norway) for the development and commercialization of Xofigo. Under the terms of the agreement, Bayer will develop, apply for health authority approvals worldwide and commercialize Xofigo globally.

Important Safety Information for Xofigo® (radium Ra 223 dichloride) Injection
Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman.

In the randomized 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 (less than 1%) was similar for patients treated with Xofigo and placebo. Myelosuppression – notably thrombocytopenia, neutropenia, pancytopenia, and leucopenia – 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.

Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be greater than or equal to 1.5×10^9/L, the platelet count greater than or equal to 100×10^9/L, and hemoglobin greater than or equal to 10 g/dL. Prior to subsequent administrations, the ANC should be greater than or equal to 1×10^9/L and the platelet count greater than or equal to 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.

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.

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.

The most common adverse reactions (greater than or equal to 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema. 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 Xofigo-treated patients (greater than or equal to 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia.

For full prescribing information visit www.xofigo-us.com.

About the ALSYMPCA Trial

The ALSYMPCA trial was a Phase III, randomized, double-blind, placebo-controlled international study of Xofigo with best standard of care vs. placebo with best standard of care in symptomatic CRPC patients with bone metastases. The trial enrolled 921 patients in more than 100 centers in 19 countries. The study treatment consisted of up to six intravenous injections of Xofigo or placebo each separated by an interval of four weeks.

The primary endpoint of the study was overall survival (OS). A key secondary endpoint was time to first symptomatic skeletal event (SSE), as defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.

About CRPC and Bone Metastases

Prostate cancer is the most common cancer among men in the United States (other than skin cancer).[9] Approximately 4% of prostate cancer cases are considered distant, which means that the cancer has spread beyond the prostate to distant areas of the body (metastasized).[10] If prostate cancer starts to spread to other areas of the body, it most commonly goes to the bone.[8]

About the Patient Assistance Program

Bayer and Algeta offer patient assistance through Xofigo Access Services℠ which will assist with obtaining coverage and patient support of Xofigo. Patients and providers may contact the program at 1-855-6XOFIGO (1-855-696-3446) for additional information.

About Oncology at Bayer

Bayer is committed to delivering *science for a better life* by advancing a portfolio of innovative treatments. The oncology franchise at Bayer now includes three oncology products and several other compounds in various stages of clinical development. Together, these products reflect the company's approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated.

About Bayer HealthCare Pharmaceuticals Inc.

Bayer HealthCare Pharmaceuticals Inc. is the U.S.-based pharmaceuticals business of Bayer HealthCare LLC, a subsidiary of Bayer AG. Bayer HealthCare is one of the world's leading, innovative companies in the healthcare and medical products industry, and combines the activities of the Animal Health, Consumer Care, Medical Care, and Pharmaceuticals divisions. As a specialty pharmaceutical company, Bayer HealthCare provides products for General Medicine, Hematology, Neurology, Oncology and Women's Healthcare. The company's aim is to discover and manufacture products that will improve human health worldwide by diagnosing, preventing and treating diseases.

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Forward-Looking Statement
This news release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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[2] Saad, MD, et. al. "Guidelines for the management of castration-resistant prostate cancer." Can Urol Assoc J 2010;4(6):380-4.
[3] Coleman R. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001;27:165-176.
[4] Tannock IF, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502-1512.
[5] Petrylak DP, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351:1513-1520.
[6] Scher, HI, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med. 2012;DOI10.1056
[7]Fizazi, K, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012; 13:983-92.
[8]Lange PH, Vasella RL. "Mechanisms, hypotheses and questions regarding prostate cancer metastatic to bone." Cancer & Metastasis Reviews.1999;17:331-336
[9]American Cancer Society. Prostate Cancer: Detailed Guide. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003134-pdf.pdf.
[10] National Cancer Institute, Surveillance Epidemiology and End Results (SEER). SEER Stat Facts: Prostate; Survival & Stage, 2002-2008.

600-28-0007-13a

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

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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.

The most common adverse reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema (Table 3). Grade 3 and 4 adverse events were reported among 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 4).

Treatment discontinuations due to adverse events occurred in 17% of patients who received Xofigo and 21% of patients who received placebo. The most common hematologic laboratory abnormalities leading to discontinuation for Xofigo were anemia (2%) and thrombocytopenia (2%).

