PRODUCT MONOGRAPH

XOFIGO®

radium Ra 223 dichloride solution for injection

1100 kBq/mL (29.7 microcurie/mL) radium-223 dichloride at reference date

Therapeutic Radiopharmaceutical

ATC Code V10XX03

Manufactured by: Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario
L4W 5R6
www.bayer.ca

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XOFIGO®

Radium Ra 223 dichloride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Solution for injection / 1100 kBq/mL (29.7 microcurie/mL) radium-223 dichloride at reference date	Each milliliter (mL) contains 0.194 mmol (equivalent to 4.5 mg) sodium. For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

DESCRIPTION

Physical Characteristics

XOFIGO (radium Ra 223 dichloride) is a therapeutic alpha particle-emitting pharmaceutical with targeted anti-tumour effect on bone metastases.

Each mL of solution contains 1100 kBq (29.7 microcurie) radium Ra 223 dichloride (radium-223 dichloride), corresponding to 0.58 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 [6600 kBq (178 microcurie) radium-223 dichloride at the reference date].

Radium-223 is an alpha particle-emitter with 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 lead-207 occurs via short-lived daughters, and is accompanied by a number of alpha, 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 5.0 -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).

INDICATIONS AND CLINICAL USE

XOFIGO (radium Ra 223 dichloride) is indicated for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease.

This product should be administered under the supervision of a qualified health professional who is experienced in the use of therapeutic radiopharmaceuticals.

Geriatrics (> 65 years of age)

No dosage adjustment is considered necessary in elderly patients. Of the 600 patients treated with XOFIGO in the randomized Phase III study, 75% were 65 years of age and over (25% were below 65 years of age), while 33% were 75 years of age and over. Although no overall differences in safety or efficacy were observed between elderly (aged ≥65 years) and younger patients (aged <65 years), the potential for greater sensitivity of some older individuals cannot be ruled out.

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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.
- Bone marrow suppression: measure blood counts prior to treatment initiation and before every dose (see **Hematologic**, ***Bone marrow suppression***, for more detailed information).

General

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Spinal Cord Compression

In patients with untreated, imminent or established spinal cord compression (SCC), treatment for SCC with standard of care, as clinically indicated, should be completed before starting or resuming treatment with XOFIGO (radium Ra 223 dichloride).

Bone Fractures

In patients with bone fractures, orthopedic stabilization of fractures should be performed before starting or resuming treatment with XOFIGO. (1)

Contamination

For patient care

Whenever possible, patients should use a toilet and the toilet should be flushed twice 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.

Gastrointestinal

Safety and efficacy of XOFIGO in patients with castration-resistant prostate cancer and concomitant Crohn's disease or ulcerative colitis have not been studied. XOFIGO is known to be eliminated from the bowel. Patients with inflammatory bowel disease and increased risk of bowel obstruction should be treated with caution with XOFIGO. Appropriate monitoring and consideration of additional supportive measures may be required in patients with constipation.

Hematologic

Bone marrow suppression

Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with XOFIGO (see **ADVERSE REACTIONS**, **Thrombocytopenia and Neutropenia**). Therefore, hematological 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 ≥ 10.0 g/dL. Before subsequent administrations, the ANC should be $\geq 1.0 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. In case there is no recovery in these values within 6 weeks after the last administration of XOFIGO, despite receiving standard of 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.

Discontinue XOFIGO in patients who experience life-threatening complications despite supportive care for bone marrow failure.

Patients with severely compromised bone marrow reserves at baseline prior to XOFIGO therapy (not meeting the hematological evaluation criteria noted above) should not receive XOFIGO (see **DRUG INTERACTIONS**).

Hepatic

Safety and efficacy of XOFIGO have not been studied in patients with hepatic impairment.

Based on subgroup analyses for the randomized 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. However, since radium-223 is neither metabolized by the liver nor eliminated via the bile, hepatic impairment is not expected to affect the pharmacokinetics of radium Ra 223 dichloride.

Renal

No dedicated study for XOFIGO in patients with renal impairment has been conducted. Based on subgroup analysis in the randomized clinical trial, no dose adjustment should be needed for patients with mild renal impairment (creatinine clearance [CLCR]: 50 to 80 mL/min) or moderate (CLCR: 30 to 50 mL/min) renal impairment. As there are limited data available on patients with severe (CLCR <30 mL/min) renal impairment (n=4) and no data on end-stage renal disease, no dose adjustment can be recommended for these patients. 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 Ra 223 dichloride.

Sexual Function/Reproduction

Animal reproduction studies have not been conducted with XOFIGO. Because of potential effects on spermatogenesis associated with radiation, men who are sexually active should be advised to use condoms. Female partners of reproductive potential should use effective contraceptive methods during, and for 6 months after their partner's treatment with XOFIGO. (2, 3)

There are no human data on the effect of XOFIGO on fertility. No animal fertility studies have been performed to determine the effects of XOFIGO on fertility. There is a potential risk that radiation from XOFIGO could cause adverse effects on testes (see **TOXICOLOGY - Reproductive Toxicology**). (3, 4) Patients should be informed accordingly.

Special Populations

Pregnant Women

XOFIGO is not indicated in women. XOFIGO is not to be used in women who are, or may be, pregnant.

Nursing Women

XOFIGO is not indicated in women. XOFIGO is not to be used in women who are, or may be, breast-feeding.

Pediatrics (< 18 years of age)

The safety and efficacy of XOFIGO in pediatric patients have not been studied.

Geriatrics (> 65 years of age)

No dosage adjustment is considered necessary in elderly patients. Of the 600 patients treated with XOFIGO in the randomized Phase III study, 75% were 65 years of age and over (25% were below 65 years of age), while 33% were 75 years of age and over. Although no overall differences in safety or efficacy were observed between elderly (aged ≥65 years) and younger patients (aged <65 years), the potential for greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety profile of XOFIGO (radium Ra 223 dichloride) is based on data from 600 patients with metastatic castration-resistant prostate cancer with symptomatic bone metastases treated with the best standard of care and XOFIGO in the Phase III study. The most serious adverse drug reactions were thrombocytopenia and neutropenia (see **WARNINGS AND PRECAUTIONS - Hematologic** and **Thrombocytopenia and Neutropenia**). The most frequently observed adverse drug reactions (≥10%) in patients receiving XOFIGO were diarrhea, nausea, vomiting and thrombocytopenia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of XOFIGO has been evaluated in a double-blind, randomized, multiple dose, placebo-controlled, multicenter, Phase III study (ALSYMPCA) in castration-resistant prostate cancer patients with symptomatic bone metastases. Safety is based on 901 patients treated with either radium-223 dichloride (n=600) or placebo (n=301). The dose of radium-223 dichloride administered intravenously was 55 kBq/kg body weight scheduled at 4 week intervals for up to 6 injections, compared to matching placebo. Table 2 shows adverse reactions occurring in ≥1% of patients treated with XOFIGO or placebo.

