Attachment 1: Product information for AusPAR Xofigo radium (223Ra) dichloride Bayer Australia Ltd PM-2013-00738-1-2 Final 10 July 2014. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

XOFIGO® Solution for Injection

Radium (223Ra) dichloride 6.0 MBq/6 mL

NAME OF THE MEDICINE

Australian Approved Name:	Radium (223Ra) dichloride
Structural Formula:	The active moiety of the radium (223Ra) dichloride drug substance is the divalent cation of radium-223 ($^{223}Ra^{2+}$).
Molecular Formula:	$^{223}RaCl_2$
Molecular Weight:	293.9 g/mol
CAS Name:	Radium-223 chloride ($^{223}RaCl_2$)
CAS Number:	444811-40-9

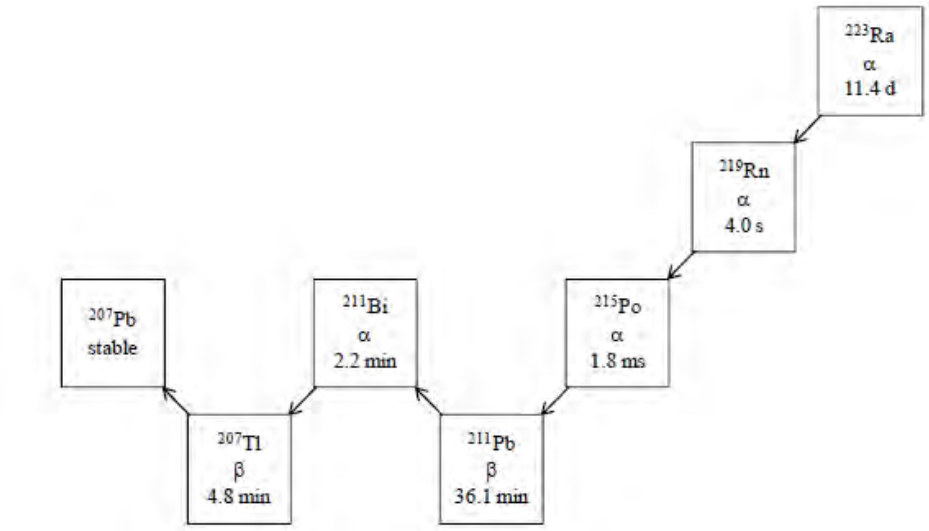
DESCRIPTION

XOFIGO is a clear, colourless and sterile isotonic solution for injection with pH between 6 and 8. Each mL of solution contains 1000 kBq radium (223Ra) dichloride (Ra-223 dichloride), corresponding to 0.53 ng Ra-223, at the reference date. Radium is present in the solution as a free ion. The solution also contains hydrochloric acid, sodium chloride, sodium citrate and water for injections. Each vial contains 6 mL of solution (6.0 MBq Ra-223 at the reference date).

Ra-223 is an alpha particle-emitter with a half-life of 11.4 days. The specific activity of Ra-223 is 1.9 MBq/ng.

The six-stage-decay of Ra-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 Ra-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:



PHARMACOLOGY

Mechanism of action

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

The active moiety of XOFIGO is the isotope Ra-223 (as Ra-223 dichloride), which mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in a potent and localised anti-tumour effect. The alpha particle range from Ra-223 is less than 100 micrometers (less than 10 cell diameters) which minimises damage to the surrounding normal tissue.

Pharmacodynamics

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); and bone resorption markers: C-terminal crosslinking telopeptide of type I collagen (S-CTX-I) and type I collagen crosslinked C-telopeptide (ICTP)].

Pharmacokinetics

Pharmacokinetic, biodistribution and dosimetry data have been obtained from three phase I studies. Pharmacokinetic data were obtained in 25 patients at doses ranging from 46 to 250 kBq/kg. Pharmacokinetic, biodistribution and dosimetry data were obtained in 6 patients at a dose of 100 kBq/kg given twice, 6 weeks apart, and in 10 patients at a dose of 50, 100 or 200 kBq/kg.

The pharmacokinetics of Ra-223 dichloride were linear in the dose range investigated (46 to 250 kBq/kg).

<u>Absorption</u>

XOFIGO is administered as an intravenous injection and is therefore 100% bioavailable.

Distribution

After intravenous injection, Ra-223 is cleared rapidly 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.

Metabolism

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

Excretion

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.

