ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Xofigo 1100 kBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

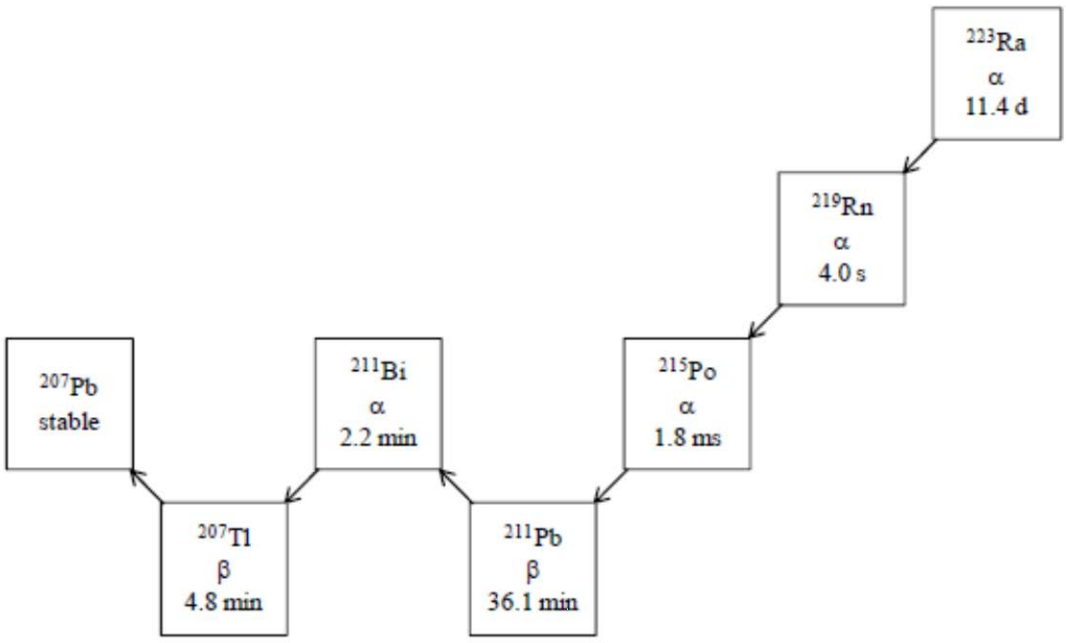
Each mL of solution contains 1100 kBq radium Ra 223 dichloride (radium-223 dichloride), corresponding to 0.58 ng radium-223 at the reference date. Radium is present in the solution as a free ion.

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).

Figure 1: Radium-223 decay chain with physical half-lives and mode of decay:



Excipients with known effect
Each mL of solution contains 0.194 mmol (equivalent to 4.5 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless isotonic solution with pH between 6.0 and 8.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Xofigo should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

Posology

The dose regimen of Xofigo is an activity of 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 12.

Elderly
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.

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.

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 for patients with moderate (CLCR: 30 to 50 mL/min) renal impairment. No data are available for patients with severe (CLCR < 30 mL/min) renal impairment or 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.

Method of administration

Xofigo is for intravenous use. It must be administered by slow injection (generally up to 1 minute).

The intravenous access line or cannula must be flushed with isotonic sodium chloride 9 mg/mL (0.9%) solution for injection before and after injection of Xofigo.

For additional instructions on the use of the medicinal product, see sections 6.6 and 12.

4.3 Contraindications

There are no known contraindications to the use of Xofigo.

4.4 Special warnings and precautions for use

Bone marrow suppression

Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with Xofigo (see section 4.8).

Therefore, haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/l, the platelet count $\geq 100 \times 10^9$/l and haemoglobin ≥ 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 only be continued after a careful benefit/risk evaluation.

Patients with evidence of compromised bone marrow reserve e.g. following prior cytotoxic chemotherapy and/or radiation treatment (EBRT) or prostate cancer patients with advanced diffuse infiltration of the bone (EOD4; "superscan") should be treated with caution. An increased incidence of haematological adverse reactions such as neutropenia and thrombocytopenia was observed in these patients during the phase III study (see section 4.8).

