1. NAME OF THE MEDICINAL PRODUCT
Xofigo solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution contains 1100 kBq 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.

Each vial contains 6 ml of solution (6.6 MBq 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/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).

3. PHARMACEUTICAL FORM
Solution for injection.

4. CLINICAL PARTICULARS
4.1 Indication(s)
Xofigo is indicated for the treatment of castration-resistant prostate cancer patients with symptomatic bone metastases and no known visceral metastatic disease.

4.2 Dosage and method of administration
4.2.1 Method of administration
Xofigo is to be administered by slow intravenous injection (generally up to 1 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 section 'Instructions for use/handling'.

4.2.2 Dosage regimen
The dose regimen of Xofigo is 55 kBq per kg body weight, given at 4 week intervals for 6 injections.
Safety and efficacy beyond 6 injections with Xofigo have not been studied.
For details on the calculation of the volume to be administered see section 'Instructions for use/ handling'.

Elderly patients
No overall differences in safety or efficacy were observed between elderly (aged ≥ 65 years) and younger patients (aged < 65 years) in the phase III study.
No dose adjustment is considered necessary in elderly patients.

Patients with hepatic impairment
Safety and efficacy of Xofigo have not been studied in patients with hepatic impairment.
Since radium-223 is neither metabolised by the liver nor eliminated via the bile, hepatic impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.
No dose adjustment is considered necessary in patients with hepatic impairment.

Patients with renal impairment
In the phase III clinical study, no relevant differences in safety or efficacy were observed between patients with mild renal impairment (creatinine clearance [CLCR]: 50 to 80 mL/min) and normal renal function. Limited data are available on patients with moderate (CLCR: 30 to 50 mL/min) and severe (CLCR: <30ml/min) renal impairment. No data are available on patients with end-stage renal disease.
However, since excretion in urine is minimal and the major route of elimination is via the faeces, renal impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

No dose adjustment is considered necessary in patients with renal impairment.

Paediatric population
The safety and efficacy of Xofigo in children and adolescents below 18 years of age have not been studied. There is no relevant use of this medicinal product in the paediatric population in the indication of prostate cancer.

4.3 Contraindications
Xofigo is contraindicated in combination with abiraterone acetate plus prednisone/prednisolone (see section 'Special warnings and precautions for use')
4.4 Special warnings and precautions for use
4.4.1 Bone marrow suppression
Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with Xofigo (see section 'Undesirable effects').

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 ≥ 1.5 x 10^9/L, the platelet count ≥ 100 x 10^9/L and hemoglobin ≥ 10.0 g/dL.

Before subsequent administrations, the ANC should be ≥ 1.0 x 10^9/L and the platelet count ≥ 50 x 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 only be continued after a careful benefit/risk evaluation.

Patients with evidence of compromised bone marrow reserve should be treated with caution.

4.4.2 Crohn's disease and ulcerative colitis
Safety and efficacy of Xofigo in patients with Crohn's disease and with ulcerative colitis have not been studied. Due to the faecal excretion of Xofigo, radiation may lead to aggravation of acute inflammatory bowel disease. Xofigo should only be administered after a careful benefit-risk assessment in patients with acute inflammatory bowel disease.

4.4.3 Spinal cord compression
In patients with untreated imminent or established spinal cord compression, treatment with standard of care, as clinically indicated, should be completed before starting or resuming treatment with Xofigo.

4.4.4 Bone fractures
In patients with bone fractures, orthopedic stabilization of fractures should be performed before starting or resuming treatment with Xofigo.

4.4.5 Combination with abiraterone plus prednisone/prednisolone
The clinical efficacy and safety of concurrent initiation of Xofigo treatment and abiraterone acetate plus prednisone/prednisolone treatment was assessed in a randomized, placebo-controlled multicenter phase 3 study (ERA-223 trial) in 806 patients with asymptomatic or mildly symptomatic castration resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee Recommendation.
At an interim analysis an increased incidence of fractures (26% vs 8.1%) and deaths (34.7% vs 28.2%) among patients receiving Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone was observed. Concurrent use of bisphosphonates or denosumab reduced the incidence of fractures in both treatment arms.
Therefore, Xofigo is contraindicated in combination with abiraterone acetate plus prednisone/prednisolone (see section 'Contraindications').