Whole body measurements at 7 days after injection (after correcting for decay) indicated that a median of 76% of administered activity had been excreted from the body. The rate of elimination of Ra-223 dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population, with the normal range from once daily to once weekly bowel evacuation.

Additional information on special populations

Patients with hepatic impairment

No pharmacokinetic studies in patients with hepatic impairment have been conducted. However, since Ra-223 as an isotope is not metabolised, it is not expected that hepatic impairment will affect the pharmacokinetics of Ra-223 dichloride (see DOSAGE AND ADMINISTRATION).

Patients with renal impairment

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

CLINICAL TRIALS

The clinical safety and efficacy of XOFIGO have been evaluated in a double-blind, randomised, multiple dose, phase III, multicentre study (ALSYMPCA) in castration-resistant

prostate cancer patients with symptomatic bone metastases. Patients with visceral metastases and malignant lymphadenopathy exceeding 3 cm were excluded.

The primary efficacy endpoint was overall survival (OS). Main secondary endpoints included time to symptomatic skeletal events (SSE), time to total alkaline phosphatase (ALP) progression, time to Prostate Specific Antigen (PSA) progression, total ALP response and total ALP normalisation.

At the cut-off date of the pre-planned interim analysis, a total of 809 patients were randomised 2:1 to receive XOFIGO 50 kBq/kg intravenously every 4 weeks for 6 cycles (N=541) plus best standard of care (BSoC) or matching placebo plus BSoC (N=268). BSoC included, for example, local external beam radiotherapy, bisphosphonates, corticosteroids, anti-androgens, oestrogens, estramustine and ketoconazole. At the recommendation of the Independent Data Monitoring Committee, the study was unblinded after the interim analysis due to evidence of favourable efficacy based on the pre-specified stopping criteria. An updated descriptive analysis of safety and of overall survival was performed in 921 randomised patients prior to implementing crossover (i.e. prior to offering XOFIGO treatment to patients in the placebo group).

Patients with Crohn's disease, ulcerative colitis, visceral metastases, prior hemibody radiation and untreated imminent or established spinal cord compression were excluded from the study. Demographic and baseline disease characteristics (interim analysis population) were comparable 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, and 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 interim and updated analysis revealed that OS was significantly longer in patients treated with XOFIGO plus BSoC compared to patients treated with placebo plus BSoC (see Table 1, Figure 1). For both databases, the OS improvement was 44% based on the hazard ratios.

For the interim analysis, an increase in median OS of 2.8 months was seen with XOFIGO plus BSoC compared to placebo plus BSoC with a more than 30% reduction in the risk of death. For the updated analysis, an increase in median OS of 3.6 months was seen with XOFIGO plus BSoC compared to placebo plus BSoC.

