Radium-223 Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy or in combination with LHRH analogues for the treatment of adult patients with castration-resistant metastatic prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available licensed systemic mCRPC treatment	C61	00257a	ODMS 01/05/2015

TREATMENT:

The continuation of the drug details below may be adjusted by prescribing clinician, using their independent medical judgement, to consider each patient individual clinical circumstances.

Radium-223 is administered IV, given at 4 week (28 days) intervals for 6 injections or until disease progression or unacceptable toxicity develops.
Safety and efficacy beyond 6 injections have not been studied.
It should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings which satisfy radiation safety and regulation requirements.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Radium-223	55kBq/kg	IV	Slow injection up to 1 min	Repeat every 28 days for 6 cycles

The IV access line or cannula must be flushed with 0.9% sodium chloride for injection before and after injection of radium-223.
Prescribers and persons administering radium-223 should be aware that the National Institute of Standards and Technology (NIST) has revised in 2015 the primary standardization for radium-223, referred to as the NIST 2015-traceable reference material.
As a result the numerical value of the radioactivity concentration (in Bq/mL) contained in vials of Xofigo® and hence the patient dose in Bq/kg body weight will increase by approx. 10%:

- an increase of the nominal value for the radioactivity from 1000 kBq/mL to 1100 kBq/mL at reference date
- an apparent increase in patient dose, from 50 kBq/kg body weight to 55 kBq/kg body weight

This does not reflect a real change in the actual product radioactivity or in the amount of radioactivity given to the patient and therefore will not impact the safety and efficacy of Xofigo® (radium-223 dichloride).
Starting from April 14th, 2016, Xofigo® product manufactured, tested, and released according to the updated NIST 2015-traceable reference material will be distributed.
The Xofigo® product information has been updated to reflect the numerical change of the radioactivity concentration.
Once the first vial manufactured according to NIST 2015 reference material arrives at your facility, the new dial setting on the dose calibrators must be used.

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

- Patient's body weight (kg)
- Dosage level (55 kBq/kg body weight)
- Radioactivity concentration of the product (1100 kBq/mL) at reference date.
  The reference date is stated on the vial and lead pot label.
- Decay correction (DK) factor to correct for physical decay of radium-223.
  A table of DK factors is provided with each vial as part of the booklet (preceeding the package leaflet).
- The amount of radioactivity in the dispensed volume shall be confirmed by measurement in a properly calibrated activimeter.

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

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

ELIGIBILITY:

- Indications as above including
  - two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment
- Age ≥18
- ECOG status 0-2
- Castration refractory metastatic prostate carcinoma (clinical or biochemical progression, despite achieving castration) with symptomatic bone metastases
- No visceral metastasis or malignant lymphadenopathies (≥ 3 cm)
- Adequate bone marrow reserve defined by:
  - Prior to treatment initiation and 1st injection: ANC ≥1.5x10^9/L, platelets ≥100x10^9/L, HB ≥10g/dL.
  - Prior to subsequent injections (2nd to 6th): ANC ≥1 x10^9/L, platelets ≥50x10^9/L , HB ≥8g/dL.

EXCLUSIONS:

- Contraindicated in combination with abiraterone acetate and prednisone/prednisolone
- Safety and efficacy of radium-223 in combination with cancer therapies other than LHRH analogues have not been established; an increased risk of mortality and fractures was demonstrated in combination with abiraterone and cannot be excluded with others. The combination of radium-223 with other systemic cancer therapies other than LHRH analogues is therefore not recommended.
  - Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of radium-223.
- Presence of visceral metastases or extensive metastatic lymphadenopathies
- Prior treatment with radium-223
- Active spinal cord compression (including impending spinal cord compression) until completion of standard of therapy, however previously treated spinal cord compression with recovery of mobility and an ECOG 0-2 does not constitute a contra-indication
- Non-stabilised fracture [orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with radium-223]

CAUTION IN USE:

- **Eligibility:**
  - Recommendation: predicted life expectancy of more than 6 months.
  - Treatment of patients with asymptomatic or mildly symptomatic bone metastases: Radium-223 is 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. The use of radium-223 in patients with a low level of osteoblastic bone metastases (evaluated by imaging or others) is not recommended.
  - Patients with Crohns disease / Ulcerative colitis disease should be carefully assessed. Due to the faecal excretion of radium-223, radiation may lead to aggravation of acute inflammatory bowel disease. Radium-223 should only be administered after a careful benefit-risk assessment in patients with acute inflammatory bowel disease.
- **Washout periods:**
  - Data on a safe period after which radium-223 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 radium-223 and abiraterone, it is recommended that subsequent treatment with radium-223 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 radium-223.
- **Risk / Benefit:**
  - **Bone fractures**: Radium-223 increases the risk of bone fractures. Increased fracture risk has been found especially in patients with medical history of osteoporosis and in patients with less than 6 bone metastases. Other factors such as concomitant use of steroids may further increase the risk of fracture. Prior to starting radium-223, bone metastatic status (by imaging, e.g. by scintigraphy, and CT scan, evaluating extent of the metastatic bone disease and ostoeblastic/clastic activity levels) and baseline patient individual risk of fractures evaluated by clinical criteria e.g. concomitant medication, low body mass index and imaging e.g. bone mineral density measurements, should be carefully assessed, and closely monitored for at least 24 months. Preventive measures such as correction of risk factors and the use of bisphosphonates or denosumab should be considered before starting or resuming treatment with radium-223. In patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk. Orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with radium-223.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Radiation Oncologist with expertise in treatment of prostate cancer and radio-isotope prescription.