The efficacy and safety of cytotoxic chemotherapy performed after treatment with Xofigo has not been established. The limited available data indicates that patients receiving chemotherapy after Xofigo had a similar haematological profile compared to patients receiving chemotherapy after placebo (see also section 5.1).

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.

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.

Bone fractures

In patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo.

Osteonecrosis of the jaw

In patients treated with bisphosphonates and Xofigo, an increased risk of development of osteonecrosis of the jaw (ONJ) cannot be excluded. In the phase III study, cases of ONJ have been reported in 0.67% patients (4/600) in the Xofigo arm compared to 0.33% patients (1/301) in the placebo arm. However, all patients with

ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid) and prior chemotherapy (e.g. docetaxel).

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.

Gastrointestinal toxicity

Xofigo increases the incidence of diarrhoea, nausea, and vomiting (see section 4.8) which may result in dehydration. Oral intake and fluid status of patients should be carefully monitored. Patients should be advised to seek medical advice if they experience severe or persistent diarrhoea, nausea, vomiting. Patients who display signs or symptoms of dehydration or hypovolemia should be promptly treated.

Excipients with known effect

Depending on the volume administered, this medicinal product can contain up to 2.35 mmol (54 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed.

As interactions with calcium and phosphate cannot be excluded, pausing supplementation with these substances and/or Vitamin D should be considered some days before starting with Xofigo treatment.

Concomitant chemotherapy with Xofigo may have additive effects on bone marrow suppression (see section 4.4). Safety and efficacy of concomitant chemotherapy with Xofigo have not been established.

4.6 Fertility, pregnancy and lactation

Contraception in males

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.

Pregnancy and breast-feeding

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

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 5.3). Male patients should seek advice on conservation of sperm prior to treatment.

4.7 Effects on ability to drive and 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

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 frequently** observed adverse reactions (≥ 10%) in patients receiving Xofigo were diarrhoea, nausea, vomiting and thrombocytopenia.

The **most serious** adverse reactions were thrombocytopenia and neutropenia (see section 4.4 and 'Description of selected adverse reactions' below).

Tabulated list of adverse reactions

The adverse 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 reactions from clinical trials are classified according to their frequencies. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse 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	Diarrhoea, Vomiting, Nausea		
General disorders and administration site conditions		Injection site reactions	

Description of selected adverse reactions

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 4.4). 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). In EOD4 ("superscan") patients, thrombocytopenia (all grades) was reported in 19.6% of patients treated with Xofigo and in 6.7% of patients receiving placebo. Grade 3 and 4 thrombocytopenia was observed in 5.9% of patients treated with Xofigo and in 6.7% of patients receiving placebo (see section 4.4).

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.

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.

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. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 haematological and gastrointestinal toxicity should be undertaken.

Single Xofigo doses containing an activity of 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

Mechanism of action

Xofigo is a therapeutic alpha particle-emitting pharmaceutical.

Its active moiety radium-223 (as radium-223 dichloride) 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/µm) leads to a high frequency of double-strand DNA breaks in adjacent tumour cells, resulting in a potent cytotoxic effect. Additional effects on the tumour microenvironment including osteoblasts and osteoclasts also contribute to the *in vivo* efficacy. The alpha particle range from radium-223 is less than 100 µm (less than 10 cell diameters) which minimises damage to the surrounding normal tissue.

Pharmacodynamic effects

Compared with placebo, there was a significant difference in favour of Xofigo for all five serum biomarkers for bone turnover studied in a phase II randomised 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]).

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).

Clinical efficacy and safety

The clinical safety and efficacy of Xofigo have been evaluated in a double-blind, randomised, multiple dose, phase III, multicentre 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 normalisation of total ALP.

At the cut-off date of the pre-planned interim analysis (confirmatory analysis), a total of 809 patients were randomised 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, oestrogens, estramustine or ketoconazole.

An updated descriptive analysis of safety and of overall survival was performed in 921 randomised 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 luteinising hormone-releasing hormone (LHRH) agonists and 21% of patients received anti-androgens concomitantly.