Table 1: Survival Results from the Phase III ALSYMPCA Study

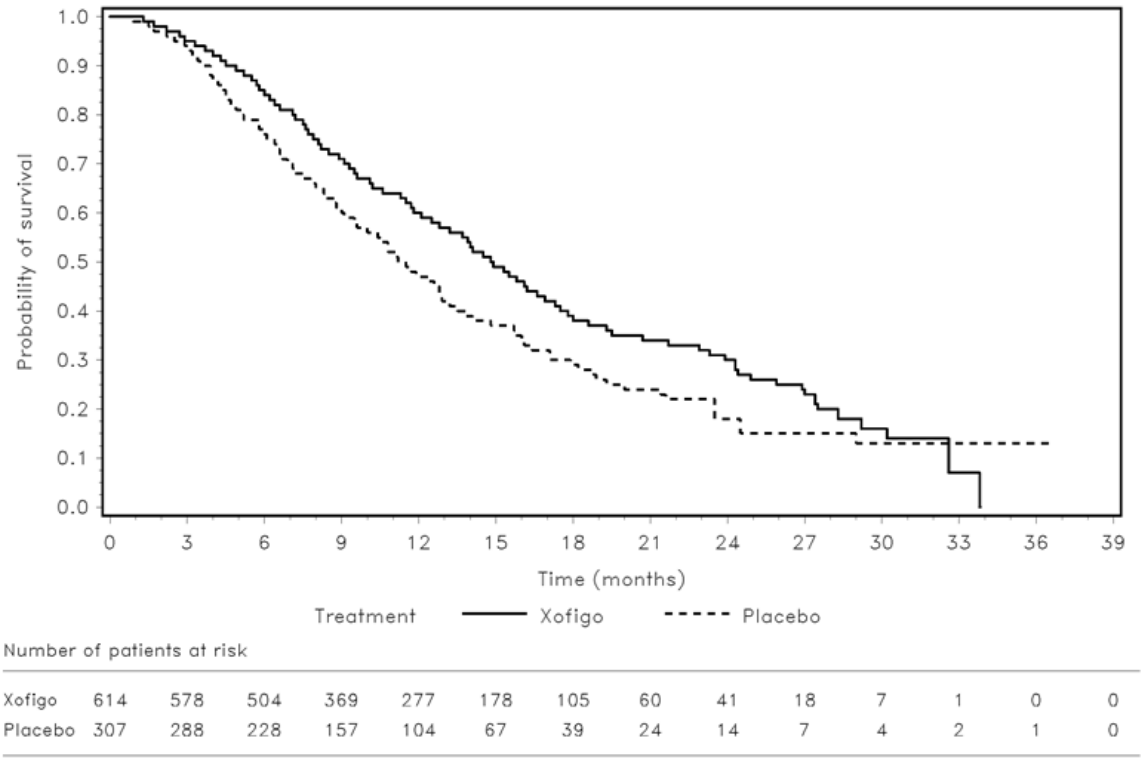
Efficacy Parameter	XOFIGO	Placebo
Interim Analysis	**N = 541**	**N = 268**
Number of deaths (%)	191 (35.3%)	123 (45.9%)
Median OS (months) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
p-value[a] (2-sided)	0.00185	
Hazard Ratio[b] (95% CI)	0.695 (0.552 - 0.875)	
Updated Analysis	**N = 614**	**N = 307**
Number of deaths (%)	333 (54.2%)	195 (63.5%)
Median OS (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; OS = Overall survival; HR = Hazard ratio (XOFIGO over placebo)

[a] The phase III 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 < 1 favours XOFIGO.

Figure 1: Kaplan-Meier Overall Survival Curves (Updated Analysis)



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

The 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 2).

Occurrence of symptomatic skeletal events (SSE, defined as occurrence of any of the following: external beam radiotherapy to relieve pain, or spinal cord compression, or tumour-related orthopaedic surgical intervention or pathologic fracture) was significantly delayed in patients receiving XOFIGO compared to patients receiving placebo (see Table 2).

- The delay of occurrence of SSE with XOFIGO was mainly driven by the statistically significant delay in time to external beam radiation therapy (EBRT) for pain relief.
- A delay in time to spinal cord compression was observed in patients receiving XOFIGO compared to patients receiving placebo.
- A delay in time to surgical intervention was observed in patients receiving XOFIGO compared to patients receiving placebo.
- A delay in time to bone fracture was observed in patients receiving XOFIGO compared to patients receiving placebo.

Table 2: Secondary efficacy endpoints from the phase III ALSYMPCA study (interim analysis)

			Incidence		**Time-to-event analysis** (95% CI)			
			[no. (%) of patients]		[median no. of months]		**Hazard Ratio**[e]	**p-value**
			XOFIGO N = 541	Placebo N = 268	XOFIGO N = 541	Placebo N = 268		
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	EBRT 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[b]	NE[b]	0.443 (0.223 – 0.877)	0.01647
		Surgical intervention	9 (1.7%)	5 (1.9%)	NE[b]	NE[b]	0.801 (0.267 – 2.398)	0.69041
		Bone fractures	20 (3.7%)	18 (6.7%)	NE[b]	NE[b]	0.450 (0.236 – 0.856)	0.01255
Total ALP progression[c]			79 (14.6%)	116 (43.3%)	NE[b]	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; EBRT = External beam radiation therapy; 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 due to insufficient events, i.e. median was not reached at the time of data cut-off.

[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.

[e] Hazard ratio < 1 favours XOFIGO.

Treatment with XOFIGO was superior to placebo in prolonging the time to total ALP progression (defined as ≥ 25% increase compared to baseline/nadir). Time to PSA progression (defined as a ≥ 25% increase and an increase in absolute value of ≥ 2 ng/mL compared to baseline/nadir) was also significantly prolonged in patients receiving XOFIGO compared to patients receiving placebo (see Table 2).

A higher percentage of patients in the XOFIGO group achieved total ALP response (confirmed ≥ 30% reduction compared to baseline) at week 12 compared to the placebo group (Interim analysis: 46.2% in the XOFIGO group, 2.5% in the placebo group, $p < 0.001$).