Table 2 – Most Common Clinical Trial Adverse Drug Reactions (≥1%)

System Organ Class[a]	XOFIGO (n=600)		Placebo (n=301)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and lymphatic system disorders				
Leukopenia	4.2	1.3	0.3	0.3
Neutropenia	5.0	2.2	1.0	0.7
Pancytopenia	2.0	1.2	0.0	0.0
Thrombocytopenia	11.5	6.3	5.6	2.0
Gastrointestinal disorders				
Diarrhea	25.0	1.5 (grade 3 only)	15.0	1.7 (grade 3 only)
Nausea	35.5	1.7 (grade 3 only)	34.6	1.7 (grade 3 only)
Vomiting	18.5	1.7 (grade 3 only)	13.6	2.3 (grade 3 only)
General disorders and administration site conditions				
Injection site reactions (including erythema, pain and swelling)	1.2	0.0	0.0	0.0
Peripheral edema	13	2	10	1

a Adverse reactions are identified using MedDRA version 14.1 and graded according to CTCAE version 3.0.

Thrombocytopenia and Neutropenia

Thrombocytopenia (all grades) occurred in 11.5% of patients treated with XOFIGO and 5.6% of patients receiving placebo. Grade 3 and 4 thrombocytopenia was observed in 6.3% of patients treated with XOFIGO and in 2% of patients receiving placebo (see **WARNINGS AND PRECAUTIONS - Hematologic**). Overall, the frequency of grade 3 and 4 thrombocytopenia was lower in patients who did not previously receive docetaxel (2.8% in patients treated with XOFIGO versus 0.8% in patients receiving placebo) compared to patients who previously received docetaxel (8.9% in patients treated with XOFIGO versus 2.9% in patients receiving placebo).

Neutropenia (all grades) was reported in 5% of patients treated with XOFIGO and in 1% of patients receiving placebo. Grade 3 and 4 neutropenia was observed in 2.2% of patients treated with XOFIGO and in 0.7% of patients receiving placebo. Overall, the frequency of grade 3 and 4 neutropenia was lower in patients who did not previously receive docetaxel (0.8% in patients treated with XOFIGO versus 0.8% in patients receiving placebo) compared to patients who previously received docetaxel (3.2% in patients treated with XOFIGO versus 0.6% in patients receiving placebo).

In a Phase I study, neutrophil and platelet count nadirs occurred at 2 to 3 weeks after intravenous administration of a single dose of XOFIGO.

Fluid Status

Dehydration occurred in 3% of patients on XOFIGO (1% of patients on placebo). XOFIGO increases adverse reactions such as diarrhea, nausea and vomiting, which may predispose and result in dehydration. Oral intake and fluid status in patients should be monitored and treated promptly if signs or symptoms of dehydration or hypovolemia are displayed.

Injection Site Reactions

Erythema, pain and swelling at the injection site were reported in 1.2 % 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. No cases of XOFIGO-induced cancer, including sarcomas of the bone, have been reported in clinical trials in follow-up of up to three years but the expected latency period for the development of secondary solid malignancies exceeds the duration of follow-up for patients on the trial. (5) Due to its mechanism of action and neoplastic changes noted in rats following radium Ra 223 dichloride administration (including osteosarcoma), XOFIGO may increase the risk of secondary malignant neoplasms.

Less Common Clinical Trial Adverse Drug Reactions

The following adverse drug reactions were seen at a frequency of <1% in pivotal clinical trials with XOFIGO.

Blood and Lymphatic System Disorders: Lymphopenia

DRUG INTERACTIONS

Overview

No clinical interaction studies have been performed.

Concomitant chemotherapy, concomitant use of other systemic therapeutic radioisotopes or hemibody external beam radiotherapy with XOFIGO (radium Ra 223 dichloride) may have additive effects on bone marrow suppression (see **WARNINGS AND PRECAUTIONS - Hematologic**). Safety and efficacy of concomitant chemotherapy, concomitant use of other systemic therapeutic radioisotopes or hemibody external beam radiotherapy with XOFIGO have not been established.

Drug-Lifestyle Interactions

There is neither evidence, nor is it expected that XOFIGO will affect the ability to drive or use machines.

DOSAGE AND ADMINISTRATION

Dosage

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 a total of 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 (55 kBq (1.49 microcurie)/kg body weight)
- Radioactivity concentration of the product (1100 kBq/mL; 29.7 microcurie/mL) at reference date. The reference date is stated on the vial and lead container label.
- Decay correction (DK) factor to correct for physical decay of radium-223 (see Table 3).

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

$$\textbf{Volume to be administered (mL)} = \frac{\textbf{Body weight in kg x 55 kBq/kg body weight}}{\textbf{Decay factor x 1100 kBq/mL}}$$

or

$$\textbf{Volume to be administered (mL)} = \frac{\textbf{Body weight in kg x 1.49 microcurie/kg body weight}}{\textbf{Decay factor x 29.7 microcurie/mL}}$$

Table 3 - 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.

Pediatric Patients (< 18 years of age)

The safety and efficacy of XOFIGO in pediatric patients have not been studied.

Geriatric Patients (≥ 65 years of age)

No dose adjustment is considered necessary in elderly patients.

Hepatic Insufficiency

No dose adjustment is considered necessary in patients with mild hepatic impairment (see **WARNINGS AND PRECAUTIONS - Hepatic**).

Renal Insufficiency

No dose adjustment is considered necessary in patients with mild to moderate renal impairment (see **WARNINGS AND PRECAUTIONS - Renal**).

Administration

The patient dose should be measured by a suitable radioactivity calibration system prior to administration.

XOFIGO is to be administered by slow intravenous injection (generally up to one minute).

The intravenous access line or cannula must be flushed with isotonic saline before and after injection of XOFIGO. For additional instructions on the use of the product see **SPECIAL HANDLING INSTRUCTIONS**.

This medicinal product should be visually inspected before use. XOFIGO is a clear, colorless solution and should not be used in case of discoloration, the occurrence of particulate matter or a defective container.

