Medicine matters

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Positioning Xofigo®▼ (radium-223 dichloride) in the metastatic castration-resistant prostate cancer (mCRPC) treatment pathway

Introduction

Castration-resistant prostate cancer (CRPC) is an advanced state of prostate cancer that is no longer responsive to androgen deprivation therapy.[1] Patients with CRPC usually develop metastases as their disease progresses.[2,3] Approximately 90% of men with mCRPC develop bone metastases,[3–5] which are associated with a poor quality of life and low overall survival (OS).[5–7]

Radium-223 dichloride is a therapeutic, alpha particle-emitting radiopharmaceutical that mimics calcium and selectively targets bone when injected intravenously, creating cytotoxic double-stranded DNA breaks in tumour cells.[8,9] Radium-223 dichloride specifically targets areas of high bone turnover and has a relatively low impact on normal myeloproliferative tissue.[9,10]

Radium-223 dichloride was initially licensed in Europe in 2013 for the treatment of adults with mCRPC, symptomatic bone metastases and no known visceral metastases, based on the results of the ALSYMPCA trial.[8,11] ALSYMPCA included patients with progressive and symptomatic mCRPC; however, those with malignant lymphadenopathy exceeding 3 cm in short axis diameter were excluded.[11] Results showed that radium-223 dichloride plus best standard of care (BSC) significantly improved the OS and time to first symptomatic skeletal event (SSE) of patients with mCRPC compared with placebo plus BSC (median OS: 14.9 vs 11.3 months, respectively [hazard ratio {HR}: 0.70; 95% confidence interval {CI}: 0.58–0.83; p<0.001]; median time to first SSE: 15.6 vs 9.8 months, respectively [HR: 0.66; 95% CI: 0.52–0.83; p<0.001]).[11] This improvement in OS was independent of prior docetaxel exposure.[12] Radium-223 dichloride also demonstrated an acceptable tolerability profile that was comparable with placebo (all adverse events [AEs]: 93% vs 96%; Grade 3–4 AEs: 56% vs 62%; serious AEs: 47% vs 60%; and discontinuations due to AEs: 16% vs 21%).[11] The tolerability of radium-223 dichloride has been shown to be consistent for up to 3 years after the first dose of treatment, with no further major safety signals identified in that period.[13]

Since the ALSYMPCA study, the body of evidence on the efficacy and safety of radium-223 dichloride has expanded and include another Phase 3 trial, ERA-223.[14] The ERA-223 trial showed that radium-223 dichloride in combination with abiraterone acetate plus prednisone/prednisolone increased the incidence of fractures (28.6% vs 11.4%) and reduced median OS (30.7 months vs 33.3 months [HR: 1.195; 95% CI: 0.950–1.505; p=0.13]) among patients receiving radium-223 dichloride in combination

Declaration of interests
This article is based on the discussions and findings of a roundtable meeting organised by Bayer, in which the authors were participants. Bayer selected the authors, briefed them on the content of the meeting and paid them honoraria. This publication has been commissioned and sponsored by Bayer. Bayer provided financial support for its publication and verified that the content was factually accurate, balanced and compliant with the Association of the British Pharmaceutical Industry Code of Practice.

Prescribing Information for Xofigo® (radium-223 dichloride) can be found on page 7 of this publication.

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with abiraterone plus prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone plus prednisone/prednisolone.[9] In light of these findings, the label for radium-223 dichloride was amended following regulatory review to: radium-223 dichloride, as monotherapy or in combination with a luteinising hormone-releasing hormone (LHRH) analogue, is indicated for the treatment of adult patients with mCRPC, symptomatic bone metastases and no known visceral metastases, who have progressed after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or are ineligible for any available systemic mCRPC treatment.[9,15]

Following this change in label, it is apparent that clarification on the position of radium-223 dichloride in the mCRPC treatment pathway and guidance on how to optimise its use is required. A Bayer-sponsored multidisciplinary roundtable meeting of UK-based prostate cancer experts was held to establish a consensus on the position of radium-223 dichloride in the mCRPC treatment pathway. This article consolidates the key discussions from the meeting and outlines the consensus on:

- The position of radium-223 dichloride in the mCRPC pathway
- Ineligibility criteria for chemotherapy
- When discontinuation of abiraterone acetate/enzalutamide treatment should be considered

It is hoped that this guidance will assist physicians in selecting patients who are likely to benefit from radium-223 dichloride, thereby ensuring patients are offered the choice of all therapies for which they are eligible.