4.4.6 Secondary malignant neoplasms

Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Therefore, long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. In particular, the risk for osteosarcoma, myelodysplastic syndrome and leukaemias may be increased. No cases of Xofigo-induced cancer have been reported in clinical trials in follow-up of up to three years.

4.5 Interaction with other medicinal products and other forms of interaction
No clinical interaction studies have been performed.

Concomitant chemotherapy with Xofigo may have additive effects on bone marrow suppression (see section 'Special warnings and precautions for use'). Safety and efficacy of concomitant chemotherapy with Xofigo have not been established.

4.6 Fertility, pregnancy and lactation
4.6.1 Contraception
Animal reproduction studies have not been conducted with Xofigo.
Because of potential effects on spermatogenesis associated with radiation, men should be advised to use effective contraceptive methods during and up to 6 months after treatment with Xofigo.

4.6.2 Pregnancy and lactation
Xofigo is not indicated in women. Xofigo is not to be used in women who are, or may be, pregnant or breast-feeding.

4.6.3 Fertility

There are no human data on the effect of Xofigo on fertility.
Based on studies in animals, there is a potential risk that radiation from Xofigo could cause adverse effects on fertility (see section *Embryotoxicity / Reproduction toxicity*). Male patients should seek advice on conservation of sperm prior to treatment.

4.7 Effects on ability to drive or use machines
There is neither evidence nor is it expected that Xofigo will affect the ability to drive or use machines.

4.8 Undesirable effects
4.8.1 Summary of the safety profile
The overall safety profile of Xofigo is based on data from 600 patients treated with Xofigo in the phase III study.
The most serious adverse drug reactions were thrombocytopenia and neutropenia (see section 'Special warnings and precautions for use' and subsection 'Description of selected adverse reactions' below).
The most frequently observed adverse drug reactions (≥ 10%) in patients receiving Xofigo were diarrhea, nausea, vomiting and thrombocytopenia.

4.8.2 Tabulated list of adverse reactions
The adverse drug reactions observed with Xofigo are represented in the table below (see Table 1). They are classified according to System Organ Class. The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions from clinical trials are classified according to their frequencies.
Frequency groupings are defined according to the following convention:
very common: ≥ 1/10,
common: ≥ 1/100 to < 1/10,
uncommon: ≥1/1,000 to < 1/100
Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in clinical trials in patients treated with Xofigo

System Organ Class (MedDRA)	Very Common	Common	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia	Neutropenia, Pancytopenia, Leukopenia	Lymphopenia
Gastrointestinal disorders	Diarrhea, Vomiting, Nausea		
General disorders and administration site conditions		Injection site reactions	

4.8.3 Description of selected adverse reactions

4.8.3.1 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 section 'Special warnings and precautions for use'). Overall, the frequency of grade 3 and 4 thrombocytopenia was lower in patients that did not previously receive docetaxel (2.8% in patients treated with Xofigo versus 0.8% in patients receiving placebo) compared to patients that 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 that did not previously receive docetaxel (0.8% in patients treated with Xofigo versus 0.8% in patients receiving placebo) compared to patients that 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.

4.8.3.2 Injection site reactions

Grade 1 and 2 injection site reactions, such as erythema, pain and swelling, were reported in 1.2% of patients treated with Xofigo and in 0% of patients receiving placebo.

4.8.3.3 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 have been reported in clinical trials in follow-up of up to three years.

4.9 Overdose

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, general supportive measures, including monitoring for potential hematological and gastrointestinal toxicity should be undertaken.
Single Xofigo doses up to 276 kBq per kg body weight were evaluated in a phase I clinical trial and no dose-limiting toxicities were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various therapeutic radiopharmaceuticals

ATC code: V10XX03

5.1.1 Mechanism of action

Xofigo is a therapeutic alpha particle-emitting pharmaceutical with targeted anti-tumor effect on bone metastases.

The active moiety of Xofigo is the isotope radium-223 (as radium-223 dichloride) that mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. 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 potent and localized anti-tumor effect. The alpha particle range from radium-223 is less than 100 micrometers (less than 10 cell diameters) which minimizes damage to the surrounding normal tissue.