XOFIGO is a ready-to-use solution and should not be diluted or mixed with any solutions.

Each vial is for single use only.

RADIATION DOSIMETRY

The absorbed radiation dose was calculated based on clinical biodistribution data which was obtained from whole body planar images acquired on gamma energy windows of radium Ra 223 (1.1% of emissions consist of photons) in five patients with castration-resistant prostate cancer. The methodology to estimate dosimetry for alpha emitters such as radium Ra 223 dichloride, is at a relatively early stage and is still under development. Calculations of absorbed doses were performed using OLINDA/EXM (Organ Level INternal Dose Assessment/EXponential Modeling), a software based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used, and was mainly designed for established beta and gamma emitting radionuclides. (6) For radium-223, primarily an alpha emitter, additional assumptions were made to modify the dosimetry calculation for the intestine, red marrow and bone/osteogenic cells, to provide the best possible absorbed dose calculations. (7-10)

The calculated absorbed radiation doses to different organs are listed in Table 4. 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. The radiation exposure for individual patients may differ from values given in the dosimetry table based on their individual characteristics like bone metabolism in normal bone and extent and location of bone metastases.

The current method in dosimetry calculation may overestimate the absorbed dose to red marrow. This may be related to the very short range of the alpha particle emissions, as only a small fraction of the marrow volume would be irradiated.

Table 4 – Calculated Absorbed Radiation Doses to Organs[a]

TARGET ORGAN	Alpha emission[b] (Gy/MBq)	Beta emission (Gy/MBq)	Gamma emission (Gy/MBq)	Total Dose (Gy/MBq)	Total Dose (rad/mCi)
Adrenals	0.00000	0.00002	0.00009	0.00012	0.44
Brain	0.00000	0.00002	0.00008	0.00010	0.37
Breasts	0.00000	0.00002	0.00003	0.00005	0.18
Gallbladder wall	0.00000	0.00002	0.00021	0.00023	0.85
LLI Wall	0.00000	0.04561	0.00085	0.04645	171.88
Small intestine wall	0.00319	0.00360	0.00047	0.00726	26.87
Stomach wall	0.00000	0.00002	0.00011	0.00014	0.51
ULI wall	0.00000	0.03149	0.00082	0.03232	119.58
Heart wall	0.00161	0.00007	0.00005	0.00173	6.40
Kidneys	0.00299	0.00011	0.00011	0.00321	11.86
Liver	0.00279	0.00010	0.00008	0.00298	11.01
Lungs	0.00109	0.00007	0.00005	0.00121	4.47
Muscle	0.00000	0.00002	0.00010	0.00012	0.44
Ovaries	0.00000	0.00002	0.00046	0.00049	1.80
Pancreas	0.00000	0.00002	0.00009	0.00011	0.41
Red marrow	0.13217	0.00642	0.00020	0.13879	513.51
Osteogenic cells	1.13689	0.01487	0.00030	1.15206	4262.60
Skin	0.00000	0.00002	0.00005	0.00007	0.27
Spleen	0.00000	0.00002	0.00007	0.00009	0.33
Testes	0.00000	0.00002	0.00006	0.00008	0.31
Thymus	0.00000	0.00002	0.00003	0.00006	0.21
Thyroid	0.00000	0.00002	0.00005	0.00007	0.27
Urinary bladder wall	0.00371	0.00016	0.00016	0.00403	14.90
Uterus	0.00000	0.00002	0.00023	0.00026	0.94
Whole body	0.02220	0.00081	0.00012	0.02312	85.56

a No value for the effective dose (ED) has been included here, since there remains controversy regarding the value of the radiation weighting factor for α particles, which ranges from 1 to 20, with the value of 20 being the most conservative, and use of the ED in this instance has limitations for assessing the exposure of patients.
b As there was no uptake of radium-223 in most of the soft tissues observed, the alpha contribution to the total organ dose was set to zero for these organs.
LLI: lower large intestine
ULI: upper large intestine

The biodistribution data from a patient with diffuse skeletal metastases and a significant prolonged resident time of skeleton was excluded from the final dosimetry calculation.

OVERDOSAGE

There have been no reports of inadvertent overdosing of XOFIGO (radium Ra 223 dichloride) during clinical studies. There is no specific antidote. In the event of an inadvertent overdose, general supportive measures, including monitoring for potential hematological and gastrointestinal toxicity should be undertaken. Single XOFIGO doses up to 276 kBq (7.46 microcurie) per kg body weight were evaluated in a Phase I clinical trial in cancer patients with bone metastases and no dose-limiting toxicities were observed.

For management of suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Radium Ra 223 dichloride is a therapeutic alpha particle-emitting radiopharmaceutical. (11) The active moiety is the isotope radium-223 (as radium Ra 223 dichloride) that mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. (12, 13) 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 a localized anti-tumour effect on bone metastases. (14-17) The alpha particle range from radium-Ra 223 is less than 100 micrometers (less than 10 cell diameters) (14) which minimizes damage to the surrounding normal tissue. (18)

Pharmacodynamics

In a phase II study involving 33 patients treated with XOFIGO at a dose of 55 kBq/kg for four injections, and 31 patients in the placebo group, a significant difference in favor of XOFIGO for serum bone metabolism markers in patients treated with radium Ra 223 dichloride was observed from baseline to 4 weeks after last study injection, compared with placebo. The bone formation markers studied were: bone alkaline phosphatase [ALP], total ALP and procollagen I N propeptide [PINP], bone resorption markers: C-terminal crosslinking telopeptide of type I collagen / serum C-terminal crosslinked telopeptide of type I collagen [S-CTX-1] and type I collagen crosslinked C-telopeptide [ICTP]). (19)

Pharmacokinetics

The pharmacokinetics of radium-223 dichloride in blood was linear in terms of dose proportionality and time independence in the dose range investigated (51 to 276 kBq [1.38 to 7.46 microcurie] per kg body weight).

Absorption

Radium Ra 223 dichloride is administered intravenously and is thus 100% bioavailable.

Distribution

After intravenous injection, radium Ra 223 dichloride is rapidly cleared from the blood and is distributed primarily into bone and bone metastases, or is excreted into the intestine.

Fifteen minutes post injection, about 20% of the injected activity remained in the blood. At 4 hours, about 4% of the injected activity remained in the blood, decreasing to less than 1% at 24 hours after the injection. The volume of distribution was higher than the blood volume indicating distribution to peripheral compartments.

