APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

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.
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 (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 – 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).

Excipients with known effect
Each mL of solution contains 0,194 mmol (equivalent to 4,5 mg) of sodium.
Sugar free
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, sterile isotonic solution for injection with a pH between 6,0 and 8,0, free of particulate matter solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

XOFIGO should be received, used and administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6).

APPROVED PROFESSIONAL INFORMATION

Posology

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.

For details on the calculation of the volume to be administered, see section 12.

Special populations

Elderly
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 radium-223 dichloride is neither metabolised by the liver nor eliminated via the bile, hepatic impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

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

Patients with renal impairment

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

Paediatric patients

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

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 0, 9 % sodium chloride before and after injection of XOFIGO.
For additional instructions on the use of the medicinal product, see sections 6.6 and 12.

4.3 Contraindications

APPROVED PROFESSIONAL INFORMATION

XOFIGO is contraindicated in patients with hypersensitivity to radium-223 dichloride or any of the other ingredients of XOFIGO.

XOFIGO is also contraindicated in 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 section 4.2).

4.4 Special warnings and precautions for use

Bone marrow suppression

Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with XOFIGO (see section 4.8).
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 $\geq 1{,}5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L and haemoglobin $\geq 10{,}0$ 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.
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 section 4.6).

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 section 4.8).

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 section 4.4).

Bone fractures

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

APPROVED PROFESSIONAL INFORMATION

Combination with abiraterone plus prednisone/prednisolone

XOFIGO is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone. The clinical efficacy and safety of concurrent initiation of XOFIGO treatment and abiraterone acetate plus prednisone/prednisolone treatment was assessed in a randomized, placebo-controlled multicenter phase 3 study (ERA-223 trial) in 806 patients with asymptomatic or mildly symptomatic castration resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee Recommendation.
At the primary analysis an increased incidence of fractures (28,6% vs 11,4%) and deaths (38,5% vs 35,5%) among patients receiving XOFIGO in combination with abiraterone acetate plus prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone was observed. Concurrent use of bisphosphonates or denosumab reduced the incidence of fractures in both treatment arms.

Excipients with known effect

Depending on the volume administered, XOFIGO 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. It should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

No clinical interaction studies have been performed.

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females

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 section 4.4).

Pregnancy and Breastfeeding

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.

There is a potential risk that radiation from XOFIGO could cause adverse effects on testes (see section 5.3).

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 section 4.4).

4.7 Effects on ability to drive and use machines

APPROVED PROFESSIONAL INFORMATION

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

4.8 Undesirable effects

a. Summary of the safety profile

The overall safety profile of XOFIGO is based on data from 600 patients treated with XOFIGO in the phase III study.
The most serious adverse reactions were thrombocytopenia and neutropenia (see section 4.4 and subsection 'Description of selected adverse reactions').
The most frequently observed adverse reactions (≥10 %) in patients receiving XOFIGO were diarrhoea, nausea, vomiting and thrombocytopenia.

b. Tabulated list of adverse reactions

Table 1: 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	

c. 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 section 4.4). 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Therapeutic radiopharmaceuticals, other therapeutic radiopharmaceuticals, various therapeutic radiopharmaceuticals, ATC code: V10XX03

Mechanism of action

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 high linear energy transfer of alpha particles (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells of the tumour and the bone microenvironment such as tumour promoting osteoblasts and osteoclasts, 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.

Pharmacodynamic effects

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/ serum C-terminal crosslinked telopeptide of type I collagen [S-CTX-I] and type I collagen crosslinked C-telopeptide [ICTP]).

Clinical efficacy and safety

The clinical safety and efficacy of XOFIGO have been evaluated in a double-blind, randomized, multiple dose, phase III, multicentre study (ALSYMPCA) in castration-resistant prostate cancer patients with bone

metastases. Patients were randomized 2:1 to receive XOFIGO 55 kBq(0,00149mCi)/kg intravenously every 4 weeks for 6 cycles plus best standard of care or matching placebo pus best standard of care.

The primary efficacy endpoint was overall survival. Main secondary endpoints included time to symptomatic skeletal events (SSE), time to progression of total alkaline phosphatase (ALP), time to progression of prostate specific antigen (PSA), response of total ALP and normalization of total ALP.

Best standard of care included e.g. local external beam radiotherapy, bisphosphonates, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole.

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. The ALSYMPCA study showed that XOFIGO plus best standard of care significantly increased median overall survival by 3,6 months compared to best standard of care plus placebo (14,9 months vs 11,3 months; HR =0,695; 95% CI 0,581 to 0,832).
XOFIGO significantly delayed the occurrence of symptomatic skeletal events (SSE, defined as occurrence of any of the following; external beam radiotherapy to relieve pain, or pathological fracture, or spinal cord compression, or tumour-related orthopedic surgical intervention).