A higher percentage of patients in the XOFIGO group reached total ALP normalisation (defined as return of total ALP value to within normal range) at week 12 compared to the placebo group (Interim analysis: 32.9% in the XOFIGO group, 0.9% in the placebo group, $p < 0.001$).

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). Results from the EQ-5D analysis showed that XOFIGO had greater HRQOL benefits over the course of the trial as measured by the utility index (-0.101 versus -0.161, $p = 0.002$) and self-reported Visual Analogue health status scores (-5.225 versus -8.516, $p = 0.008$) compared to placebo. The FACT-P analyses demonstrated that, relative to placebo over the course of the trial, XOFIGO was associated with significantly greater HRQOL as measured by the FACT-P total score (-4.828 versus -8.689, $p = 0.004$). Visit-specific analysis showed that at week 16 there was improvement in the FACT-P total score ($p = 0.006$), Trial Outcome Index score ($p = 0.012$), FACT-G score ($p = 0.004$), emotional well-being ($p < 0.001$), functional well-being ($p = 0.012$) and prostate cancer subscale ($p = 0.012$). All patients received best standard of care.

Pain relief

The results from the phase III ALSYMPCA study (time to 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. This is further supported by the effects seen on bone pain using specific pain measures in a single dose phase II study.

Subsequent use of cytotoxic drugs

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.

INDICATIONS

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

CONTRAINDICATIONS

There are no known contraindications to the use of XOFIGO.

PRECAUTIONS

Bone marrow suppression

Bone marrow suppression, notably thrombocytopenia, neutropenia, leucopenia and pancytopenia, has been reported in patients treated with XOFIGO (see ADVERSE EFFECTS).

Haematological evaluation of patients must be performed at baseline and prior to every dose of XOFIGO. Before the first administration of XOFIGO, the absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L, the platelet count ≥ 100 x 10^9/L and haemoglobin ≥ 10.0 g/dL. Before subsequent administrations, the ANC should be ≥ 1.0 x 10^9/L and the platelet count ≥ 50 x 10^9/L. In case there is no recovery in these values within 6 weeks after the last administration of XOFIGO despite receiving standard of care, further treatment with XOFIGO should only be continued after a careful benefit/risk evaluation.

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

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.

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.

Contraception

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

Effects on fertility

No animal fertility or reproduction studies have been conducted with XOFIGO. Patients should be informed of a potential risk that radiation from XOFIGO could cause adverse effects on testes and impair fertility (see PRECAUTIONS – Contraception).

Use in pregnancy

Pregnancy Category X

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

Use in lactation

XOFIGO is not indicated in women. XOFIGO, a radioactive therapeutic agent, is not to be used in women who are breastfeeding.

Paediatric use

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

Use in the elderly

Of the 600 patients treated with XOFIGO in the ALSYMPCA phase III study, 447 patients (74.5%) were 65 years of age and over, while 196 patients (32.7%) were 75 years of age and over. No overall differences in safety or effectiveness were observed between patients aged ≥ 65 years and patients aged < 65 years. No dose adjustment is considered necessary in elderly patients.

Genotoxicity

Studies on the mutagenic potential of XOFIGO have not been performed. However, radium-223 dichloride acts by the induction of double-strand breaks in DNA, a known effect of radiation.

Carcinogenicity

Studies on the carcinogenic potential of XOFIGO have not been performed. Osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses in repeat-dose toxicity studies in rats 7 to 12 months after start of treatment.

INTERACTIONS WITH OTHER MEDICINES

No clinical interaction studies have been performed. Concomitant chemotherapy with XOFIGO may have additive effects on bone marrow suppression (see PRECAUTIONS – Bone marrow suppression). Safety and efficacy of concomitant chemotherapy with XOFIGO have not been established.

ADVERSE EFFECTS

The overall safety profile of XOFIGO is based on data from 600 patients treated with XOFIGO in the ALSYMPCA phase III study.

The most serious adverse drug reactions were thrombocytopenia and neutropenia (see PRECAUTIONS – Bone marrow suppression and below for description of selected adverse reactions). The most frequently observed adverse drug reactions (≥ 10%) in patients receiving XOFIGO were diarrhoea, nausea, vomiting and thrombocytopenia.