At 10 minutes post injection, activity was observed in the bone and in the intestine. The level of activity in the bone was in the range of 44% to 77% and in the intestine, in the range of 19% to 69%, at 4 hours post injection.

No significant uptake was seen in other organs such as heart, liver, kidneys, urinary bladder and spleen at 4 hours post injection.

Metabolism

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

Excretion

Fecal excretion is the major route of elimination from the body. At 48 hours post-injection the cumulative fecal excretion was about 13% with a range of 0% to 34%. About 5% is excreted in the urine and there is no evidence of hepato-biliary excretion based on imaging data.

The whole body measurements at 7 days after injection (after correcting for decay) indicate that a median of 76% of administered activity was excreted from the body.

The rate of elimination of radium Ra 223 dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population, with the normal range from once daily to once weekly bowel evacuation. Patients with a slower intestinal transit rate could potentially receive a higher intestinal radiation exposure, but the clinical significance of this is not known.

Special Populations and Conditions

Safety and effectiveness of XOFIGO have not been studied in children and adolescents below 18 years of age.

Hepatic Insufficiency

No pharmacokinetic studies in patients with hepatic impairment have been conducted. However, since radium-223 as an isotope is not metabolized and there is no evidence of hepato-biliary excretion based on imaging data, it is not expected that hepatic impairment will affect the pharmacokinetics of radium Ra 223 dichloride (see **DOSAGE AND ADMINISTRATION - Dosage**).

Renal Insufficiency

No pharmacokinetic studies in patients with renal impairment have been conducted. However, since excretion in urine is minimal and the major route of elimination is via the feces, it is not expected that renal impairment will affect the pharmacokinetics of radium Ra 223 dichloride (see **DOSAGE AND ADMINISTRATION - Dosage**).

STORAGE AND STABILITY

Storage of XOFIGO (radium Ra 223 dichloride) should be in accordance with Canadian Nuclear Safety Commission regulations on radioactive materials. Store at room temperature, below 40°C. Store XOFIGO in the original container or equivalent radiation shielding.

SPECIAL HANDLING INSTRUCTIONS

XOFIGO (radium Ra 223 dichloride, an alpha particle-emitting pharmaceutical) 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 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.

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.

The administration of XOFIGO is associated with potential risks for other persons (e.g. medical staff, care givers and patient's household members) from radiation or contamination from body fluids such as spills of urine, feces and vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations. Although radium-223 is predominantly an alpha emitter, gamma and beta radiation is associated with the decay of radium-223 and its radioactive daughter isotopes. The external radiation exposure associated with handling of patient doses is considerably lower in comparison to other radiopharmaceuticals for therapeutic purposes as the administered radioactivity will usually be below 8 MBq (216 microcurie). However, in keeping with the ALARA ("As Low As Reasonably Achievable") 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 of XOFIGO are to be treated as radioactive waste and should be disposed of in accordance with 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

XOFIGO (radium Ra 223 dichloride) is provided as a clear, colorless and sterile isotonic solution for injection with pH between 6.0 and 8.0. Each mL of solution contains 1100 kBq (29.7 microcurie) radium Ra 223 dichloride (radium-223 dichloride), corresponding to 0.58 ng radium-223, at the reference date. Radium is present in the solution as a free ion. Nonmedicinal ingredients include hydrochloric acid, sodium chloride, sodium citrate and water for injection.

Each vial contains 6 mL of solution [6.6 MBq (178 microcurie) radium-223 dichloride at the reference date].

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	radium Ra 223 dichloride
Chemical name:	radium-223 dichloride
Molecular formula:	$^{223}RaCl_2$
Molecular weight:	293.9 g/mol
Structural formula:	The active moiety of the radium-223 chloride drug substance is the divalent cation of radium-223, $^{223}Ra^{2+}$.
Physicochemical properties:	The drug substance solution is a radioactive, clear and colorless aqueous solution at pH 6.0 – 7.0. Due to the radioactive properties and the very small amounts of radium-223 dichloride present in the drug substance solution, the solubility has not been determined experimentally.

CLINICAL TRIALS

Study Demographics and Trial Design

The clinical safety and efficacy of XOFIGO (radium Ra 223 dichloride) have been evaluated in a double-blind, randomized, multiple dose, placebo-controlled, multicenter Phase III, study (ALSYMPCA) in castration-resistant prostate cancer patients with symptomatic bone metastases. Patients with visceral metastases and malignant lymphadenopathy exceeding 3 cm were excluded. The primary efficacy endpoint was overall survival (OS). The 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 tumour-related orthopedic surgical intervention, was one of the studies secondary efficacy endpoints. There were no scheduled radiographic assessments performed on study. (20)

Patients were stratified by baseline ALP, bisphosphonate use, and prior docetaxel exposure.

Patients with Crohn's disease, ulcerative colitis, visceral metastases, prior hemibody radiation and untreated imminent or established spinal cord compression were excluded from the study.

At the cut-off date of the pre-planned interim analysis, a total of 809 patients were randomized 2:1 to receive XOFIGO 55 kBq (1.49 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, eg, local external beam radiotherapy, bisphosphonates, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole.

Demographic and baseline disease characteristics (interim analysis population) were comparable between the XOFIGO and placebo groups, and are shown below for the pooled treatment groups:

- The median age of patients was 71 years (range 44 to 94 years)
- Racial distribution was 94 % Caucasian, 4% Asian, 2% Black and < 1% Other
- 86% of patients enrolled had an ECOG performance status score of 0-1
- 41% received prior bisphosphonates
- 58% had prior use of docetaxel
- 42% of patients did not receive prior docetaxel because they were deemed ineligible or refused to receive docetaxel
- Opiate pain medication was used for cancer-related pain in 54% of patients and non-opiate pain medications in 44%.
- 45% of patients had between 6 and 20 bone metastases, 40% of patients had more than 20 bone metastases or superscan (85% had 6 or more bone scan lesions)

During the treatment period, 83% of XOFIGO patients (82 % of placebo patients) received luteinizing hormone-releasing hormone (LHRH) agonists and 21% of XOFIGO patients (34% of placebo patients) received anti-androgens concomitantly.

Study Results

The results of the interim analysis revealed that overall survival was significantly longer in patients treated with XOFIGO plus best standard of care compared to patients treated with placebo plus best standard of care (see Table 5). The updated descriptive analysis, performed before patient crossover with an additional 214 events, resulted in consistent findings. For both databases, the risk of death was reduced by 30.5% based on the hazard ratios (eg, Interim analysis, HR: 0.695, 95% CI: 0.552, 0.875).