The results of both the 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 and Figure 2). 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

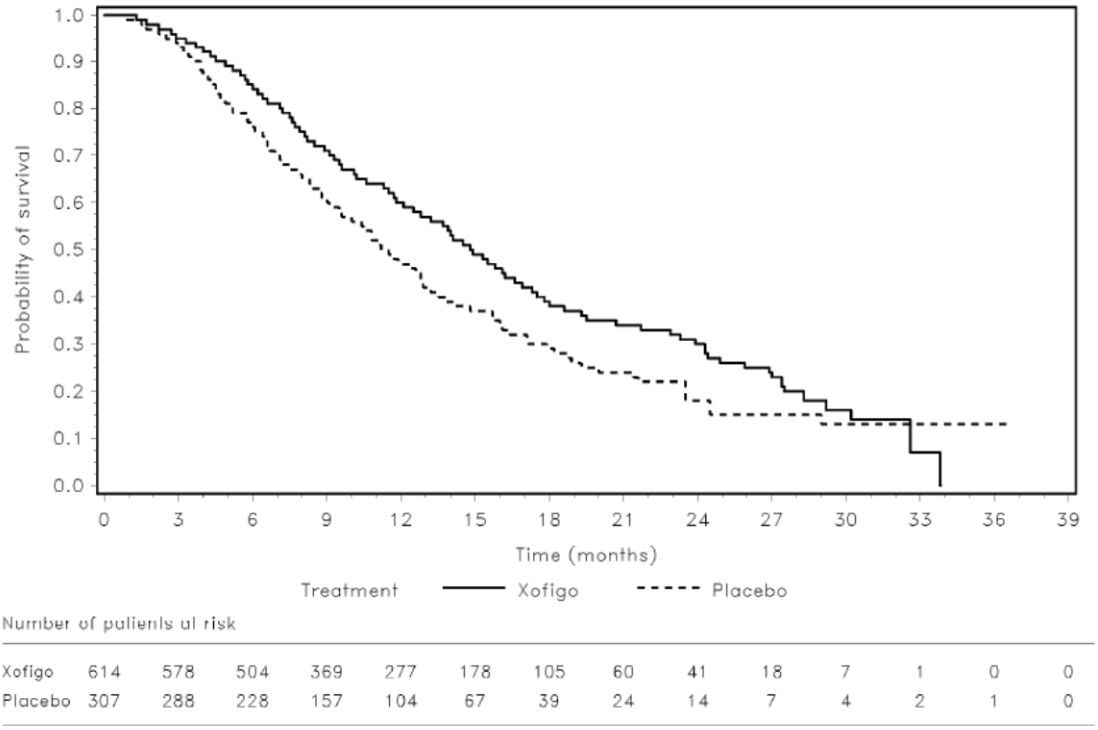
	Xofigo	Placebo
Interim analysis	N = 541	N = 268
Number (%) of deaths	191 (35.3%)	123 (45.9%)
Median overall survival (months) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
Hazard ratio[b] (95% CI)	0.695 (0.552 – 0.875)	
p-value[a] (2-sided)	0.00185	
Updated analysis	N = 614	N = 307
Number (%) of deaths	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 2: 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 = 541	**Placebo** N = 268	**Xofigo** N = 541	**Placebo** N = 268	**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 ALSYPMCA 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 haematological laboratory values were apparent between the two groups.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xofigo in all subsets of the paediatric population in prostate carcinoma (excluding rhabdomyosarcoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

General introduction

Pharmacokinetic, biodistribution and dosimetry data have been obtained from 3 phase I studies. Pharmacokinetic data were obtained in 25 patients at activities ranging from 51 to 276 kBq/kg. Pharmacokinetic, biodistribution and dosimetry data were obtained in 6 patients at an activity of 110 kBq/kg given twice, 6 weeks apart, and in 10 patients at an activity of 55, 110 or 221 kBq/kg.

Absorption

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

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.

Biotransformation

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

Elimination

Faecal excretion is the major route of elimination from the body. About 5% is excreted in the urine and there is no evidence of hepatobiliary 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.

