1. NAME OF THE MEDICINAL PRODUCT

Xofigo 1100 kBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

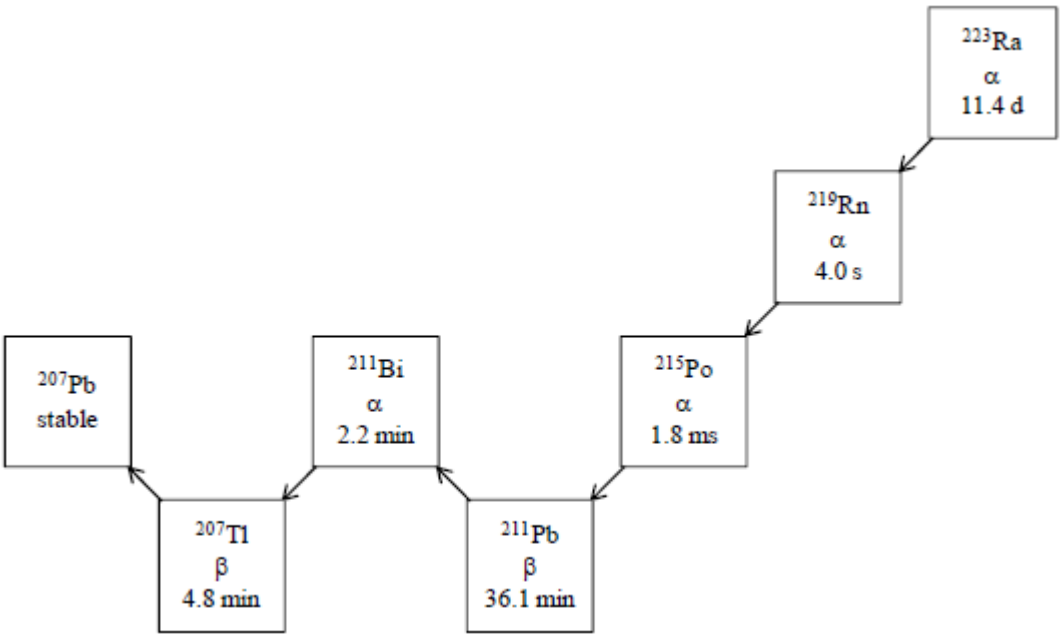
Each mL of solution contains 1100 kBq radium Ra 223 dichloride (radium-223 dichloride), corresponding to 0.58 ng radium-223 at the reference date. Radium is present in the solution as a free ion.

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 monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for advanced PC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment (see section 4.4).

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 10.

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 10.

4.3 Contraindications

Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone (see section 4.4).

4.4 Special warnings and precautions for use

Combination with abiraterone and prednisone/prednisolone or with systemic cancer therapies other than LHRH analogues

An interim analysis from a clinical trial in chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration resistant prostate cancer and progressive disease with bone metastases showed an increased risk of fractures and a trend for increased mortality among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone (see section 5.1).
Therefore, Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone (see section 4.3).

Safety and efficacy of Xofigo in combination with cancer therapies other than LHRH analogues have not been established; an increased risk of mortality and fractures is possible. The combination of radium-223 with other systemic cancer therapies other than LHRH analogues is therefore not recommended.

Data on a safe period after which Xofigo can be administered following treatment with abiraterone acetate in combination with prednisone/prednisolone and vice versa is limited. Based on the elimination half-life of Xofigo and abiraterone, it is recommended that subsequent treatment with Xofigo is not initiated for at least 5 days after the last administration of abiraterone acetate in combination with prednisone/prednisolone.
Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of Xofigo.

Treatment of patients with asymptomatic or mildly symptomatic bone metastases

An increased risk of death and fractures was observed in a clinical study, where Xofigo was added to abiraterone acetate and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic castration resistant prostate cancer.