Table 5 – Results of ALSYMPCA Study for Patients with Castration-resistant Prostate Cancer with Bone Metastases

Efficacy Parameter	XOFIGO	Placebo
Interim Analysis	N=541	N=268
Number of deaths (%)	191 (35.3%)	123 (45.9%)
Censored (%)	350 (64.7%)	145 (54.1%)
Median overall Survival (months) (95% CI)[a]	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
p-value[b] (2-sided)	0.00185	
Hazard Ratio[c] (99.725% CI)[d]	0.695 (0.489 – 0.988)	
Updated analysis	N=614	N=307
Number of deaths (%)	333 (54.2%)	195 (63.5%)
Censored (%)	281 (45.8%)	112 (36.5%)
Median overall Survival (months) (95% CI)	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)
Hazard Ratio[c] (95% CI)	0.695 (0.581 – 0.832)	

CI=Confidence interval, HR=Hazard ratio (XOFIGO over placebo)

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 last date subject was known to be alive or lost to follow-up

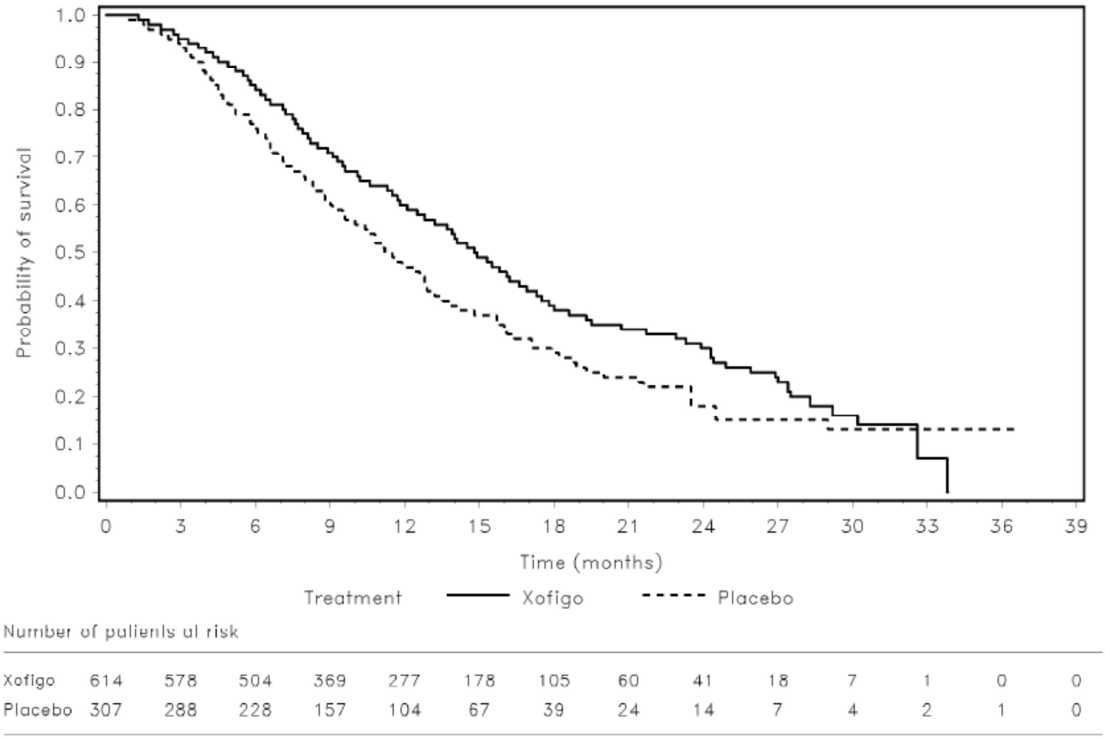
b p-value is from a log-rank test stratified by total ALP, use of bisphosphonates at baseline, and prior use of docetaxel

c Hazard ratio < 1 favours Xofigo. Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, use of bisphosphonates at baseline, and prior use of docetaxel

d The 99.725% CI is provided based on the two-sided significance level of 0.00275 used at the interim analysis

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 (Updated Analysis)



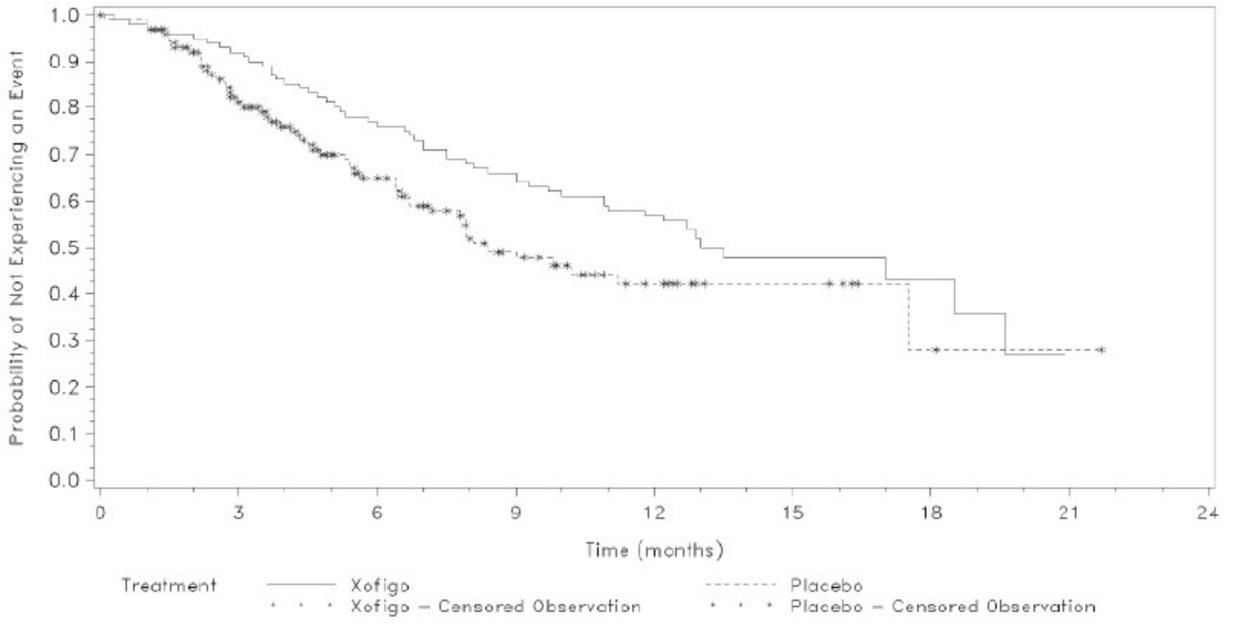
Subgroup survival analysis

Subgroup survival analysis showed a consistent survival benefit for treatment with XOFIGO, independent of total alkaline phosphatase (ALP), use of bisphosphonates at baseline and prior use of docetaxel (the three binary variables used for stratification).