5.1.2 Pharmacodynamic effects

Compared with placebo, there was a significant difference in favor of Xofigo for all five serum biomarkers for bone turnover studied in a phase II 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/ serum C-terminal crosslinked telopeptide of type I collagen [S-CTX-I] and type I collagen crosslinked C-telopeptide [ICTP]).

5.1.3 Clinical efficacy and safety

The clinical safety and efficacy of Xofigo have been evaluated in a double-blind, randomized, multiple dose, phase III, multicenter study (ALSYMPCA; EudraCT. 2007-006195-1) 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. Main secondary endpoints included time to symptomatic skeletal events (SSE), time to progression of total alkaline phosphatase (ALP), time to progression of prostate specific antigen (PSA), response of total ALP and normalization of total ALP. At the cut-off date of the pre-planned interim analysis (confirmatory analysis), a total of 809 patients were randomized 2:1 to receive Xofigo 55 kBq /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 e.g. local external beam radiotherapy, bisphosphonates, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole.
An updated descriptive analysis of safety and of overall survival was performed in 921 randomized patients prior to implementing crossover (i.e. offering patients in the placebo group to receive Xofigo treatment).

Demographic and baseline disease characteristics (interim analysis population) were similar between the Xofigo and placebo groups and are shown below for Xofigo:

- the mean age of patients was 70 years (range 49 to 90 years).
- 87% of patients enrolled had an ECOG performance status score of 0-1.
- 41% received bisphosphonates.
- 42% of patients did not receive prior docetaxel because they were deemed ineligible or refused to receive docetaxel.
- 46% of patients had no pain or WHO scale 1 (asymptomatic or mildly symptomatic) and 54% had pain WHO scale 2-3.
- 16% of patients had <6 bone metastases, 44% of patients had between 6 and 20 bone metastases, 40% of patients had more than 20 bone metastases or superscan.

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

The results of both interim and updated 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 2, Figure 1). A higher rate of non-prostate cancer related deaths was observed in the placebo group (26/541, 4.8% in the Xofigo arm compared to 23/268, 8.6% in the placebo arm).

Table 2: Survival results from the phase III ALSYMPCA study

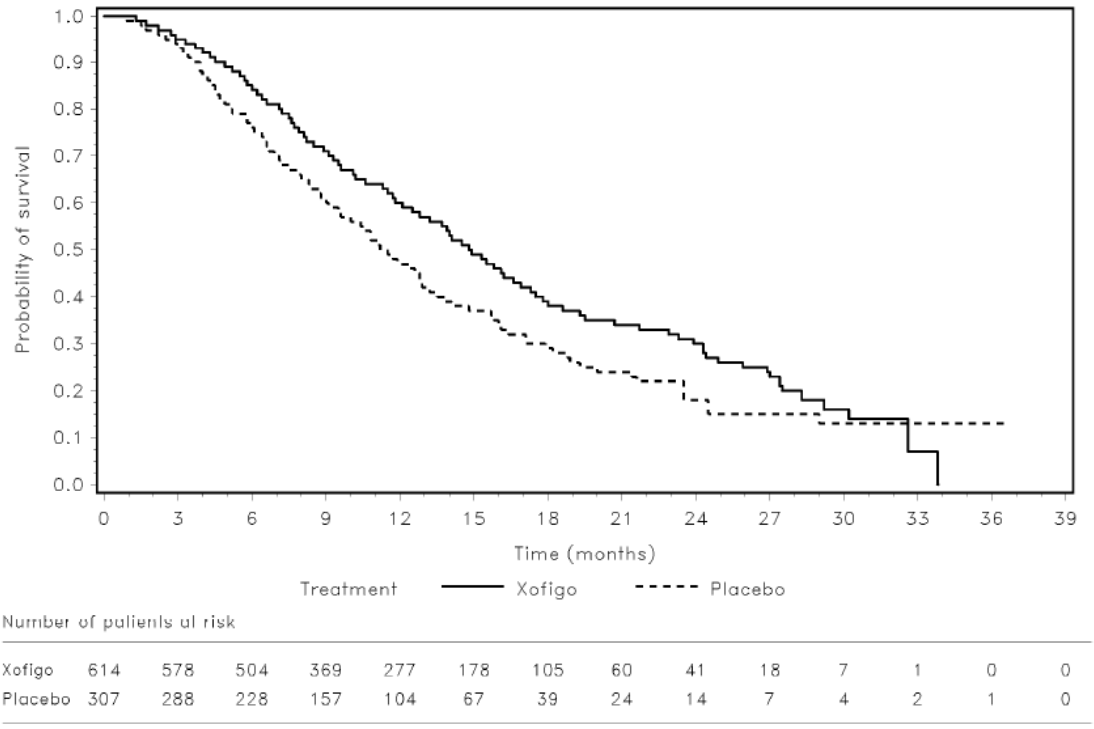
	Xofigo	**Placebo**
Interim analysis	N = 541	N = 268
Number (%) of deaths	191 (35.3%)	123 (45.9%)
Median overall survival (months) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
Hazard ratio[b] (95% CI)	0.695 (0.552 – 0.875)	
p-value[a] (2-sided)	0.00185	
Updated analysis	N = 614	N = 307
Number (%) of deaths	333 (54.2%)	195 (63.5%)
Median overall survival (months) (95% CI)	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)
Hazard ratio[b] (95% CI)	0.695 (0.581 – 0.832)	