TESTS:

Baseline tests:

- Blood, renal and liver profile
- Bone scan and CT scan at time of disease progression
- PSA and testosterone levels.

Regular tests:

- FBC prior to each injection

Post therapy tests: FBC at 4 weeks post completion of therapy.

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- No dose modification required, only delay injection to be considered.
- Any treatment delays should be discussed with a Consultant.

Haematological:

At time of the subsequent (2nd to 6th) injections, if haematological eligibility criteria are not fulfilled, the injection should be delayed by 2-4 weeks. In case there is no recovery in these values within 6 weeks after the last administration of radium-223, despite receiving standard of care, further treatment with radium-223 should only be continued after careful benefit/risk evaluation.

Renal and Hepatic Impairment:

Table 1: Dose modification of radium-223 in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustment / treatment timing is considered necessary in patients with renal impairment.	No dose adjustment / treatment timing is considered necessary in patients with renal impairment.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low **(Refer to local policy).**

PREMEDICATIONS: None usually required.

OTHER SUPPORTIVE CARE:

- Maintenance hormonal therapy (minimum GnRh agonist or orchidectomy required).
- Biphosphonates/anti-RANKL antibody as directed by consultant.
- Best supportive care (if indicated and left to consultant preference, e.g. analgesic medication, external beam radiation therapy, analgesics, external radiation therapy, etc.)

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Bone marrow suppression:** Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with radium-223. Haematological evaluation must be carried out at baseline and prior to every dose.
  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.
- **Crohn's disease and ulcerative colitis**: Safety and efficacy of radium-223 in patients with Crohn's disease and with ulcerative colitis have not been studied. Due to the faecal excretion of radium-223, radiation may lead to aggravation of acute inflammatory bowel disease. Radium-223 should only be administered after a careful benefit-risk assessment in patients with acute inflammatory bowel disease.
- **Gastrointestinal toxicity**: Radium-223 increases the incidence of diarrhoea, nausea, and vomiting 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.
- **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 radium-223.
- **Osteonecrosis of the jaw**: In patients treated with bisphosphonates and radium-223, an increased risk of development of osteonecrosis of the jaw (ONJ) cannot be excluded.

- **Secondary malignant neoplasms**: 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 radium-223-induced cancer have been reported in clinical trials in follow-up of up to three years.
- **Excipients with known effect:** Depending on the volume administered, this medicinal product can contain up to 2.35 mmol (54 mg) sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

DRUG INTERACTIONS:

- 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 radium-223 treatment
- Concomitant chemotherapy with radium-223 may have additive effects on bone marrow suppression. Safety and efficacy of radium-223 in combination with other cancer therapies have not been established; an increased risk of mortality and fractures is possible. The combination of radium-223 with other systemic cancer therapies is therefore not recommended.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP
Xofigo® (radium-223-dichloride) - Important safety information from Bayer AG as approved by HPRA- March 2018.
http://www.hpra.ie/docs/default-source/Safety-Notices/important-safety-information---xofigo-(radium-223-dichloride)-(march-2018).pdf?sfvrsn=0

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5. XOFIGO® Summary of Product Characteristics. Last updated 18/05/2020. Accessed June 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	15/6/2015	Version 1	Dr PierreThirion
2	11/04/2016	Update of protocol to reflect Change in NIST Standard Reference Material. Clarification Regarding Hb levels	Dr PierreThirion
3	16/09/2016	Removal of reference to Orange label and clarification of reimbursement status	Dr PierreThirion
4	15/12/16	Revised wording to clarify the prescriptive authority requirement detailing that the treatment plan must be initiated by Consultant Radiation Oncologist with expertise in treatment of prostate cancer and radio-isotope prescription. Applied new NCCP regimen template	Dr PierreThirion
5	15/1/2018	Inclusion of Safety Notice from HPRA December 2017	Dr Pierre Thirion
6	16/4/2018	Updated exclusion criteria as per safety notice from HPRA March 2018 and clarified supportive care	Dr Pierre Thirion
7	21/10/2018	Updated to include EMA restrictions on use July 2018. Sections updated: • Indication • Eligibility, Inclusion/ Exclusion • Caution in use	Dr Pierre Thirion
8	16/06/2022	Reviewed. Updated eligibility, exclusion criteria, baseline tests, dose modifications, adverse effects and drug interactions.	Dr Pierre Thirion

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.