An improvement in the secondary endpoint, Confirmed Total ALP Response, in the XOFIGO arm, compared to the placebo arm, was noted. At week 12, based on an analysis that accounts for subjects with missing total ALP data using the last observation carried forward (LOCF) methodology, confirmed total ALP response (defined as >/= 30% reduction of the blood level compared to the baseline value, confirmed by a second total ALP value approximately 4 or more weeks later), was reported in 176/541 (32.5%) patients in the XOFIGO arm and 4/268 (1.5%) patients in the placebo arm.

The survival results were supported by a delay in the time to first SSE (symptomatic skeletal event) favouring the XOFIGO arm (SSE, defined as occurrence of any of the following: external beam radiotherapy [EBRT] to relieve pain, or pathologic fracture, or spinal cord compression, or tumour-related orthopedic surgical intervention). The majority of events consisted of external beam radiotherapy to bone metastases. In a post-hoc analysis of time to first SSE (in which deaths were considered as events) supporting the OS results, the hazard ratio was 0.657 in favour of the XOFIGO.

Figure 2 - Kaplan-Meier Curve for Symptomatic Skeletal Events (Interim Analysis)



Number of subjects remaining under observation

Xofigo	541	376	211	107	49	22	6	0	0
Placebo	268	160	72	29	15	7	2	1	0

Subsequent/concomitant use of cytotoxic drugs

The safety and efficacy of concomitant chemotherapy with XOFIGO have not been established. In the course of the ALSYMPCA study, 93 patients (16%) in the XOFIGO group and 54 patients in the placebo group (18%) received cytotoxic chemotherapy at varying times after the last treatment. There is the potential for additive myelosuppression (see **PART I: HEALTH PROFESSIONAL INFORMATION**, **DRUG INTERACTIONS**).

DETAILED PHARMACOLOGY

Human Pharmacology

Pharmacokinetic, biodistribution and dosimetry data has been obtained from 3 Phase I studies. Pharmacokinetic data was obtained in 25 patients at doses ranging from 51 to 276 kBq (1.38 to 7.46 microcurie)/kg. Pharmacokinetic, biodistribution and dosimetry data was obtained in 6 patients at a dose of 110 kBq (2.97 microcurie)/kg given twice, 6 weeks apart, and in 10 patients at a dose of 55 (1.49 microcurie), 110 (2.97 microcurie) or 221 kBq (5.97 microcurie)/kg.

TOXICOLOGY

The overall non-clinical safety profile is attributed to radiobiological toxicity. There were no signals for unexpected or untoward toxicities which preclude the use of radium Ra 223 dichloride in castration-resistant prostate cancer patients with bone metastases at the intended human clinical dose of 55 kBq/kg.

The non-clinical toxicology program were conducted to characterize the toxicological profile of radium-223 dichloride to support clinical trials up to 6 months of treatment duration with a dosing regimen of an intravenous injection every 4 weeks for 6 cycles (6 q4w cycles). Repeated dose studies of radium 223 dichloride were conducted using the same treatment regimen (q4w).

The scope and the extent of the toxicology program as well as the safety pharmacology program with radium-223 dichloride are outlined in Table 6.

Table 6 - Toxicology and Safety Pharmacology Programs

Type of Study / Regimen / Duration	Subjects (Species, Strain; No. /Sex / Group)	Route of Administration	Doses
Single dose toxicity + 29 days post dosing; biodistribution	Mouse, Balb/C; 8/sex/group 6M 20/sex/group	Intravenous	Preliminary Dose Range Finding: 1381, 2072, 2418, 2762 kBq/kg Biodistribution: 1381 kBq/kg Main: 0, 1381, 2762, 4144 kBq/kg
Single dose toxicity + 29 days post dosing; biodistribution	Rat, Wistar; 2/sex/group 5/sex/group	Intravenous	Preliminary: 1390, 2433, 3475, 4170 kBq/kg Biodistribution: 1390 kBq/kg Main: 0, 1135, 2270, 3404 kBq/kg

Table 6 - Toxicology and Safety Pharmacology Programs

Type of Study / Regimen / Duration	Subjects (Species, Strain; No. /Sex / Group)	Route of Administration	Doses
Single dose toxicity + 30 days post dosing; biodistribution	Dog, Beagle; 2/sex/group	Intravenous	0, 55, 166, 497 kBq/kg
Single-dose and repeated-dose [once every 4 weeks (q4w)] x 4 + 12 months post dosing	Rat, Wistar; 8/sex/group	Intravenous	Single-dose: 0,22, 88, 359, 1436 kBq/kg Repeated-dose: 0, 22, 359, 718 kBq/kg
Repeat dose toxicity: 12-month (once monthly) x 12 + 4 weeks post dosing	Rat, Wistar 12/sex/group	Intravenous	0, 28, 55, 110 kBq/kg
Repeat dose toxicity: 6-month, (once monthly) x 6 + approximately 35 days post dosing, biodistribution	Dog, Beagle; 2/sex/control group 4/sex/treatment group	Intravenous	0, 55 kBq/kg
Safety Pharmacology: Effects on central nervous system system, single dose	Rat, Sprague-Dawley; 8 M/group	Intravenous	0; 55, 276, 1100 kBq/kg
Safety Pharmacology: Effects on respiratory system, single dose	Rat, Sprague-Dawley; 10 M/group	Intravenous	0; 55, 276, 1100 kBq/kg
Safety Pharmacology: Effects on cardiovascular system	Dog, Beagle, telemetered conscious; 4 M per study with balanced Latin-Square crossover design	Intravenous	0; 55, 166, 497 kBq/kg

Systemic toxicity

The severely toxic dose of radium-223 dichloride to 10% of the animals (STD10) after single administration was approximately 40 (rat) to 50 (mice) times the recommended human clinical dose of 55 kBq/kg based on body weight.