Linearity/non-linearity

The pharmacokinetics of radium-223 dichloride were linear in the activity range investigated (51 to 276 kBq/kg).

Paediatric population

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

5.3 Preclinical safety data

Systemic toxicity

In single and repeated dose toxicity studies in rats, the main findings were reduced body weight gain, haematological changes, reduced serum alkaline phosphatase and microscopic findings in the bone marrow (depletion of haematopoietic cells, fibrosis), spleen (secondary extra-medullary haematopoiesis) and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganisation of the physis/growth line). These findings were related to radiation-induced impairment of haematopoiesis and a reduction of osteogenesis and started at the lowest activity of 22 kBq per kg body weight (0.4 times the clinically recommended dose).

In dogs, haematological changes were observed starting at the lowest activity of 55 kBq/kg, the clinically recommended dose. Dose-limiting myelotoxicity was seen in dogs after single administration of 497 kBq radium-223 dichloride per kg body weight (9 times the clinically recommended activity).

After repeated administration of the clinically recommended activity 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 activities of 166 and 497 kBq per kg body weight (3 and 9 times the clinically recommended dose), but not after repeated administration of the clinically recommended activity of 55 kBq per kg body weight once every 4 weeks for 6 months. The exact mechanism for induction of retinal detachment is unknown, but literature data suggests that 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 (see section 4.8).

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 4.6).

Genotoxicity / Carcinogenicity

Studies on the mutagenic and carcinogenic potential of Xofigo have not been performed. In general, radionuclides are considered to be genotoxic and carcinogenic.

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 activities from 497 to 1100 kBq per kg body weight (9 [dog] to 20 [rat] times the clinically recommended activity).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium citrate
Sodium chloride
Hydrochloric acid, dilute

6.2 Incompatibilities

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

6.3 Shelf life

28 days.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Storage of Xofigo should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Colourless Type I glass vial closed with a grey bromobutyl rubber stopper with foil-clad made of Ethylene tetrafluoroethylene (ETFE) and aluminium seal, containing 6 mL of solution for injection.

The vial is stored in a lead pot.

6.6 Special precautions for disposal and other handling

General warnings

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organisation.

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

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 radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, faeces, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Care should be used when handling materials, such as bed linen, that come into contact with such body fluids. 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 minimisation of radiation exposure, it is recommended to minimise the time spent in radiation areas, to maximise the distance to radiation sources, and to use adequate shielding.

Any unused product or waste materials should be disposed of in accordance with local regulations.
Any materials used in connection with the preparation or administration of Xofigo are to be treated as radioactive waste.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/873/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 2013

10. DATE OF REVISION OF THE TEXT

11. 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 (see Table 4).

Table 4: Calculated absorbed radiation doses to organs

Target Organ	Alpha[1] emission (Gy/MBq)	Beta emission (Gy/MBq)	Gamma emission (Gy/MBq)	Total dose (Gy/MBq)	Coefficient of variation (%)
Adrenals	0.00000	0.00002	0.00009	0.00012	56
Brain	0.00000	0.00002	0.00008	0.00010	80
Breasts	0.00000	0.00002	0.00003	0.00005	120
Gallbladder wall	0.00000	0.00002	0.00021	0.00023	14
LLI[2] Wall	0.00000	0.04561	0.00085	0.04645	83
Small intestine wall	0.00319	0.00360	0.00047	0.00726	45
Stomach wall	0.00000	0.00002	0.00011	0.00014	22
ULI[3] wall	0.00000	0.03149	0.00082	0.03232	50
Heart wall	0.00161	0.00007	0.00005	0.00173	42
Kidneys	0.00299	0.00011	0.00011	0.00321	36
Liver	0.00279	0.00010	0.00008	0.00298	36
Lungs	0.00109	0.00007	0.00005	0.00121	--[4]
Muscle	0.00000	0.00002	0.00010	0.00012	41
Ovaries	0.00000	0.00002	0.00046	0.00049	40
Pancreas	0.00000	0.00002	0.00009	0.00011	43
Red marrow	0.13217	0.00642	0.00020	0.13879	41
Osteogenic cells	1.13689	0.01487	0.00030	1.15206	41
Skin	0.00000	0.00002	0.00005	0.00007	79
Spleen	0.00000	0.00002	0.00007	0.00009	54
Testes	0.00000	0.00002	0.00006	0.00008	59
Thymus	0.00000	0.00002	0.00003	0.00006	109
Thyroid	0.00000	0.00002	0.00005	0.00007	96
Urinary bladder wall	0.00371	0.00016	0.00016	0.00403	63
Uterus	0.00000	0.00002	0.00023	0.00026	28
Whole body	0.02220	0.00081	0.00012	0.02312	16