Table 3 shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 3: Adverse Reactions in the Randomized Trial

System/Organ Class Preferred Term	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and lymphatic system disorders				
Pancytopenia	2	1	0	0
Gastrointestinal disorders				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
General disorders and administration site conditions				
Peripheral edema	13	2	10	1
Renal and urinary disorders				
Renal failure and impairment	3	1	1	1

Laboratory Abnormalities

Table 4 shows hematologic laboratory abnormalities occurring in ≥ 10% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 4: Hematologic Laboratory Abnormalities

Hematologic Laboratory Abnormalities	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Anemia	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia	18	2	5	<1

Laboratory values were obtained at baseline and prior to each 4-week cycle.

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Xofigo and in 2% of patients on placebo. Among patients who received Xofigo, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

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 *[see Nonclinical Toxicology (13.1)]*. 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% patients in the Xofigo group and 18% 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.

7 DRUG INTERACTIONS

No formal clinical drug interaction studies have been performed.

Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Xofigo in the randomized clinical trial.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category X *[see Contraindications (4)]*

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of Xofigo in pregnancy and Xofigo is not indicated for use in women, maternal use of a radioactive therapeutic agent could affect development of a fetus. Xofigo is contraindicated in women who are or may become pregnant while receiving the drug. 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 and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with Xofigo.

8.3 Nursing Mothers

Xofigo is not indicated for use in women. It is not known whether radium-223 dichloride is excreted in human milk. Because many drugs are excreted in human milk, and because of potential for serious adverse reactions in nursing infants from Xofigo, a decision should be made whether to discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Xofigo in pediatric patients have not been established.

In single- and repeat-dose toxicity studies in rats, findings in the bones (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line) and teeth (missing, irregular growth, fibro-osseous lesions in bone socket) correlated with a reduction of osteogenesis that occurred at clinically relevant doses beginning in the range of 20 – 80 kBq (0.541 - 2.16 microcurie) per kg body weight.

8.5 Geriatric Use

Of the 600 patients treated with Xofigo in the randomized trial, 75% were 65 years of age and over and while 33% were 75 years of age and over. No dosage adjustment is considered necessary in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

No dedicated hepatic impairment trial for Xofigo has been conducted. Since radium-223 is neither metabolized by the liver nor eliminated via the bile, hepatic impairment is unlikely to affect the pharmacokinetics of radium-223 dichloride *[see Clinical Pharmacology (12.3)]*. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with mild hepatic impairment. No dose adjustments can be recommended for patients with moderate or severe hepatic impairment due to lack of clinical data.

8.7 Patients with Renal Impairment

No dedicated renal impairment trial for Xofigo has been conducted. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with existing mild (creatinine clearance [CrCl] 60 to 89 mL/min) or moderate (CrCl 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CrCl less than 30 mL/min) due to limited data available (n = 2) *[see Clinical Pharmacology (12.3)]*.

8.8 Males of Reproductive Potential

Contraception

Because of potential effects on spermatogenesis associated with radiation, advise men who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective contraceptive method during and for 6 months after completing treatment with Xofigo.

Infertility

There are no data on the effects of Xofigo on human fertility. There is a potential risk that radiation by Xofigo could impair human fertility *[see Nonclinical Toxicology (13.1)]*.

10 OVERDOSAGE

There have been no reports of inadvertent overdosing of Xofigo during clinical studies.

There is no specific antidote. In the event of an inadvertent overdose of Xofigo, utilize general supportive measures, including monitoring for potential hematological and gastrointestinal toxicity, and consider using medical countermeasures such as aluminum hydroxide, barium sulfate, calcium carbonate, calcium gluconate, calcium phosphate, or sodium alginate.[1]

Single Xofigo doses up to 250 kBq (6.76 microcurie) per kg body weight were evaluated in a phase 1 clinical trial and no dose-limiting toxicities were observed.

11 DESCRIPTION

Radium Ra 223 dichloride, an alpha particle-emitting pharmaceutical, is a radiotherapeutic drug.

Xofigo is supplied as a clear, colorless, isotonic, and sterile solution to be administered intravenously with pH between 6 and 8.

Each milliliter of solution contains 1,000 kBq radium-223 dichloride (27 microcurie), corresponding to 0.53 ng radium-223, at the reference date. Radium is present in the solution as a free divalent cation.

Each vial contains 6 mL of solution (6,000 kBq (162 microcurie) radium-223 dichloride at the reference date). The inactive ingredients are 6.3 mg/mL sodium chloride USP (tonicity agent), 7.2 mg/mL sodium citrate USP (for pH adjustment), 0.2 mg/mL hydrochloric acid USP (for pH adjustment), and water for injection USP.