Discussion and recommendations

Positioning of radium-223 dichloride in the mCRPC treatment pathway

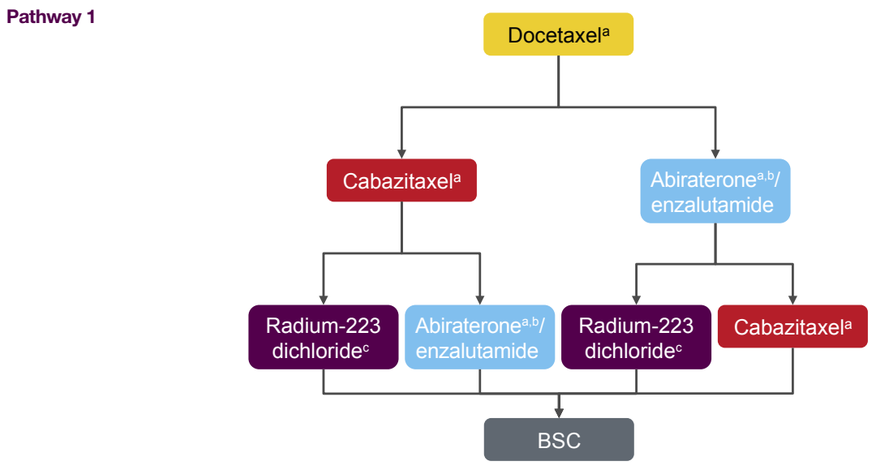
Three likely treatment pathways involving radium-223 dichloride were agreed upon at the meeting, taking into account its change in label and the UK treatment landscape at the time of writing (Figure 1). The principles highlighted by these three likely treatment pathways can be applied to other scenarios that physicians may encounter.

Pathway 1

The patient received docetaxel plus prednisone/prednisolone as a first-line therapy. Following disease progression, cabazitaxel plus prednisone/prednisolone may be prescribed. The rationale for this decision is based on a number of factors, including if the patient is eligible for further chemotherapy. If the patient's disease continues to progress, abiraterone acetate plus prednisone/prednisolone, enzalutamide or radium-223 dichloride should be considered. Radium-223 dichloride should be considered in patients with symptomatic bone-only metastases and lymphadenopathy <3 cm, among the other label stipulations.[9] Comorbidities such as diabetes should also be taken into account before offering abiraterone acetate plus prednisone/prednisolone, as treatment with glucocorticoids is associated with hyperglycaemia.[16]

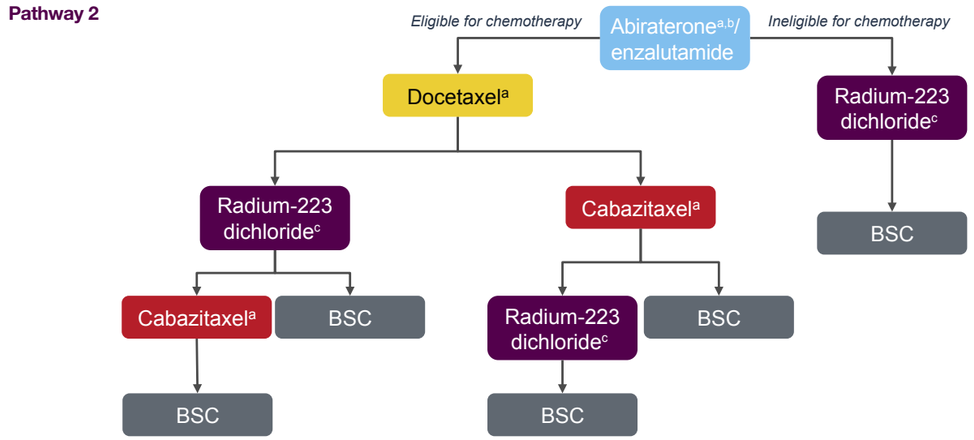
Abiraterone acetate plus prednisone/prednisolone or enzalutamide may be considered as an alternative to cabazitaxel in patients who have progressed following first-line treatment with docetaxel. If the patient's disease continues to progress following novel androgen receptor treatment, cabazitaxel plus prednisone/prednisolone or radium-223 dichloride may be prescribed. Radium-223 dichloride should be considered in patients with symptomatic bone-only metastases with lymphadenopathy <3 cm, among the other label stipulations. Cabazitaxel may be favoured for patients with rapidly progressing disease or where non-bone metastases predominate.[9, 17–19] If the disease continues to progress after treatment with abiraterone acetate plus prednisone/prednisolone or enzalutamide and radium-223 dichloride or cabazitaxel, best supportive care and clinical trials should be considered.