In single and repeated dose toxicity studies in rats, the main findings were reduced body weight gain, hematological changes (decreased white blood cells, neutrophils, eosinophils, basophils, lymphocytes , monocytes, red blood cells, hemoglobin, hematocrit, increased mean cell hemoglobin and mean cell volume, compensatory increase in reticulocytes, decreased plateletst, lower pro-thrombin time, increased fibrinogen), reduced serum alkaline phosphatase and microscopic findings in the bone marrow (depletion of hematopoietic cells, fibrosis), spleen (secondary extra-medullary hematopoiesis) and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line). These findings were related to radiation-induced impairment of hematopoiesis and a reduction of osteogenesis and occurred beginning in the dose range of 22 – 88 kBq (0.59 – 2.38 microcurie) per kg body weight, with the exception of body weight decreases.

In dogs, hematological changes (decreased white blood cells, lymphocytes, monocytes, granulocytes, platelets, and red blood cell parameters) were observed starting at the lowest dose of 55 kBq/kg, the clinically recommended dose. Dose-limiting myelotoxicity (dose related decrease in bone marrow hematopoietic cellularity and percentage bone marrow corresponding to observed blood count changes) was seen in dogs after single administration of 497 kBq (13.43 microcurie) radium-223 dichloride per kg body weight (9 times the clinically recommended dose).

Retinal detachment was seen in dogs after a single injection of doses of 166 and 497 kBq (4.49 and 13.43 microcurie) per kg body weight (3 and 9 times the clinically recommended dose), but not after repeated administration of the clinically recommended dose of 55 kBq (1.49 microcurie) per kg body weight once every 4 weeks for 6 months. Radium is specifically taken up in the tapetum lucidum of the canine eye. (21, 22) Since humans do not have a tapetum lucidum, the clinical relevance of these findings for humans is uncertain. No case of retinal detachment has been reported in clinical trials.

No histological changes were observed in organs involved in the excretion of radium-223 dichloride.

Osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses in rats 7 – 12 months after start of treatment. Osteosarcomas were not observed in dog studies. No case of osteosarcoma has been reported in clinical studies with Radium Ra 223 dichloride. The risk for patients to develop osteosarcomas with exposure to radium-223 is unknown at present. (23-25) The presence of neoplastic changes, other than osteosarcomas, was also reported in the longer term (12 to 15 months) rat toxicity studies. Due to its mode of action, and as seen with conventional radiotherapy and other radiotherapeutics, radium-223 dichloride may have the potential to induce secondary malignancies (see **ADVERSE REACTIONS - Secondary Malignant Neoplasms**). (26)

Genotoxicity/Carcinogenicity

Studies on the mutagenic and carcinogenic potential of Radium Ra 223 dichloride have not been performed.

Reproductive Toxicology

Studies on reproductive and developmental toxicity have not been performed. Since radium-223 binds to bone, the potential risk for adverse effects in the male gonads in cancer patients with castration-resistant prostate cancer is very low, but cannot be excluded (see **WARNINGS AND PRECAUTIONS - Sexual Function/Reproduction**).

Safety Pharmacology

No significant effects were seen on vital organ systems, ie, cardiovascular (dog), respiratory or central nervous systems (rat), after single dose administration of 497 to 1100 kBq (13.43 to 29.7 microcurie) per kg body weight (9 [dog] to 20 [rat] times the clinically recommended dose).

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PART III: CONSUMER INFORMATION

XOFIGO®

radium Ra 223 dichloride

This leaflet is Part 3 of a three-part "Product Monograph" published when XOFIGO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XOFIGO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

XOFIGO is used in men to treat advanced (castration-resistant) prostate cancer that has spread mainly to the bone and is causing symptoms (eg, pain).

What it does:

XOFIGO is known as a radiopharmaceutical drug that contains small amounts of the radioactive isotope radium-223 which as a substance can act similar to calcium, a major component of bones. XOFIGO goes to where the cancer has spread in the bone and gives off radiation (alpha particles) which kills the tumour cells without major effects to the healthy cells.

When it should not be used:

Your doctor will monitor your blood cell counts; if they are too low, XOFIGO will not be administered.

What the medicinal ingredient is:

Radium-223 dichloride

What the nonmedicinal ingredients are:

Hydrochloric acid, sodium chloride, sodium citrate and water for injection

What dosage forms it comes in:

XOFIGO is a clear and colorless solution for injection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Radiopharmaceuticals such as XOFIGO should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

BEFORE you are given XOFIGO talk to your doctor if:

- You suffer from bone marrow suppression (decreased blood cell production in the bone marrow). In this case your physician will treat you with caution. Your doctor will assess your individual situation by doing blood lab tests before you receive this drug and also during therapy to monitor these matters; if results from the lab tests are too low, you may not receive this product or a delay may be needed.
- You suffer from untreated spinal cord compression (severe back pain spreading to the legs or arms) or if it is thought likely that you are developing spinal cord compression (which can be caused by a tumour or other lesion) your doctor will first treat this disease with standard treatment before starting or continuing treatment with XOFIGO
- You experience a broken bone, your doctor will first stabilize the fractured bone before starting or continuing treatment with XOFIGO
- You tend to suffer from constipation (infrequent or difficult emptying of your bowels); for example, if going to the bathroom to empty your bowels only once every few days is the normal for you, tell your doctor.

XOFIGO can lead to a decrease in the number of your white blood cells and blood platelets. Before starting treatment and before each subsequent treatment, your doctor will perform blood tests. Depending on the results of these tests your doctor will decide if the treatment can be started, can be continued, or needs to be postponed or discontinued.

There is no data available on the use of XOFIGO in patients with Crohn's disease (a chronic inflammatory disease of the intestines) and with ulcerative colitis (a chronic inflammation of the colon). If you have either of these conditions, be sure to speak to your doctor about this matter.

XOFIGO is not for use in women and must not be given to women who are, or may be, pregnant or who are breast-feeding.

If you are having sex, you should use condoms to prevent transfer of bodily fluids. If your partner is a woman who can become pregnant, you should use effective birth control methods during and for 6 months after your treatment to prevent pregnancy.

There is a potential risk that radiation from XOFIGO could harm your testicles and this can impact your ability to have children. Please ask your doctor how this may affect you, especially if you are planning on having children in the future.

INTERACTIONS WITH THIS MEDICATION

No interaction studies to determine how XOFIGO behaves with other medicinal products have been done. There is no data on the use of XOFIGO at the same time as chemotherapy (other medicines to kill your cancer cells). XOFIGO and chemotherapy used together may enhance the decrease in the number of your blood cells and blood platelets. The doctors monitor your blood cell counts while you are on XOFIGO.