The molecular weight of radium-223 dichloride, $^{223}RaCl_2$, is 293.9 g/mol.

Radium-223 has a half-life of 11.4 days. The specific activity of radium-223 is 1.9 MBq (51.4 microcurie)/ng.

The six-stage-decay of radium-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. The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5 - 7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active moiety of Xofigo is the alpha particle-emitting isotope radium-223 (as radium Ra 223 dichloride), which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases (see Table 2). The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

12.2 Pharmacodynamics

Compared with placebo, there was a significant difference in favor of Xofigo for all five serum biomarkers for bone turnover studied in a phase 2 randomized study (bone formation markers: bone alkaline phosphatase [ALP], total ALP and procollagen I N propeptide [PINP], bone resorption markers: C-terminal crosslinking telopeptide of type I collagen [S-CTX-I] and type I collagen crosslinked C-telopeptide [ICTP]).

12.3 Pharmacokinetics

The pharmacokinetics of radium-223 dichloride in blood was linear in terms of dose proportionality and time independence in the dose range investigated (46 to 250 kBq [1.24 to 6.76 microcurie] per kg body weight).

Distribution

After intravenous injection, radium-223 is rapidly cleared from the blood and is distributed primarily into bone or is excreted into intestine. Fifteen minutes post-injection, about 20% of the injected radioactivity remained in blood. At 4 hours, about 4% of the injected radioactivity remained in blood, decreasing to less than 1% at 24 hours after the injection. At 10 minutes post-injection, radioactivity was observed in bone and in intestine. At 4 hours post-injection, the percentage of the radioactive dose present in bone and intestine was approximately 61% and 49%, respectively. No significant uptake

was seen in other organs such as heart, liver, kidneys, urinary bladder, and spleen at 4 hours post-injection *[see Dosage and Administration (2.3)]*.

Metabolism

Radium-223 is an isotope that decays and is not metabolized.

Elimination

The whole body measurements indicated that approximately 63% of the administered radioactivity was excreted from the body within 7 days after injection (after correcting for decay). Fecal excretion is the major route of elimination from the body. At 48 hours after injection, the cumulative fecal excretion was 13% (range 0 - 34%), and the cumulative urine excretion was 2% (range 1 - 5%). There was no evidence of hepato-biliary excretion based on imaging data.

The rate of elimination of radium-223 dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population. Patients with a slower intestinal transit rate could potentially receive a higher intestinal radiation exposure. It is not known whether this will result in increased gastrointestinal toxicity.

Special Populations

Pediatric patients

Safety and effectiveness of Xofigo have not been established in children and adolescents below 18 years of age.

Patients with hepatic impairment

No dedicated pharmacokinetic study in patients with hepatic impairment has been conducted. However, since radium-223 is not metabolized and there is no evidence of hepato-biliary excretion based on imaging data, hepatic impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

Patients with renal impairment

No dedicated pharmacokinetic study in patients with renal impairment has been conducted. However, since excretion in urine is minimal and the major route of elimination is via the feces, renal impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

12.6 Cardiac Electrophysiology

The effect of a single dose of 50 kBq/kg of radium-223 dichloride on the QTc interval was evaluated in a subgroup of 29 patients (21 received Xofigo and 8 received placebo) in the randomized clinical trial. No large changes in the mean QTc interval (i.e., greater than 20 ms) were detected up to 6 hours post-dose. The potential for delayed effects on the QT interval after 6 hours was not evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic potential of radium-223 dichloride. However, in repeat-dose toxicity studies in rats, osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses 7 to 12 months after the start of treatment. The presence of other neoplastic changes, including lymphoma and mammary gland carcinoma, was also reported in 12- to 15-month repeat-dose toxicity studies in rats.

Genetic toxicology studies have not been conducted with radium-223 dichloride. However, the mechanism of action of radium-223 dichloride involves induction of double-strand DNA breaks, which is a known effect of radiation.

Animal studies have not been conducted to evaluate the effects of radium-223 dichloride on male or female fertility or reproductive function. Xofigo may impair fertility and reproductive function in humans based on its mechanism of action.