Figure 1a. Radium-223 dichloride may be prescribed as third-line therapy in patients with mCRPC who have received two prior systemic therapies



Please note, radium-223 dichloride should only be used in patients with symptomatic, bone-metastatic mCRPC.
[a]Plus prednisone/prednisolone; [b]Abiraterone/enzalutamide is licensed for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen; [c]Radium-223 dichloride, as monotherapy or in combination with an LHRH analogue, is indicated for the treatment of adult patients with 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 systemic mCRPC treatment.
BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer.

Figure 1b. Radium-223 dichloride may be prescribed as a second-line therapy in patients with mCRPC who are ineligible for chemotherapy



Please note, radium-223 dichloride should only be used in patients with symptomatic, bone-metastatic mCRPC.
[a]Plus prednisone/prednisolone; [b]Abiraterone/enzalutamide is licensed for the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated; [c]Radium-223 dichloride, as monotherapy or in combination with an LHRH analogue, is indicated for the treatment of adult patients with 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 systemic mCRPC treatment.
BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer.

Pathway 2

The patient received abiraterone acetate plus prednisone/prednisolone or enzalutamide as a first-line therapy. If a subsequent therapy is required and the patient is eligible for chemotherapy, docetaxel plus prednisone/prednisolone is recommended. If the patient's disease subsequently progresses and is symptomatic, radium-223 dichloride can be considered. Alternatively, cabazitaxel plus prednisone/prednisolone can be considered in symptomatic or asymptomatic patients. Factors influencing the choice between radium-223 dichloride and cabazitaxel include patient choice and eligibility for further chemotherapy, as well as the presence of biochemical, clinical and/or radiographic disease progression. Cabazitaxel may be favoured for patients with rapidly progressing disease or where non-bone metastases predominate.[9, 17–19]

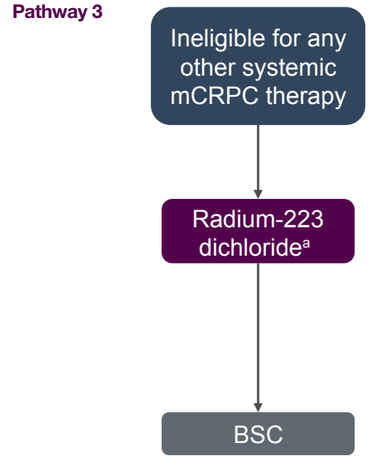
If disease progression continues after either cabazitaxel plus prednisone/prednisolone or radium-223 dichloride, treatment with cabazitaxel plus prednisone/prednisolone, radium-223 dichloride or best supportive care may be considered, depending on prior treatment and clinical eligibility.

If after abiraterone acetate plus prednisone/prednisolone or enzalutamide the patient is ineligible for chemotherapy and has bone-only metastases, radium-223 dichloride may be considered.

Pathway 3

If a patient is ineligible for any other systemic mCRPC therapy, radium-223 dichloride may be considered as a first-line therapy.

Figure 1c. Radium-223 dichloride may be prescribed as a first-line therapy in patients with mCRPC who are ineligible for all other systemic therapies



[a]Radium-223 dichloride, as monotherapy or in combination with an LHRH analogue, is indicated for the treatment of adult patients with 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 systemic mCRPC treatment.
BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer.

Guidance on criteria for patient ineligibility for chemotherapy

Treatments for mCRPC fall into three main classes: novel androgen receptor therapy, targeted alpha therapy and chemotherapy (Figure 1). Determining if a patient is eligible for chemotherapy is important as fitness, a major eligibility criterion, worsens as a patient's disease progresses. Thus, physicians must be confident with their decision regarding eligibility as it may permanently remove a class of therapy from a patient's treatment options.