CI = confidence interval

[a] The Phase 3 study ALSYMPCA was stopped for efficacy after the interim analysis. As the updated analysis is provided for descriptive purposes only, a p-value is not provided.

[b] Hazard ratio (Xofigo over placebo) < 1 favours Xofigo.

Figure 1: Kaplan-Meier overall survival curves (updated analysis)



The results of the interim analysis and the updated analysis also showed a significant improvement in all main secondary endpoints in the Xofigo arm compared to the placebo arm (see Table 3). Time to event data on ALP progression were supported by statistically significant advantage with respect to ALP normalisation and ALP responses at week 12.

Table 3: Secondary efficacy endpoints from the phase III ALSYMPCA study (interim analysis)

			Incidence [no. (%) of patients]		**Time-to-event analysis** (95% CI) [median no. of months]			
			Xofigo N = 614	**Placebo** N = 307	**Xofigo** N = 614	**Placebo** N = 307	**Hazard ratio** < 1 favours Xofigo	**p-value**
Symptomatic skeletal event (SSE)	**SSE composite endpoint** [a]		132 (24.4%)	82 (30.6%)	13.5 (12.2 – 19.6)	8.4 (7.2 – NE)[b]	0.610 (0.461 – 0.807)	0.00046
	SSE components	**External beam radiation for pain relief**	122 (22.6%)	72 (26.9%)	17.0 (12.9 – NE)	10.8 (7.9 – NE)	0.649 (0.483 – 0.871)	0.00375
		Spinal cord compression	17 (3.1%)	16 (6.0%)	NE	NE	0.443 (0.223 – 0.877)	0.01647
		Surgical intervention	9 (1.7%)	5 (1.9%)	NE	NE	0.801 (0.267 – 2.398)	0.69041
		Bone fractures	20 (3.7%)	18 (6.7%)	NE	NE	0.450 (0.236 – 0.856)	0.01255
Total ALP progression [c]			79 (14.6%)	116 (43.3%)	NE	3.7 (3.5 – 4.1)	0.162 (0.120 – 0.220)	< 0.00001
PSA progression [d]			288 (53.2%)	141 (52.6%)	3.6 (3.5 – 3.7)	3.4 (3.3 – 3.5)	0.671 (0.546 – 0.826)	0.00015

ALP = alkaline phosphatase; CI = confidence interval; NE = not estimable; PSA = prostate-specific antigen; SSE = symptomatic skeletal event

a Defined as occurrence of any of the following: external beam radiotherapy to relieve pain, or pathologic fracture, or spinal cord compression, or tumor-related orthopedic surgical intervention.

b not estimable owing to insufficient events after the median

c Defined as ≥ 25% increase compared to baseline/nadir.

d Defined as a ≥ 25% increase and an increase in absolute value of ≥ 2 ng/mL compared to baseline/nadir.

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.