14 CLINICAL STUDIES

The efficacy and safety of Xofigo were evaluated in a double-blind, randomized, placebo-controlled phase 3 clinical trial of patients with castration-resistant prostate cancer with symptomatic bone metastases. Patients with visceral metastases and malignant lymphadenopathy exceeding 3 cm were excluded. The primary efficacy endpoint was overall survival. A key secondary efficacy endpoint was time to first symptomatic skeletal event (SSE) defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention. There were no scheduled radiographic assessments performed on study. All patients were to continue androgen deprivation therapy. At the cut-off date of the pre-planned interim analysis, a total of 809 patients had been randomized 2:1 to receive Xofigo 50 kBq (1.35 microcurie)/kg intravenously every 4 weeks for 6 cycles (n = 541) plus best standard of care or matching placebo plus best standard of care (n = 268). Best standard of care included local EBRT, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole. Therapy was continued until unacceptable toxicity or initiation of cytotoxic chemotherapy, other systemic radioisotope, hemi-body EBRT or other investigational drug. Patients with Crohn's disease, ulcerative colitis, prior hemibody radiation or untreated imminent spinal cord compression were excluded from the study. In patients with bone fractures, orthopedic stabilization was performed before starting or resuming treatment with Xofigo.

The following patient demographics and baseline disease characteristics were balanced between the arms. The median age was 71 (range 44-94) with a racial distribution of 94% Caucasian, 4% Asian, 2% Black and <1% Other. Patients were enrolled predominantly from Europe (85%) with 4% of patients enrolled from North America. ECOG performance status was 0-1 in 86% of patients. Eighty-five percent of patients had 6 or more bone scan lesions and of those 40% had > 20 lesions or a superscan. Opiate pain medications were used for cancer-related pain in 54% of patients, non-opiate pain medications in 44% of patients and no pain medications in 2% of patients. Patients were stratified by baseline ALP, bisphosphonate use, and prior docetaxel exposure. Prior bisphosphonates were used by 41% of patients and 58% had received prior docetaxel. During the treatment period, 83% of Xofigo patients and 82% of placebo patients received gonadotropin-releasing hormone agonists and 21% of Xofigo patients and 34% of placebo patients received concomitant antiandrogens. Use of systemic steroids (41%) and bisphosphonates (40%) was balanced between the arms.

The pre-specified interim analysis of overall survival revealed a statistically significant improvement in patients receiving XOFIGO plus best standard of care compared with patients receiving placebo plus best standard of care. An exploratory updated overall survival analysis performed before patient crossover with an additional 214 events resulted in findings consistent with the interim analysis (Table 5).

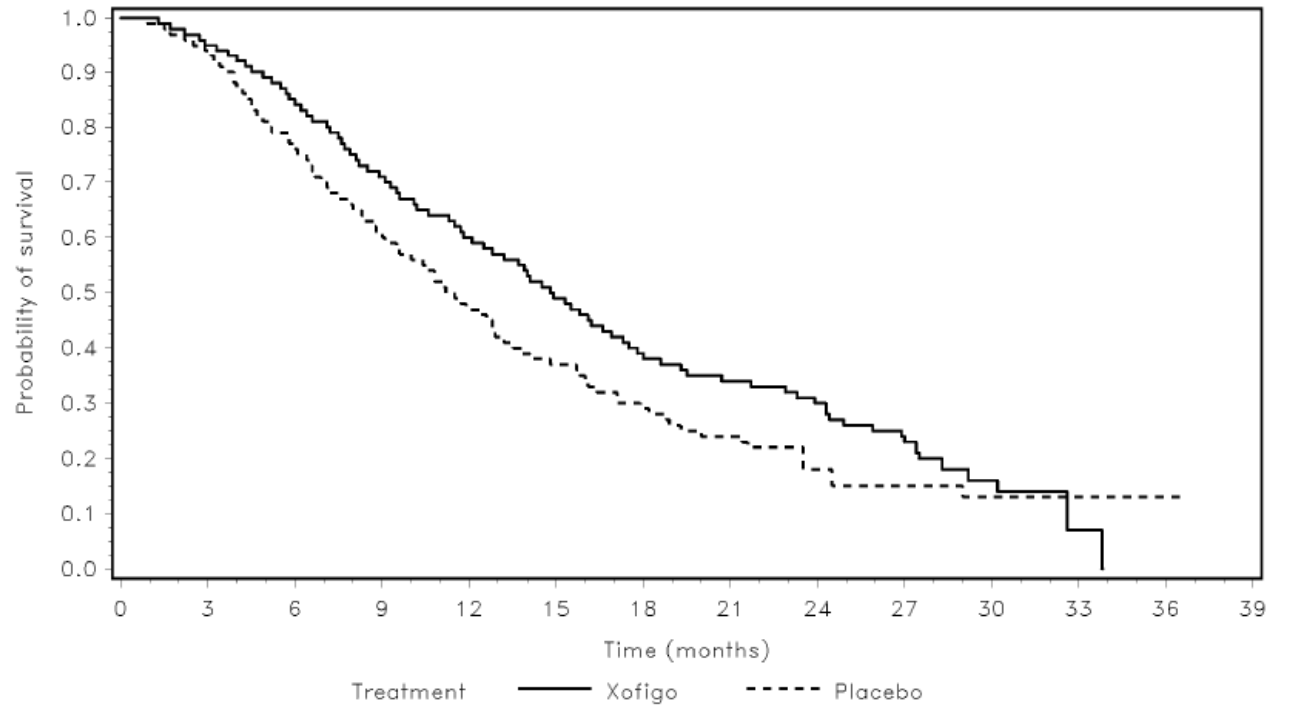
Table 5: Overall Survival Results from the Phase 3 Clinical Trial