Table 3 shows adverse reactions occurring in ≥ 1% of patients treated with XOFIGO or placebo. Adverse reactions are identified using MedDRA version 14.1 and graded according to CTCAE version 3.0.

Table 3: Incidence of Adverse Reactions in ≥ 1% of Patients Treated with XOFIGO or Placebo

System/Organ Class Preferred Term	XOFIGO (n = 600)	Placebo (n = 301)

	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Blood and lymphatic system disorders				
Thrombocytopenia	11.5	6.3	5.6	2
Neutropenia	5	2.2	1	0.7
Leucopenia	4.2	1.3	0.3	0.3
Pancytopenia	2	1.2	0	0
Gastrointestinal disorders				
Diarrhoea	25	1.5 (grade 3 only)	15	1.7 (grade 3 only)
Vomiting	18.5	1.7 (grade 3 only)	13.6	2.3 (grade 3 only)
Nausea	35.5	1.7 (grade 3 only)	34.6	1.7 (grade 3 only)
General disorders and administration site conditions				
Injection site reactions (including erythema, pain and swelling)	1.2	0	0	0

An additional clinically important adverse reaction observed in less than 1% of XOFIGO-treated patients and at a higher incidence than in placebo-treated patients was lymphopenia (0.8% versus 0.3%).

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 PRECAUTIONS – Bone marrow suppression). Overall, the frequency of grade 3 and 4 thrombocytopenia was lower in patients that did not previously receive docetaxel (2.8% in patients treated with XOFIGO versus 0.8% in patients receiving placebo) compared to patients that previously received docetaxel (8.9% in patients treated with XOFIGO versus 2.9% in patients receiving placebo).

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

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

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. No cases of XOFIGO-induced cancer have been reported in clinical trials in follow-up of up to three years.

DOSAGE AND ADMINISTRATION

Dosage regimen

The dose regimen of XOFIGO is 50 kBq per kg body weight, given at 4 week intervals for 6 injections.

Safety and efficacy beyond 6 injections have not been studied.

For details on the calculation of the volume to be administered, see Method of administration.

Additional information on special populations

No dose adjustment is considered necessary in the elderly or in patients with renal or hepatic impairment (see PHARMACOLOGY – Pharmacokinetics).

Method of administration

XOFIGO is to be administered by slow intravenous injection (generally up to 1 minute). The intravenous access line or cannula must be flushed with isotonic saline before and after injection.

XOFIGO should be inspected visually 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 solutions. In the absence of compatibility studies, XOFIGO must not be mixed with other medicinal products.

Each vial is for is for single use in one patient only. Discard any residue as described under Radiation Protection.

The volume to be administered to a given patient should be calculated using the:

- Patient's body weight (kg)
- Dose (50 kBq/kg body weight)
- Radioactivity concentration of the product (1000 kBq/mL) at reference date. The reference date is stated on the vial and lead container label.
- Decay correction (DK) factor to correct for physical decay of radium-223. A table of DK factors is provided with each vial (see Table 4).

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

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (50 kBq/kg body weight)}}{\text{DK factor} \times \text{1000 kBq/mL}}$$

Table 4: Decay Correction Factor Table corrected to 12 noon Australian Central Standard Time (CST)

Days from Reference Date	Physical Decay Factor	Days from Reference Date	Physical Decay Factor
-14	2.39	0	1.02
-13	2.25	1	0.96
-12	2.12	2	0.91
-11	1.99	3	0.85
-10	1.87	4	0.80
-9	1.76	5	0.75
-8	1.66	6	0.71
-7	1.56	7	0.67
-6	1.47	8	0.63
-5	1.38	9	0.59
-4	1.30	10	0.56
-3	1.23	11	0.52
-2	1.15	12	0.49
-1	1.09	13	0.46
		14	0.44

The Decay Correction Factor Table is corrected to 12 noon Australian Central Standard Time (CST). To determine the decay correction factor, count the number of days before or after the reference date. The Decay Correction Factor Table includes a correction to account for the 8.5 hour time difference between 12 noon Central European Time (CET) at the site of manufacture and 12 noon ACST, which is 8.5 hours earlier than CET. Changes due to daylight savings are not included in this table as the difference of 1 hour is not considered significant for a radionuclide with an 11.4 day half-life.

Instructions for use and handling

XOFIGO (an alpha particle-emitting pharmaceutical) should be received, used and administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings. The receipt, storage, use, transfer and disposal of XOFIGO are subject to license and regulation by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA).