Current resources that can be used to help determine if a patient is eligible for chemotherapy include the National Institute for Health and Care Excellence guidance and clinical trial eligibility criteria.[20,21] However, there is no clear and comprehensive consensus on how ineligibility for chemotherapy is defined. Guidance on the factors to consider when determining a patient's eligibility for chemotherapy is outlined in Table 1.[22] These include, but are not limited to, contraindications for chemotherapy (e.g. severe liver impairment, low neutrophil count [<1.5 × 10^9/L]), poor performance status, comorbidities, patient choice or lack of cognition/social support (e.g. those patients that may be non-compliant due to lack of understanding).

Guidance on criteria for discontinuing abiraterone acetate/enzalutamide treatment

While it is important for physicians to know which patients are eligible for therapy, it is equally important that they recognise when treatment should be terminated.[23] Continuing a treatment that has become ineffective may cause the patient's disease to progress more rapidly, possibly preventing the patient from receiving subsequent, alternative therapies, if contraindicated due to worsening disease characteristics, or limiting the potential benefit of subsequent therapies.[9,17,23]

As abiraterone acetate and enzalutamide are commonly offered early in the treatment pathway,[24,25] it is particularly important for clinicians to be aware of when these therapies should be discontinued. Some advice has been published on when to discontinue abiraterone acetate and enzalutamide, including the Advanced Prostate Cancer Consensus Conference (APCCC) consensus and the Prostate Cancer Working Group third consensus (PCWG3).[23,30] The APCCC states that at least two of the following criteria: prostate-specific antigen (PSA) progression, radiographic progression and clinical deterioration need to be met in order for treatment discontinuation to be considered.[23] The PCWG3 consensus describes abiraterone acetate/enzalutamide discontinuation criteria based on disease sites (Table 2).[30] Despite these publications, clear and comprehensive criteria for discontinuing abiraterone acetate/enzalutamide in clinical practice have not yet been formalised.

Table 1. Patient ineligibility for treatment with chemotherapy[22]

Patient ineligibility criterion	Details
Patients contraindicated for docetaxel due to:	• Hypersensitivity to the active substance or to any of the excipients (polysorbate 80, ethanol anhydrous, citric acid) • Baseline neutrophil count of <1,500 cells/mm^3 • Severe liver impairment
Patients with poor PS defined as:	• ECOG PS ≥3 in isolation or • ECOG PS ≥2 with the existence of comorbidities, e.g. cardiac/liver dysfunction/COPD/renal failure
Comorbidities may include:	• Charlson Comorbidity Index score of ≥5 • Severe COPD: – Defined as severe by the Global Initiative for Chronic Obstructive Lung Disease score >3[26] • Symptomatic heart failure defined as: – Class ≥2 based on the New York Heart Association functional classification[27] • A history of bowel disease including: – Significant inflammatory disease – Resection – Previous perforation – Existence/history of fistulas – Subacute obstructions • Peripheral neuropathy defined as Grade 2 or above (World Health Organization, ECOG)[28] • A low white blood cell count (or any increased risk of infection): – Neutrophil count <1.5 × 10^9/L • Platelet count <100 × 10^9/L • Ongoing treatment with immunosuppressive therapy (for any condition) • Recurrent sepsis • Ongoing treatment for tuberculosis • Recurrent pancreatitis • Poor liver function (severe liver function is contraindicated), defined as scoring 3 points in any one Child–Pugh score parameter (e.g. encephalopathy, ascites, bilirubin, albumin, prothrombin time) • Poorly controlled diabetes[29] – HbA1c >7% (53 mmol/mol) • Poor peripheral circulation • Skin ulcers • Splenectomy with prophylactic antibiotics
Patients whose cognition and/or social support will result in:	• Non-compliance with the treatment regimen • Inadequate toxicity monitoring • Inability to understand treatment fully and provide informed consent
Patient choice:	• Patients should be fully briefed, as per the General Medical Council guidelines, on all therapeutic options including alternative treatments and the option of receiving no treatment in order to provide their consent

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; HbA1c, glycated haemoglobin; PS, performance status.