In addition, XOFIGO prolonged time to total ALP progression, PSA progression and a higher percentage of patients in the XOFIGO group achieved ~~of~~ total ALP response and ALP normalization.

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.

XOFIGO was associated with significantly greater Health Related Quality of Life (HRQOL) as measured by the FACT-P total score, and EQ-5D, ~~and~~ including the Visual Analogue health status score. The FACT-Prostate cancer pain-related subscale (based on 4 FACT-P items) showed significant reduction in pain as measured by the prostate cancer pain subscale score.

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.

XOFIGO was associated with significantly greater HRQOL as measured by the FACT-P total score (-4,828 versus -8,689, p = 0,004).

Subsequent use of cytotoxic drugs

In the course of the ALSYMPCA study, 93 (15,5%) patients in the XOFIGO group and 54 (17,9%) patients in the placebo group received cytotoxic chemotherapy at varying times after the last treatment.
No differences in hematological laboratory values were apparent between the two groups.

5.2 Pharmacokinetic properties

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.

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).

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 section 4.2).

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 section 4.2).

Paediatric patients

Safety and effectiveness of XOFIGO have not been studied in children and adolescents below 18 years of age (see section 4.2).

Cardiac Electrophysiology / QT prolongation

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

5.3 Preclinical safety data

APPROVED PROFESSIONAL INFORMATION

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 hematopoietic cells, fibrosis), spleen (secondary extra-medullary haematopoiesis) and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/ disorganization of the physis/growth line). These findings were related to radiation-induced impairment of haematopoiesis and a reduction of osteogenesis and occurred beginning in the dose range of 22 – 88 kBq (0,00059 – 0,00238 mCi) per kg body weight, with the exception of body weight decreases.

Dose-limiting myelotoxicity was seen in dogs after single administration of 497 kBq (0,0134 mCi) radium-223 dichloride per kg body weight (9 times the clinically recommended dose).

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

Retinal detachment was seen in dogs after a single injection of doses of 166 and 497 kBq (0,00449 and 0,0134 mCi) per kg body weight (3 and 9 times the clinically recommended dose), but not after repeated administration of the clinically recommended dose of 55 kBq (0,00149 mCi) per kg body weight once every 4 weeks for 6 months. Radium is specifically taken up in the *tapetum lucidum* of the canine eye. Since humans do not have a *tapetum lucidum*, the clinical relevance of these findings for humans is uncertain. No case of retinal detachment has been reported in clinical trials.

No histological changes were observed in organs involved in the excretion of radium-223 dichloride.
Osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses in rats 7 – 12 months after start of treatment.
Osteosarcomas were not observed in dog studies.

No case of osteosarcoma has been reported in clinical studies with XOFIGO. The risk for patients to develop osteosarcomas with exposure to radium-223 is unknown at present. The presence of neoplastic changes, other than osteosarcomas, was also reported in the longer term (12 to 15 months) rat toxicity studies. Due to its mode of action, and as seen with conventional radiotherapy and other radiotherapeutics, radium-223 dichloride may have the potential to induce secondary malignancies (see section 4.8)

Embryotoxicity / Reproduction toxicity
Studies on reproductive and developmental toxicity have not been performed.
Since radium-223 binds 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.

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 up to 497 (0.134 mCi) per kg body weight in dogs or up to 1100 kBq (0,0297 mCi) per kg body weight in rats (corresponding to 9 [dog] and to 20 [rat] times the clinically recommended dose).

APPROVED PROFESSIONAL INFORMATION

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium citrate
Sodium chloride
Hydrochloric acid, diluted

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

28 days

6.4 Special precautions for storage

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.

6.5 Nature and contents of container

6 mL Solution for injection is packed in a 10 mL colourless glass bottle, glass type I for injection, closed with a bromobutyl gray with foil-clad ETFE (4275) stopper for injection or alternatively with bromobutyl gray (5132) 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 provide 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.

6.6 Special precautions for disposal and other handling

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

APPROVED PROFESSIONAL INFORMATION

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 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 of XOFIGO are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando
1609

8 REGISTRATION NUMBER(S)

48/32.15/0715

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

18 February 2016

10 DATE OF REVISION OF THE TEXT

11 September 2023

11 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), 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 (0,0048 Gy, 0,48 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 (Gy 0,0003 Gy, 0,03 rad), and spleen (0,0004 Gy, 0,04 rad).

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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.
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.

Table 2: 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

APPROVED PROFESSIONAL INFORMATION

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) =
Body weight (kg) x dose (55 kBq [0,00149 mCi]/kg body weight)
Decay correction factor x 1100 kBq (0,0297 mCi)/mL

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