[1]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.
[2]LLI: lower large intestine
[3]ULI: upper large intestine
[4]Absorbed dose data to the lung are based on model-derived calculation using pooled blood time-activity data from all subjects

The haematological adverse 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.

12. INSTRUCTION FOR PREPARATION OF RADIOPHARMACEUTICALS

This medicinal product should be visually inspected before use. Xofigo is a clear, colourless solution and should not be used in case of discolouration, 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 other 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 pot label.
- Decay correction (DK) factor to correct for physical decay of radium-223. A table of DK factors is provided with each vial as part of the booklet (preceding the package leaflet).

The amount of radioactivity in the dispensed volume shall be confirmed by measurement in a properly calibrated activimeter.

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

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer AS
Drammensveien 288,
NO-0283 Oslo,
Norway.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LEAD POT

1. NAME OF THE MEDICINAL PRODUCT

Xofigo 1100 kBq/mL solution for injection
Radium Ra 223 dichloride

2. STATEMENT OF ACTIVE SUBSTANCE

Radium Ra 223 dichloride

3. LIST OF EXCIPIENTS

Water for injections, sodium citrate, sodium chloride, hydrochloric acid. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
6 mL
1100 kBq/mL at 12 h (CET) ref. date: [DD/MM/YYYY]
6.6 MBq/vial at 12 h (CET) ref. date: [DD/MM/YYYY]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

[Bayer logo]

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/873/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xofigo 1100 kBq/mL solution for injection
Radium Ra 223 dichloride
For intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 mL
6.6 MBq/vial at 12 h (CET) ref. date: [DD/MM/YYYY]

6. OTHER

[Bayer logo]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xofigo 1100 kBq/mL solution for injection

Radium Ra 223 dichloride

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor who will supervise the procedure.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Xofigo is and what it is used for

This medicine contains the active substance radium Ra 223 dichloride (radium-223 dichloride).

Xofigo is used to treat adults with advanced castration-resistant prostate cancer. This is a cancer of the prostate (a gland of the male reproductive system) that does not respond to treatment that reduces male hormones. Xofigo is only used when the disease has spread to the bone but is not known to have spread to other internal organs, and is causing symptoms (e.g. pain).

Xofigo contains the radioactive substance radium-223 which mimics the calcium found in bones. When injected into the patient, radium-223 reaches the bone where the cancer has spread to and emits short-range radiation (alpha particles) which kills the surrounding tumour cells.

2. What you need to know before Xofigo is used

Xofigo must not be given

There are no known conditions in which you must not be given Xofigo.

