SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

XOFIGO® solution for injection

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 ml contains 0,194 mmol (equivalent to 4,5 mg) of sodium.

Excipients:

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

PHARMACOLOGICAL CLASSIFICATION: A.32.15 Radiopharmaceuticals

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Radium-223 dichloride is an alpha particle-emitting pharmaceutical with targeted anti-tumour effect on bone metastases with a half-life of 11,4 days.

The active moiety, the isotope radium-223 (as radium-223 dichloride) mimics calcium and targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite.

The specific activity of radium-223 is 1,9 MBq (0,0514 mCi)/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 to 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 to 1,27 MeV).

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 localised anti-tumour effect.

The alpha particle range from radium-223 is less than 100 micrometres (less than 10 cell diameters) which minimises damage to the surrounding normal tissue.

Radium-223 dichloride has an effect on serum bone markers 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(S-CTX-I) and type I collagen crosslinked C-telopeptide (ICTP)).

Pharmacokinetic properties:

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. The level of activity in the bone was in the range of 44 % to 77 % at 4 hours post injection.

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

Metabolism/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 hepato-biliary excretion. The whole body measurements at 7 days after

injection (after correcting for decay) indicate that a median of 76 % of administered activity was excreted from the body.

The rate of elimination of radium-223 dichloride from the gastrointestinal tract influenced by the high variability in intestinal transit rates across the population is within the normal range from once daily to once weekly bowel evacuation.

Linearity/Non-linearity

The pharmacokinetics of radium-223 dichloride was linear in the dose range investigated (51 to 276 kBq (0,00138 to 0,00746 mCi)/kg).

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 **I**nternal **D**ose **A**ssessment/**EX**ponential **M**odeling), a software based on the Medical Internal Radiation Dose (MIRD) algorithm. 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 radium-223 dichloride, considering its observed biodistribution and specific characteristics.

For an administered activity of 4, 02 MBq (0.1086 mCi) (55 kBq (0.00149 mCi) per kg body weight to a 73 kg adult) the calculated absorbed doses to the bone (osteogenic cells) is 4.6255 Gy (462,55 rad) and to the red marrow is 0, 5572 Gy (55,72 rad). The calculated absorbed doses to the main excretory organs are 0, 0292 Gy (2,92 rad) for the small intestine wall, 0,1298 Gy (12, 98 rad) for the upper large intestine wall and 0,1865 Gy (18, 65 rad) for the lower large intestine wall. The calculated absorbed doses to other organs are low, e.g. heart wall (0,0069 Gy, 0,69 rad), lung (0,0003 Gy, 0,03 rad), liver (0,0119 Gy, 1,19 rad), kidneys (0,0129 Gy, 1,29 rad), urinary bladder wall (0,0162 Gy, 1,62 rad), testes (0,0003 Gy, 0,03 rad), and spleen (0,0004 Gy, 0,04 rad).

Additional information on special populations

Paediatric patients

Safety and effectiveness of XOFIGO have not been studied in children and adolescents below 18 years of age (see “Dosage and Instructions for use”).

Patients with hepatic impairment

No pharmacokinetic studies in patients with hepatic impairment have been conducted. However, since radium-223 as an isotope is not metabolised, it is not expected that hepatic impairment will affect the pharmacokinetics of radium-223 dichloride (see “Dosage and directions for use”).

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 radium-223 dichloride (see “Dosage and directions for use”).

INDICATIONS:

XOFIGO is indicated for the treatment of castration-resistant prostate cancer patients with bone metastases.

CONTRAINDICATIONS:

Hypersensitivity to radium-223 dichloride or any of the other ingredients of XOFIGO.

Children and adolescents below 18 years of age. The safety and efficacy of XOFIGO in children and adolescents below 18 years of age have not been studied (see Dosage and Instructions for Use)

WARNINGS and SPECIAL PRECAUTIONS:

Bone marrow suppression

Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with XOFIGO (see “Side 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.

If there is no recovery in these values within 6 weeks after the last administration of XOFIGO despite receiving standard of care, further treatment with XOFIGO should be discontinued.

Patients with evidence of compromised bone marrow reserve should be 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.

Effect on spermatogenesis

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 treatment with XOFIGO ("see "Pregnancy and Lactation").

Secondary malignant neoplasms

XOFIGO contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer and hereditary defects. No cases of XOFIGO-induced cancer have been reported with limited duration of clinical trials follow-up (up to three years) (see "Side effects").

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 (see "Warnings and special precautions").

Bone fractures:

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

Effects on ability to drive or use machines:

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

Sodium content:

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

INTERACTIONS:

No clinical interaction studies have been performed.

Concomitant chemotherapy with XOFIGO may have additive effects on bone marrow suppression (see “Warnings and special precautions”). Safety and efficacy of concomitant chemotherapy with XOFIGO have not been established.

PREGNANCY AND LACTATION:

Pregnancy and lactation

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

Fertility

There is a potential risk that radiation from XOFIGO could cause adverse effects on testes. Since XOFIGO binds to bone, the potential risk for adverse effects in the male gonads in cancer patients with castration- resistant prostate cancer cannot be excluded. Patients should be informed accordingly (see “Warnings and special precautions”).

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 treatment with XOFIGO (see “Warnings and special precautions”).