	Xofigo	Placebo
Interim Analysis		
Subjects randomized	541	268
Number of deaths	191 (35.3%)	123 (45.9%)
Censored	350 (64.7%)	145 (54.1%)
Median survival (months) [a] (95% CI)	14.0 (12.1, 15.8)	11.2 (9.0, 13.2)
p-value[b]	0.00185	
Hazard ratio (95% CI)[c]	0.695 (0.552, 0.875)	
Updated Analysis		
Subjects randomized	614	307
Number of deaths	333 (54.2%)	195 (63.5%)
Censored	281 (45.8%)	112 (36.5%)
Median survival (months) [a] (95% CI)	14.9 (13.9, 16.1)	11.3 (10.4, 12.8)
Hazard ratio (95% CI)[c]	0.695 (0.581, 0.832)	

[a] Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.
[b] p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior use of docetaxel.
[c] Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel. Hazard ratio < 1 favors radium-223 dichloride.

The Kaplan-Meier curves for overall survival based on the updated survival results are shown in Figure 1.

Figure 1: Kaplan-Meier Overall Survival Curves from the Phase 3 Clinical Trial



Number of patients at risk

Xofigo	614	578	504	369	277	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	104	67	39	24	14	7	4	2	1	0

The survival results were supported by a delay in the time to first SSE favoring the Xofigo arm. The majority of events consisted of external beam radiotherapy to bone metastases.

15 REFERENCES

1. Radiation Emergency Medical Management. [REMM/National Library of Medicine Website.] http://www.remm.nlm.gov/int_contamination.htm#blockingagents

16 HOW SUPPLIED/STORAGE AND HANDLING

Xofigo (radium Ra 223 dichloride injection) is supplied in single-use vials containing 6 mL of solution at a concentration of 1,000 kBq/mL (27 microcurie/mL) with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date (NDC 50419-208-01).

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

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

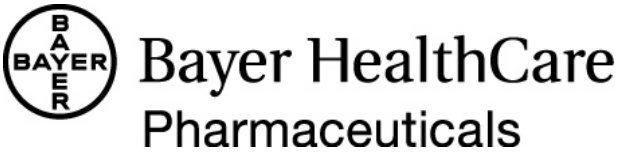
Follow procedures for proper handling and disposal of radioactive pharmaceuticals *[see Dosage and Administration (2.3)]*.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To be compliant with blood cell count monitoring appointments while receiving Xofigo. Explain the importance of routine blood cell counts. Instruct patients to report signs of bleeding or infections.
- To stay well hydrated and to monitor oral intake, fluid status, and urine output while being treated with Xofigo. Instruct patients to report signs of dehydration, hypovolemia, urinary retention, or renal failure / insufficiency.
- There are no restrictions regarding contact with other people after receiving Xofigo. Follow good hygiene practices while receiving Xofigo and for at least 1 week 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. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing. Caregivers should use universal precautions for patient care such as gloves and barrier gowns when handling bodily fluids to avoid contamination. When handling bodily fluids, wearing gloves and hand washing will protect caregivers.
- Who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective method of birth control during treatment and for 6 months following completion of Xofigo treatment.

Manufactured for:



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