Warnings and precautions
Talk to your doctor before you are given Xofigo

- Xofigo can lead to a decrease in the number of your blood cells and blood platelets. **Before starting treatment and before each subsequent dose your doctor will perform blood tests.** Depending on the results of these tests your doctor will decide if treatment can be started, can be continued, or needs to be postponed or discontinued.
- If you suffer from **decreased blood cell production in the bone marrow,** e.g. if you have received prior chemotherapy (other medicines used to kill cancer cells) and/or radiation therapy, you may be at higher risk and your doctor will give you Xofigo with caution**.**
- If your tumour has spread to the bone extensively, you may also be more likely to have decreases in your blood cells and platelets, so your doctor will give you Xofigo with caution.
- The limited data available do not suggest any major differences in the blood cell production of patients receiving chemotherapy after treatment with Xofigo compared with those who did not receive Xofigo.
- If you suffer from untreated **spinal cord compression** or if it is thought likely that you are developing spinal cord compression (pressure on the spinal cord nerves 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.
- If you experience a **bone fracture**, your doctor will first stabilise the fractured bone before starting or continuing treatment with Xofigo.
- There are no data on the use of Xofigo in patients with **Crohn's disease** (a long-term inflammatory disease of the intestines) and with **ulcerative colitis** (a long-term inflammation of the colon). As Xofigo is excreted in the faeces, it may make acute inflammation of your bowels worse. Therefore, if you suffer from these conditions your doctor will carefully consider if you can be treated with Xofigo.
- If you take or have taken bisphosphonates or have received chemotherapy prior to treatment with Xofigo, please tell your doctor. A risk of *osteonecrosis of the jaw* (dead tissue in the jaw bone which is mainly seen in patients who have been treated with bisphosphonates) cannot be excluded (see section 4).
- Xofigo contributes to your overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may increase your risk for developing cancer (in particular of bone cancer and leukaemia) and hereditary abnormalities. No cases of cancer caused by Xofigo have been reported in clinical trials with a follow-up of up to three years.

Children and adolescents
This medicine is not for use in children and adolescents.

Other medicines and Xofigo
No interaction studies with other medicinal products have been done.

If you are taking calcium, phosphate and/or Vitamin D, your doctor will carefully consider if you need to temporarily stop taking these substances before you start treatment with Xofigo.

There are no data on the **use of Xofigo at the same time as chemotherapy** (other medicines used to kill cancer cells). Xofigo and chemotherapy used together may further decrease the number of your blood cells and blood platelets.

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

Pregnancy and breast-feeding
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.

Contraception in males and females
If you are engaged in sexual activity with a woman who could become pregnant you are advised to use effective birth control methods during and up to 6 months after treatment with Xofigo.

Fertility
There is a potential risk that radiation from Xofigo could affect your fertility. Please ask your doctor how this may affect you, especially if you are planning to have children in the future. You may wish to seek advice on conservation of sperm before treatment starts.

Driving and using machines
It is considered unlikely that Xofigo will affect your ability to drive or to use machines.

Xofigo contains sodium
Depending on the volume administered, this medicine can contain up to 54 mg of sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. How Xofigo is used

There are strict laws on the use, handling and disposal of medicines 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.

The dose you receive depends on your body weight. The doctor supervising the procedure will calculate the quantity of Xofigo to be used in your case.
The recommended dose of Xofigo is 55 kBq (Becquerel, the unit used to express radioactivity) per kilogram body weight.
No dose adjustment is necessary if you are 65 years of age or older or if you have reduced kidney or liver function.

Administration of Xofigo and conduct of the procedure
Xofigo will be injected slowly via a needle into one of your veins (intravenously). The healthcare professional will flush the intravenous access line or cannula before and after injection with a saline solution.

Duration of the procedure
- Xofigo is given once every 4 weeks for a total of 6 injections.
- There are no data available on the safety and efficacy of treatment with more than 6 injections of Xofigo.

After administration of Xofigo
- Care should be taken when handling materials, such as bed linen, that come into contact with body fluids (such as spill of urine, faeces, vomiting etc.). Xofigo is excreted mainly via the faeces. The doctor will tell you if you need to take any special precautions after receiving this medicine. Contact your doctor if you have any questions.

If you have been given more Xofigo than you should
An overdose is unlikely.
However, in the case of an accidental overdose, your doctor will start appropriate supportive treatment and will check you for changes in the number of blood cells, and for gastrointestinal symptoms (e.g. diarrhoea, nausea [feeling sick], vomiting).

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effects in patients receiving Xofigo are
- **decrease in the number of blood platelets** (thrombocytopenia),
- **decrease in the number of neutrophils, a type of white blood cells** (neutropenia, which may lead to an increased risk of infection).