Treatment benefit of Xofigo in adults with castration-resistant prostate cancer and only asymptomatic bone metastases is not established. The use of Xofigo is therefore not recommended for treatment of adults with castration-resistant prostate cancer and only asymptomatic bone metastases. In adults with castration-resistant prostate cancer and mildly symptomatic bone metastases the benefit of treatment should be carefully assessed to outweigh the risks considering that high osteoblastic activity is likely to be required for treatment benefit (see section 5.1).

Patients with a low level of osteoblastic bone metastases

In clinical studies, patients with fewer than 6 bone metastases had an increased risk of fractures and did not have a statistically significant survival benefit. A pre-specified subgroup analysis also showed that overall survival was not significantly improved in patients with a total ALP < 220 U/L. Therefore in patients with a low level of osteoblastic bone metastases radium-223 is not recommended (see section 5.1).

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

Xofigo increases the risk of bone fractures. In a clinical study, the addition of Xofigo to abiraterone acetate and prednisone/prednisolone, increased the incidence of fractures approximately three-fold in the Xofigo arm (see sections 4.8 and 5.1). Increased fracture risk has been found especially in patients with medical history of osteoporosis and in patients with less than 6 bone metastases. Xofigo is believed to accumulate at sites of high bone turnover such as sites of degenerative bone disease (osteoporosis) or recent (micro-)fracture increasing the risk of fractures. Other factors such as concomitant use of steroids may further increase the risk of fracture.

Prior to starting radium-223 bone status (e.g. by scintigraphy, bone mineral density measurement) and baseline risk of fractures of patients (e.g. osteoporosis, less than 6 bone metastases, medication increasing fracture risk, low body mass index) should be carefully assessed, and closely monitored for at least 24 months. Preventive measures such as the use of bisphosphonates or denosumab should be considered before starting or resuming treatment with Xofigo (see section 4.8). In patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk. 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, equivalent to 2.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

Xofigo has no or negligible influence on the ability to drive and 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, thrombocytopenia and bone fracture.

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		
Musculoskeletal and connective tissue disorders	Bone fracture		Osteoporosis
General disorders and administration site conditions		Injection site reactions	

Description of selected adverse reactions

Bone fractures
Xofigo increases the risk of bone fractures (see section 5.1). In clinical studies, concurrent use of bisphosphonates or denosumab reduced the incidence of fractures in patients treated with radium-223 monotherapy. Fractures have occurred for up to 24 months after the first dose of radium-223.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

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: Therapeutic radiopharmaceuticals, other therapeutic radiopharmaceuticals, 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

