Radium 223 Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of adults with progressive castration-resistant metastatic prostate cancer, symptomatic bone metastases and no extensive visceral metastases	C61	00257a	ODMS

If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.

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, once every 28 days 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

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 (preceding 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:

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

ELIGIBILTY:

- Indications as above.
- Age ≥18
- ECOG status 0-2.
- Life expectancy >6 months.
- Progressive castration resistant metastatic prostate carcinoma disease, defined by a testosterone level ≤ 1.7 nml/L, and a PSA > 5 preceded by two consecutive rises (at least 1 week apart)
- Detectable (≥2 detectable bone lesions on bone scan, done within previous 12 weeks) and symptomatic bone metastases, defined by requirement for analgesic medication and/or palliative radiotherapy within previous 12 weeks
- No visceral metastasis and/or extensive metastatic lymphadenopathies on CT scan (done within previous 12 weeks)
- Having received DOCEtaxel or deemed not eligible or refusing DOCEtaxel
- Adequate bone marrow reserved defined by:
    - Prior treatment initiation and 1st injection: HB ≥ 10 g/dl (administration of 1st injection permitted if ≥ 8 g/dl), ANC ≥ 1.5 10^9/ L, platelets ≥ 100 10^9 / L.
    - Prior subsequent injections (2nd to 6th) ANC ≥ 110^9/ L, platelets ≥ 50 10^9/ L , HB ≥ 8 g/dl.

EXCLUSIONS:

- Chemotherapy administration within 4 weeks or planned concomitant administration
- Contraindicated in combination with abiraterone acetate and prednisone/prednisolone (See HPRA safety notification March 2018 in Company Resources below).
- Prior hemibody irradiation or radio-isotope (strontium-89, samarium-153, rhenium-186 or rhenium-188) administration for bone metastases within 24 weeks.
- Blood transfusion or erythropoietin administration within 4 weeks.
- Presence of visceral metastases or extensive metastatic lymphadenopathies.
- Prior treatment with radium-223
- Active spinal cord compression (including impending spinal cord compression, however previously treated spinal cord compression with recovery of mobility and a ECOG 0-2 does not constitute a contra-indication).
- Non-stabilised fracture

Caution : Patient with Crohn disease / Ulcerative colitis disease should be carefully assessed.
Due to the faecal excretion of Xofigo, radiation may lead to aggravation of acute inflammatory bowel disease. Xofigo should only be administered after a careful benefit-risk assessment in patients with acute inflammatory bowel disease

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
- CT scan TAP/bone scan done within previous 12 weeks
- 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 the absence of haematological recovery after the latter delay, treatment should be discontinued.

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.
- **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.
- **Bone fractures**: Orthopaedic stabilisation of fractures should be performed 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
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Radium 223 - V10XX03

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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1. Parker C et al. Alpha emitter Radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369 (3), 213-23.
2. O'Sullivan J et al. Hematology safety of Radium-233 Dichloride in the phase 3 ALSYMPCA trial in castration-resistant prostate cancer patients with bone metastases: baseline prognostic factor subgroup analysis Eur J cancer 2013, 49, 5688-5688 (ab 2877)
3. Sartor O et al. Safety of cytotoxic chemotherapy following Radium-223 dichloride therapy in the phase 3 ALSYMPCA study in patients with castration-resistant prostate cancer with bone metastases. Eur J cancer 2013, 49, (Poster 936P)
4. Safety Update from HRPA . Xofigo : Change in NIST Standard Reference Material-Information on Impementation. Safety Update from HRPA. Available at https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---xofigo-(radium-223-chloride).pdf?sfvrsn=0
5. XOFIGO Summary of Product Characteristics. Accessed April 2018. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002653/WC500156172.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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/