Your doctor will perform blood tests before starting treatment and before each injection to check your number of blood cells and platelets (see also section 2).

Contact your doctor immediately if you notice the following symptoms as they may be signs of thrombocytopenia or neutropenia (see above):
- any **unusual bruising**,
- more **bleeding** than usual after injury,
- **fever**,
- or if you seem to be catching a lot of **infections.**

The most frequent side effects in patients receiving Xofigo (very common [may affect more than 1 in 10 people]) are:
- **diarrhoea, nausea (feeling sick), vomiting and thrombocytopenia (decrease in the number of blood platelets)**.

Risk of dehydration: tell your doctor if you have any of the following symptoms: dizziness, increased thirst, decreased urination or dry skin as these can all be symptoms of dehydration. It is important to avoid dehydration by drinking plenty of fluids.

Other possible side effects are listed below by how likely they are:

Common (may affect up to 1 in 10 people)
- decrease in the number of white blood cells (leukopenia)
- decrease in the number of neutrophils, a type of white blood cells (neutropenia, which may lead to an increased risk of infection)
- decrease in the number of red and white blood cells and blood platelets (pancytopenia)
- injection site reactions (e.g. redness of the skin [erythema], pain and swelling)

Uncommon (may affect up to 1 in 100 people)
- decrease in the number of lymphocytes, a type of white blood cells (lymphopenia)

Xofigo contributes to your overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may increase your risk of developing cancer (in particular of bone cancer and leukaemia) and hereditary abnormalities. No cases of cancer caused by Xofigo have been reported in clinical trials with a follow-up of up to three years.

If you have symptoms of pain, swelling or numbness of the jaw, a “heavy jaw feeling” or loosening of a tooth, please contact your doctor. Cases of *osteonecrosis of the jaw* (dead tissue in the jaw bone which is mainly seen in patients who have been treated with bisphosphonates) have occurred in patients treated with Xofigo. All these cases were only seen in patients receiving bisphosphonates prior to or at the same time of treatment with Xofigo and chemotherapy prior to treatment with Xofigo.

Reporting of side effects
If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How Xofigo is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulations on radioactive materials.

The following information is intended for the specialist only:
Xofigo must not be used after the expiry date which is stated on the vial and the lead pot.
This medicinal product does not require any special temperature storage conditions.
Xofigo must not be used if discolouration, the occurrence of particulate matter or a defective container is noticed.

6. Contents of the pack and other information

What Xofigo contains

- The **active substance** is: radium Ra 223 dichloride (radium-223 dichloride).

  Each mL of solution contains 1100 kBq radium-223 dichloride, corresponding to 0.58 ng radium-223 at the reference date.

  Each vial contains 6 mL of solution (6600 kBq radium-223 dichloride at the reference date).

- The **other ingredients** are: water for injections, sodium citrate, sodium chloride and hydrochloric acid (see end of Section 2 for further information on sodium).

What Xofigo looks like and contents of the pack

Xofigo is a clear and colourless solution for injection. It is supplied in a colourless glass vial closed with a grey bromobutyl rubber stopper with foil-clad and aluminium seal. The vial contains 6 mL of solution. It is stored in a lead pot.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AS
Drammensveien 288,
NO-0283 Oslo,
Norway.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België / Belgique / Belgien
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11

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Байер България ЕООД
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This booklet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only

The complete SmPC of Xofigo is provided as a tear-off section at the end of the printed leaflet in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions
Taking into account the PRAC Assessment Report on the PSUR(s) for radium-223 dichloride, the scientific conclusions of CHMP are as follows:

The MAH has provided an extensive review of the data from clinical trials and post-marketing settings regarding the possible role of Xofigo in dehydration. Although the data are not supportive of a direct causal correlation, the relationship between potential dehydration and prolonged bouts of vomiting and diarrhoea is well characterised. Based on this outcome, section 4.4 of the SmPC is updated with precautionary wording regarding the risk of dehydration.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC Rapporteur considered that changes to the product information of medicinal products containing Radium-223 dichloride were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for radium-223 dichloride the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing radium-223 dichloride is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.