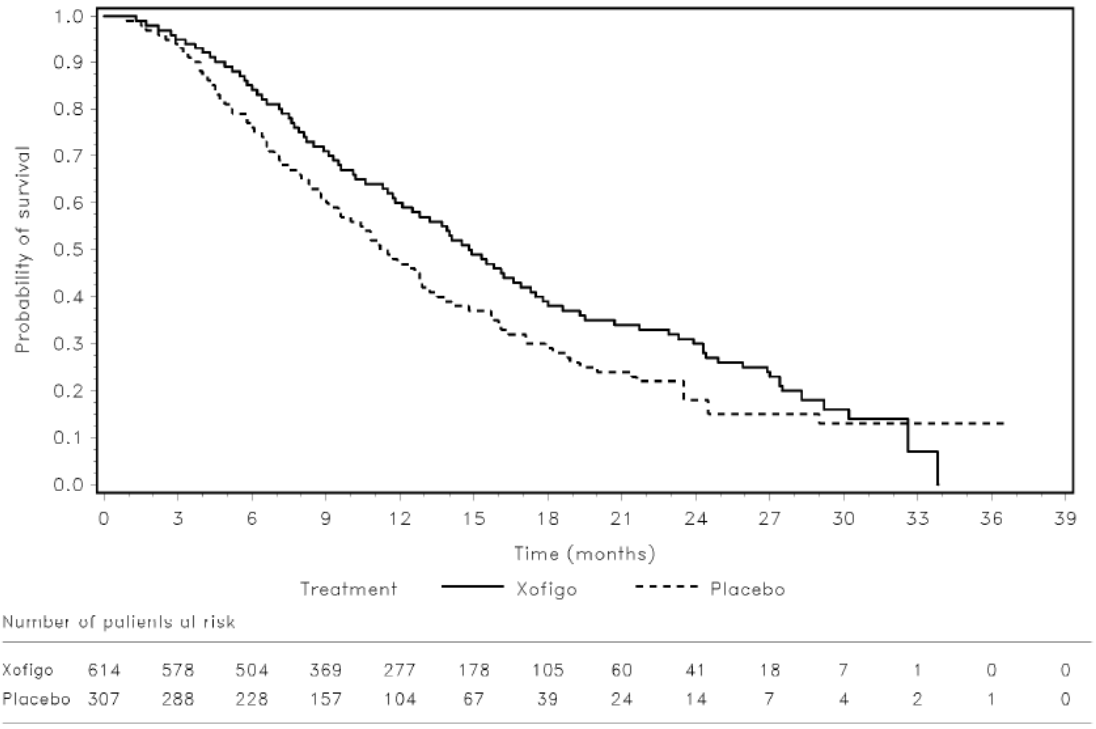
	Xofigo	**Placebo**
Interim analysis	N = 541	N = 268
Number (%) of deaths	191 (35.3%)	123 (45.9%)
Median overall survival (months) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
Hazard ratio[b] (95% CI)	0.695 (0.552 – 0.875)	
p-value[a] (2-sided)	0.00185	
Updated analysis	N = 614	N = 307
Number (%) of 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 use of bisphosphonates at baseline and prior use of docetaxel.

A statistically significant overall survival benefit of treatment could not be demonstrated in the subgroups of patients with fewer than 6 metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 -1.466], p=0.674) or a baseline total alkaline phosphatase (ALP) < 220 U/L (HR 0.823; 95% CI [0.633 -1.068], p=0.142) in the phase III ALSYMPCA study. Therefore, efficacy may be diminished in patients with a low level of osteoblastic activity from their bone metastases.

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.

Combination with abiraterone and prednisone/prednisolone
The clinical efficacy and safety of concurrent initiation of Xofigo, abiraterone acetate and prednisone/prednisolone treatment was assessed in a randomized, placebo-controlled multicenter phase III study (ERA-223 trial) in 806 chemotherapy-naïve 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 (28.6% vs 11.4%) and reduced median overall survival (30.7 months versus 33.3 months, HR 1.195, 95% CI [0.950 - 1.505], p=0.13) was observed among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone.

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 injection
Sodium citrate
Sodium chloride
Hydrochloric acid

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 either with or without foil-clad made of Ethylene tetrafluoroethylene (ETFE) both capped with 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. MANUFACTURER

Bayer AS, Oslo, Norway

8. REGISTRATION HOLDER

Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 4527702.

9. 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.

10. 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 this 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.

11. DECAY CORRECTION TABLE FOR RADIUM-223

EUROPE

12 noon Central European Time (CET=UTC+1h)

Day from reference date	Physical decay factor
-14	2.34
-13	2.20
-12	2.07
-11	1.95
-10	1.83
-9	1.73
-8	1.62
-7	1.53
-6	1.44
-5	1.35
-4	1.27
-3	1.20
-2	1.13
-1	1.06
0	1.00
1	0.94
2	0.89
3	0.83
4	0.78

5	**0.74**
6	**0.69**
7	**0.65**
8	**0.62**
9	**0.58**
10	**0.55**
11	**0.51**
12	**0.48**
13	**0.45**
14	**0.43**

A one hour time difference due to daylight savings are not considered significant for a radionuclide with an 11.4 day half-life, and is therefore not accounted for in this table.

Revised in December 2020.