Quality of life

Health Related Quality of Life (HRQOL) was assessed in the phase III ALSYMPCA study using specific questionnaires: the EQ-5D (generic instrument) and the FACT-P (prostate cancer specific instrument). Both groups experience a loss of quality of life. Relative to placebo, the decline in quality of life was slower for Xofigo during the on-treatment period as measured by EQ-5D utility index score (-0.040 versus -0.109; p=0.001), EQ-5D self-reported Visual Analogue health status scores (VAS) (-2.661 versus -5.860; p=0.018) and the FACT P total score (-3.880 versus -7.651, p=0.006) but did not reach published minimally important differences. There is limited evidence that the delay in loss of HRQOL extends beyond the treatment period.

Pain relief

The results from the phase III ALSYMPCA study regarding time to external beam radiation therapy (EBRT) for pain relief and fewer patients reporting bone pain as an adverse event in the Xofigo group indicate a positive effect on bone pain.

Subsequent treatment with cytotoxic substances

In the course of the 2:1 randomised ALSYMPCA study, 93 (15.5%) patients in the Xofigo group and 54 (17.9%) patients in the placebo group received cytotoxic chemotherapy at varying times after the last treatment. No differences in hematological laboratory values were apparent between the two groups.

5.2 Pharmacokinetic properties

5.2.1 General introduction

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 (0.00138 to 0.00746 mCi)/kg. Pharmacokinetic, biodistribution and dosimetry data was obtained in 6 patients at a dose of 110 kBq (0.00297 mCi)/kg given twice, 6 weeks apart, and in 10 patients at a dose of 55 (0.00149 mCi), 110 (0.00297 mCi) or 221 kBq (0.00597 mCi)/kg.

5.2.2 Absorption

Xofigo is administered as an intravenous injection and is thus 100% bioavailable.

5.2.3 Distribution and organ uptake

After intravenous injection, radium-223 is rapidly cleared from the blood and is incorporated 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. At 4 hours post injection, the mean 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.

5.2.4 Metabolism / Biotransformation

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

5.2.5 Elimination

Fecal excretion is the major route of elimination from the body. About 5% is excreted in the urine and there is no evidence of hepato-biliary excretion.

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-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.

5.2.6 Linearity / Non-linearity

The pharmacokinetics of radium-223 dichloride was linear in the dose range investigated (51 to 276 kBq (0.00138 to 0.00746 mCi)/kg).

5.2.7 Cardiac Electrophysiology / QT prolongation

No significant QTc prolonging effects were observed after intravenous injection of Xofigo in comparison with placebo in a subgroup of 29 patients in the phase III study (ALSYMPCA).

5.3 Preclinical safety data

5.3.1 Systemic toxicity

In single and repeated dose toxicity studies in rats, the main findings were reduced body weight gain, hematological changes, 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 (0.00059- 0.00238 mCi) per kg body weight, with the exception of body weight decreases.

Dose-limiting myelotoxicity was seen in dogs after single administration of 497 kBq (0.0134 mCi) radium-223 dichloride per kg body weight (9 times the clinically recommended dose).

After repeated administration of the clinically recommended dose of 55 kBq per kg body weight once every 4 weeks for 6 months, two dogs developed non-displaced pelvic fractures. Due to the presence of osteolysis of trabecular bone in other bone locations of treated animals in varying degree, a spontaneous fracture in the context of osteolysis cannot be excluded. The clinical relevance of these findings is unknown.

Retinal detachment was seen in dogs after a single injection of doses of 166 and 497 kBq (0.00449 and 0.0134 mCi) 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 (0.00149 mCi) per kg body weight once every 4 weeks for 6 months. Radium is specifically taken up in the *tapetum lucidum* of the canine eye. 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 Xofigo. The risk for patients to develop osteosarcomas with exposure to radium-223 is unknown at present. 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 section ‘Undesirable effects/Secondary malignant neoplasms’).

5.3.2 Embryotoxicity / Reproduction toxicity

Studies on reproductive and developmental toxicity have not been performed. In general, radionuclides induce reproductive and developmental effects.

A minimal number of abnormal spermatocytes were seen in a few seminiferous tubules in the testes of male rats after a single administration of ≥ 2270 kBq/kg body weight radium-223 dichloride (≥ 41 times the clinically recommended activity). The testes seemed to otherwise be functioning normally and the epididymides revealed a normal content of spermatocytes. Uterine polyps (endometrial stroma) were observed in female rats after single or repeated administration of ≥ 359 kBq/kg body weight radium-223 dichloride (≥ 6.5 times the clinically recommended activity).