DOSAGE AND DIRECTIONS FOR USE:

For intravenous use

XOFIGO is to be administered by slow intravenous injection (generally up to 1 minute). The intravenous access line or cannula must be flushed with 0, 9 % sodium chloride before and after injection of XOFIGO.

Dosage regimen

The dose regimen of XOFIGO is 55 kBq (0.00149 mCi) per kg body weight, given at 4 week intervals for 6 injections. Safety and efficacy beyond 6 injections with XOFIGO have not been studied.

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

- Patient's body weight (kg)
- Dosage level (55 kBq (0.00149 mCi))/kg body weight)
- Radioactivity concentration of the product (1100 kBq/mL; 0, 0297 mCi/mL) at reference date. The reference date is stated on the vial and lead container label.
- Decay correction factor to correct for physical decay of radium-223.

Decay Correction Factor Table:

Days from Reference date	Physical Decay factor	Days from Reference date	Physical Decay factor
-14	2.34	0	1.00
-13	2.20	1	0.94
-12	2.07	2	0.89
-11	1.95	3	0.83
-10	1.83	4	0.78
-9	1.73	5	0.74
-8	1.62	6	0.69
-7	1.53	7	0.65
-6	1.44	8	0.62

-5	1.35	9	0.58
-4	1.27	10	0.55
-3	1.20	11	0.51
-2	1.13	12	0.48
-1	1.06	13	0.45
		14	0.43

The Decay Correction Factor Table is corrected to 12 noon Central European Time (CET). To determine the decay correction factor, count the number of days before or after the reference date.

Immediately before and after administration, the net patient dose of administered Xofigo should be determined by measurement in an appropriate radioisotope dose calibrator that has been calibrated with a National Institute of Standards and Technology (NIST) traceable radium-223 standard (available upon request from Bayer) and corrected for decay using the date and time of calibration. The dose calibrator must be calibrated with nationally recognised standards, carried out at the time of commissioning, after any maintenance procedure that could affect the dosimetry and at intervals not to exceed one year.

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

Volume to be administered (mL) =

$$\frac{\text{Body weight (kg) x dose (55 kBq (0.00149 mCi)/kg body weight)}}{\text{Decay correction factor x 1100 kBq (0.0297 mCi)/mL}}$$

General instructions

XOFIGO 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 the regulations and/or appropriate licenses of the competent official organisation.

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 radium-223 and its daughters allows for the radioactivity measurement of XOFIGO and the detection of contaminations with standard instruments.

The administration of XOFIGO is associated with potential risks for other persons (e.g. medical staff, care givers and members of the patient's family) 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 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 administered radioactivity will usually be below 8 MBq (0, 216 mCi). 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 the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

Instructions for preparation

XOFIGO 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 solutions. Each vial is for single use only.

Additional information on special populations

Paediatric patients

The safety and efficacy of XOFIGO in children and adolescents below 18 years of age have not been studied.

Geriatric patients

Of the 600 patients treated with XOFIGO in the 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 elderly (aged ≥ 65 years) and younger patients (aged < 65 years).No dose adjustment is considered necessary in elderly patients.

Patients with hepatic impairment

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

Since XOFIGO is neither metabolised by the liver nor eliminated via the bile, hepatic impairment is not expected to affect the pharmacokinetics of XOFIGO.

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

Patients with renal impairment

In the phase III clinical study no relevant differences in safety or efficacy were observed between patients with mild renal impairment (creatinine clearance (CLCR): 50 to 80 ml/min) and normal renal function. Limited data are available on patients with moderate (CLCR: 30 to 50 ml/min) renal impairment.

No data are available on 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 XOFIGO. No dose adjustment is considered necessary in patients with renal impairment.

SIDE EFFECTS:

The overall safety profile of XOFIGO is based on data from 600 patients treated with XOFIGO in the phase III study. The most serious adverse reactions were thrombocytopenia and neutropenia (see “Warnings and special precautions”). The most frequently observed adverse reactions (≥10 %) in patients receiving XOFIGO were diarrhoea, nausea, vomiting and thrombocytopenia.

Adverse reactions reported in clinical trials in patients treated with XOFIGO:

System Organ Class **(MedDRA)**	**Very common** **(≥ 1/10)**	**Common** **(≥ 1/100 to < 1/10)**	**Uncommon** **(≥ 1/1,000 to < 1/100)**
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 thrombocytopaenia was observed in 6,3 % of patients treated with XOFIGO and in 2 % of patients receiving placebo (see “Warnings and special precautions”).

Overall, the frequency of grade 3 and 4 thrombocytopaenia 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

XOFIGO solution for injection is clear, colourless and free of particulate matter.

PRESENTATION:

Solution for injection in a 10 mL colourless glass bottle, glass type I for injection, closed with a chlorobutyl gray siliconised stopper for injection and fixed with a flanged closure made of an aluminium shell.

Each sealed vial is wrapped with an adhesive transparent film. A plastic bottom and top cap provides a cylindrical form to support the wrapping process.

The wrapped vial is inserted in a lead shielded container.

The lead shielded container is then packed in a shipping cardboard box.

STORAGE INSTRUCTIONS:

Store at or below 40 ˚C.

Store in the original package in accordance with the national regulations for radioactive materials.

Keep out of the sight and reach of children.

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

REGISTRATION NUMBER: 48/32.15/0715

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd

Reg. No.: 1968/011192/07

27 Wrench Road

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

18 February 2016