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

Radiation Protection

The gamma radiation associated with the decay of Ra-223 and its daughters allows for the radioactivity measurement of XOFIGO and the detection of contaminations with standard instruments.

The administration of XOFIGO is associated with potential risks for other persons (e.g. medical staff, care givers and patient's household members) from radiation or contamination from body fluids such as spills of urine, faeces and vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations. Although Ra-223 is predominantly an alpha emitter, gamma and beta radiation is associated with the decay of Ra-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 materials used in connection with preparation or administration of XOFIGO are to be treated as radioactive waste and should be disposed of in accordance with the "*Code of Practice for the Disposal of Radioactive Wastes by the User*". This code is published on the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) website as "Radiation Health Series (RHS) No. 13".

Dosimetry

The absorbed radiation dose calculation was performed based on clinical biodistribution data. Calculations of absorbed doses were performed using OLINDA/EXM (Organ Level INternal Dose Assessment/EXponential Modeling), software based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For Ra-223, 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.

The calculated absorbed radiation doses to different organs are listed in Table 5 (mGy/MBq). The organs with highest absorbed radiation doses were bone (osteogenic cells), red marrow, upper large intestine wall and lower large intestine wall. The calculated doses to other organs are lower.

Table 5: Calculated absorbed radiation doses to organs

Target Organ	Alpha[1] emission (mGy/MBq)	Beta emission (mGy/MBq)	Gamma emission (mGy/MBq)	Total dose (mGy/MBq)	Coefficient of variation (%)
Adrenals	0.00	0.02	0.09	0.12	56
Brain	0.00	0.02	0.08	0.10	80
Breasts	0.00	0.02	0.03	0.05	120
Gallbladder wall	0.00	0.02	0.21	0.23	14
Lower large intestine wall	0.00	45.60	0.85	46.45	83
Small intestine wall	3.19	3.60	0.47	7.26	45
Stomach wall	0.00	0.02	0.12	0.14	22
Upper large intestine wall	0.00	31.50	0.82	32.32	50
Heart wall	1.61	0.07	0.05	1.73	42
Kidneys	2.99	0.11	0.11	3.20	36

Target Organ	Alpha[1] emission (mGy/MBq)	Beta emission (mGy/MBq)	Gamma emission (mGy/MBq)	Total dose (mGy/MBq)	Coefficient of variation (%)
Liver	2.79	0.10	0.08	2.98	36
Lungs	0.00	0.02	0.05	0.07	90
Muscle	0.00	0.02	0.10	0.12	41
Ovaries	0.00	0.02	0.46	0.49	40
Pancreas	0.00	0.02	0.09	0.11	43
Red marrow	132.00	6.42	0.20	138.79	41
Osteogenic cells	11400.00	14.90	0.30	1152.06	41
Skin	0.00	0.02	0.05	0.07	79
Spleen	0.00	0.02	0.07	0.09	54
Testes	0.00	0.02	0.06	0.08	59
Thymus	0.00	0.02	0.03	0.06	109
Thyroid	0.00	0.02	0.05	0.07	96
Urinary bladder wall	3.71	0.16	0.16	4.03	63
Uterus	0.00	0.02	0.23	0.26	28
Whole body	22.20	0.81	0.12	23.11	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.

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

OVERDOSAGE

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

There is no specific antidote. In the event of an inadvertent overdose, general supportive measures, including monitoring for potential haematological and gastrointestinal toxicity should be undertaken. Contact the Poison Information Centre on 13 11 26 for information on the management of overdose.

Single XOFIGO doses up to 250 kBq per kg body weight were evaluated in a phase I clinical trial and no dose-limiting toxicities were observed.

PRESENTATION AND STORAGE CONDITIONS

XOFIGO is a ready-to-use, clear and colourless solution for injection supplied in one single dose glass vial closed with a rubber stopper. The vial is wrapped with an adhesive transparent film and stored in a lead container.

Each vial contains 6 mL Ra-223 solution for injection with an activity concentration of 1000 kBq per mL (corresponding to a total activity of 6.0 MBq per vial) at the reference date.

XOFIGO should not be used in case of discolouration, the occurrence of particulate matter or a defective container.

Store below 40ºC. Storage should be in accordance with national regulations on radioactive materials.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
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POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION IN THE ARTG

20 May 2014

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