Since radium-223 distributes mainly 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 section ‘Fertility, pregnancy and lactation’).

5.3.3 Genotoxicity / Carcinogenicity

Studies on the mutagenic and carcinogenic potential of Xofigo have not been performed.

5.3.4 Safety pharmacology

No significant effects were seen on vital organ systems, i.e. cardiovascular (dog), respiratory or central nervous systems (rat), after single dose administration of 497 to 1100 kBq (0.0134 to 0.0297 mCi) per kg body weight (9 [dog] to 20 [rat] times the clinically recommended dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium chloride
Sodium citrate
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, Xofigo must not be mixed with other medicinal products.

6.3 Shelf life

28 days.

6.4 Special precautions for storage

Storage of Xofigo should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Vial with fill volume of 6 mL

6.6 Instructions for use / handling

6.6.1 General instructions

Xofigo (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.

6.6.2 Radiation protection

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

6.6.3 Instructions for preparation
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.
The volume to be administered to a given patient should be calculated using the:

- Patient's body weight (kg)
- Dosage level (55 kBq/kg body weight)
- Radioactivity concentration of the product (1100 kBq/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. A table of DK factors is provided for each vial.

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

$$\textbf{Volume to be administered (mL)} = \frac{\textbf{Body weight (kg)} \times \textbf{dose (55 kBq /kg body weight)}}{\textbf{DK factor} \times \textbf{1100 kBq/mL}}$$

6.6.4 Dosimetry
The absorbed radiation dose calculation was performed based on clinical biodistribution data. Calculations of absorbed doses were performed using OLINDA/EXM (**O**rgan **L**evel **In**ternal **D**ose **A**ssessment/**EX**ponential **M**odeling), a software based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For radium-223, as primarily an alpha emitter, additional assumptions were made for the intestine, red marrow and bone/osteogenic cells, to provide the best possible absorbed dose calculations for Xofigo, considering its observed biodistribution and specific characteristics.

For an administered activity of 4.02 MBq (55 kBq per kg body weight to a 73-kg adult) the calculated absorbed doses to the bone (osteogenic cells) is 4.6255 Gy and to the red marrow is 0.5572 Gy. The calculated absorbed doses to the main excretory organs are 0.0292 Gy for the small intestine wall, 0.1298 Gy for the upper large intestine wall and 0.1865 Gy for the lower large intestine wall.

The calculated absorbed doses to other organs are low, e.g. heart wall (0.0069 Gy), lung (0.0048 Gy), liver (0.0119 Gy), kidneys (0.0129 Gy), urinary bladder wall (0.0162 Gy), testes (0.0003 Gy), and spleen (0.0004 Gy).

The hematological adverse drug reactions observed in the clinical studies with Xofigo are much lower in frequency and severity than what could be expected from the calculated absorbed doses to the red marrow. This may be related to spatial distribution of alpha particle radiation resulting in non-uniform radiation dose to the red marrow.

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[i] Nilsson S et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. The Lancet Oncology 2007; 8(7): 587-594

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Date of revision: 1 Nov 2019

DECAY CORRECTION TABLES FOR RADIUM-223

Bayer Health Care

Global Chemical and Pharmaceutical Development

Changes due to daylight savings are not included in this table as the changes of

1 hour is not considered significant for a radionuclide with an 11.4 day half-life.

Hong Kong/ Singapore/Malaysia

12 noon Hong Kong / Singapore/Malaysia Time

Standard Time (HKT / SST/ MYT)

Day from reference date	Physical decay factor
-14	2.38
-13	2.24
-12	2.11
-11	1.98
-10	1.87
-9	1.76
-8	1.65
-7	1.56
-6	1.46
-5	1.38
-4	1.30
-3	1.22
-2	1.15
-1	1.08

0	**1.02**
1	**0.96**
2	**0.90**
3	**0.85**
4	**0.80**
5	**0.75**
6	**0.71**
7	**0.67**
8	**0.63**
9	**0.59**
10	**0.56**
11	**0.52**
12	**0.49**
13	**0.46**
14	**0.44**