Please tell your physician if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription.

See also ABOUT THIS MEDICATION: When it should not be used, and SIDE EFFECTS AND WHAT TO DO ABOUT THEM**.**

PROPER USE OF THIS MEDICATION

XOFIGO will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

There are strict laws on the use, handling and disposal of products like XOFIGO. It will only be used in special controlled areas. This product will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this product and will keep you informed of their actions.

Usual dose

The dose you receive depends on your body weight. The physician supervising the procedure will calculate the quantity of XOFIGO to be used in your case.

The recommended quantity to be administered is 55 kBq (kilobecquerel, the unit used to express radioactivity) of XOFIGO per kilogram of your body weight.

No dosage adjustment is considered necessary if you are 65 years of age or older or if you have poor kidney or liver function.

You will usually have an injection into a vein once every 4 weeks for a total of 6 injections. There are no data available on the use of treatment with more than 6 cycles of XOFIGO.

XOFIGO will be injected slowly via a needle into one of your veins (a process known as intravenous injection).

XOFIGO is removed from the body mainly by going through the bowels and into the feces (and then passed when going to the bathroom to empty your bowels). The physician will tell you if you need to take any special precautions after receiving this medicine. Contact your physician if you have any questions or if you develop a change in your usual bowel habit, such as a change in bowel frequency or constipation (difficult or less frequent bowel movements).

As your doctor will want to monitor your blood cell counts, it is important that you keep any appointments to give the blood samples needed for the tests.

Be sure to report to your doctor any signs of bleeding or infections such as unusual bruising, bleeding more than usual after a minor cut, a fever, or if you seem to be catching a lot of infections (cold, flu, or so on).

It is important to remember to maintain good fluid intake during treatment with XOFIGO (e.g., drinking water, juice, etc); this can be particularly important if you develop diarrhea (loose and frequent bowel movements) or vomiting (throwing up) as these unwanted effects can cause you to become dehydrated (have too little water in your system); if you have questions, ask your doctor.

Be sure to report to your doctor if you experience nausea and vomiting (not feeling well and throwing up), or diarrhea.

There are no special restrictions regarding contact with other people after receiving XOFIGO (there are with some other types of radiopharmaceuticals). Follow good personal cleanliness and hand-washing practices while receiving XOFIGO and for at least 1 week after the last injection in order to minimize the potential for radiation exposure received from bodily fluids (such as vomit or fecal matter) to household members and caregivers. Whenever possible, you should use a toilet and the toilet should be flushed twice after each use. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing. Your healthcare providers will use some standard precautions and procedures such as gloves and barrier gowns when handling your bodily fluids to avoid contamination (getting radiation on themselves from the body fluids); this approach is normal under these circumstances and should not be upsetting for you. When handling bodily fluids, wearing gloves and hand washing will help protect healthcare providers from any unnecessary radiation dose they might otherwise be exposed to.

Overdose

There have been no reports of accidental overdose of XOFIGO during clinical studies.

However, in the case of an accidental overdose, your physician will initiate appropriate supportive treatment and will check you for changes in the number of blood cells, and for gastrointestinal symptoms (eg diarrhea, nausea (feeling sick), vomiting).

If you have any further questions on the use of XOFIGO, please ask the physician who supervises the procedure.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most serious side effects in patients receiving XOFIGO were:

- Thrombocytopenia (decrease in the number of blood platelets)
- Neutropenia (decrease in the number of a specific type of white blood cells (neutrophils))

Your physician will perform blood tests before starting treatment and before each treatment cycle to check your number of blood cells and platelets. It is important that you keep any appointments to give the blood samples needed for the tests.

Contact your physician immediately if you notice the following symptoms as they may be signs of thrombocytopenia (decrease in the number of blood platelets) or neutropenia (decrease in the number of a specific type of white blood cells):

- Any unusual bruising
- More bleeding than usual after injury
- Fever
- If you seem to be catching a lot of infections

The most frequently seen side effects in patients receiving XOFIGO (may affect more than 1 in 10 people) are: diarrhea, nausea (feeling sick), vomiting and thrombocytopenia (decrease in the number of blood platelets).

Possible side effects are listed below by how likely they are.

Very common (may affect more than 1 in 10 people)

- Thrombocytopenia (decrease in the number of blood platelets)
- Diarrhea
- Vomiting
- Nausea (feeling sick)

Common (may affect up to 1 in 10 people)

- Neutropenia (decrease in the number of a specific type of white blood cells (neutrophils))
- Pancytopenia (decrease in the number of red and white blood cells and blood platelets)
- Leukopenia (decrease in the number of white blood cells)
- Injection site reactions (eg erythema (redness of the skin), pain and swelling)

Uncommon (may affect up to 1 in 100 people)

- Lymphopenia (decrease in the number of a specific type of white blood cells (lymphocytes))

XOFIGO contributes to your overall long-term cumulative radiation exposure (the amounts of radiation that an individual typically receives from different sources over a longer period of time). Long-term cumulative radiation exposure may increase your risk for developing new cancers and increase the chances for your future children to have hereditary (from a parent) abnormalities. No cases of cancer caused by XOFIGO have been reported in clinical trials with a follow-up of up to three years but this is a short follow-up period and such cancers, if they occur, are expected to take many years to form or be detected.

If you get any side effects talk to your physician. This includes any possible side effects not listed in this leaflet.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk with your doctor or pharmacist	
		Only if severe	**In all cases**
Common	Thrombocytopenia (marked by unusual bruising, more bleeding than usual after injury, fever, catching infections more frequently)		✓
	Neutropenia (marked by unusual bruising, more bleeding than usual after injury, fever, catching infections more frequently)		✓

This is not a complete list of side effects. For any unexpected effects while taking XOFIGO, contact your doctor or pharmacist.

HOW TO STORE IT

You will not have to store this medicine as it is kept at the hospital or clinic and it will be administered to you by the doctor or staff.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online:	www.healthcanada.gc.ca/medeffect
Call toll-free at:	866-234-2345
Complete a Canada Vigilance Reporting Form and:	
Fax toll-free to:	866-678-6789
Mail to:	Canada Vigilance Program Health Canada Postal Locator 0701E Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or Canada.medinfo@bayer.com.

This document plus the full Product Monograph, prepared for health professionals can be found at: http://www.bayer.ca or by contacting the manufacturer at the above-mentioned phone number and email address.

This leaflet was prepared by:

Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario
L4W 5R6
Canada

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Bayer