At the roundtable meeting, discontinuation criteria highlighted in the APCCC and PCWG3 were expanded upon and separated into two categories: biochemical progression (PSA dynamics/kinetics, haemoglobin levels, alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels) and radiological progression (computed tomography [CT] scan, bone scan, magnetic resonance imaging [MRI] scan and positron emission tomography [PET]). In addition to this, toxicity (e.g. liver function, hypertension) and patient choice are also important considerations for discontinuing abiraterone acetate/enzalutamide therapy.[23,30]

To conclude, biochemical progression (PSA dynamics/kinetics, haemoglobin levels, ALP levels and LDH levels), radiological progression (CT scan, bone scan, MRI fingerprint scan and PET), site-specific progression (Table 2), treatment toxicity and patient choice are factors of which the presence of each should cause a physician to consider discontinuing abiraterone acetate/enzalutamide.

Summary

Following its recent change in label, this article clarifies the current position of radium-223 dichloride in the UK mCRPC treatment pathway. The three treatment pathways identified here clearly demonstrate that radium-223 dichloride remains an important treatment option as a monotherapy or in combination with LHRH for eligible patients with symptomatic, bone-metastatic mCRPC without visceral metastases.

We also highlight the importance of determining a) patient eligibility for chemotherapy; and b) when to discontinue treatment with abiraterone acetate/enzalutamide, both of which are critical to ensuring that patients receive the most appropriate treatment at the most appropriate time. Factors that can help determine whether a patient is ineligible for chemotherapy include contraindications for chemotherapy, poor performance status, comorbidities, patient choice or lack of cognition/social support (e.g. patients that may be non-compliant due to lack of understanding).[22] Criteria for discontinuing abiraterone acetate/enzalutamide include biochemical progression, radiological progression, site-specific progression (Table 2), treatment toxicity and patient choice.[30]

Taken together, this article provides key guidance that can be used to help inform treatment decisions and ensure that patients with mCRPC are treated appropriately at each stage of their disease.

Table 2. PCWG3 consensus on discontinuation criteria for abiraterone acetate and enzalutamide[30]

Area	Details
Nodes:	• Nodal progression sufficient for trial entry independent of PSA • Measurable lesions not required for entry • Modified RECIST v1.1 criteria, separate pelvic and extrapelvic disease, and up to five nodal lesions recorded • Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis to be considered as having progressed • If the node progresses to ≥1.5 cm in the short axis, it is measurable; nodes that have progressed to <1.5 cm are pathological, subject to clinical discretion and are non-measureable • For existing pathological adenopathy, progression is defined per RECIST v1.1 • Record presence of nodal and/or visceral disease separately Nodal sites: – Locoregional: pelvic only – Extrapelvic: retroperitoneal, mediastinal, thoracic, or other
Viscera:	• Visceral progression sufficient for trial entry independent of PSA and recorded separately by site of spread (lung, liver, adrenal, CNS); up to five lesions per site of spread • Measurable lesions not required for entry • Use RECIST v1.1 to record visceral lesions as target or non-target • Record presence of nodal and/or visceral disease (visceral sites: lung, liver, adrenal, CNS) separately
Bone:	• Two new lesions • Confirm ambiguous results by use of other imaging modalities (e.g. CT or MRI) but only positivity on the bone scan defines metastatic disease to bone

CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Working Group 3; PSA, prostate-specific antigen; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Disclosures

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Xofigo® 1100 kBq/mL solution for injection (radium-223 dichloride) Prescribing Information

▼ **Xofigo® 1100 kBq/mL solution for injection (radium-223 dichloride) Prescribing Information**
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: Each vial contains 6 mL of solution (6.6 MBq radium-223 dichloride at the reference date). 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. **Indication(s):** Xofigo monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with metastatic castration-resistant 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 systemic mCRPC treatment. **Posology & method of administration:** Xofigo should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings, and after evaluation of the patient by a qualified physician. Xofigo is for intravenous use and must be administered by slow injection (generally up to 1 minute). The intravenous access line or cannula must be flushed with isotonic sodium chloride 9 mg/mL (0.9%) solution for injection before and after injection of Xofigo. ***Adults:*** The dose regimen of Xofigo is an activity of 55 kBq per kg body weight, given at 4 week intervals for 6 injections. ***Hepatic impairment:*** No dose adjustment is considered necessary in patients with hepatic impairment. ***Renal impairment:*** No dose adjustment is considered necessary in patients with renal impairment. ***Elderly patients:*** No dose adjustment is considered necessary in elderly patients. ***Children & adolescents:*** There is no relevant use of this medicinal product in the paediatric population for prostate cancer. **Contra-indications:** Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone. **Warnings & precautions:** The safety and efficacy of Xofigo in combination with cancer therapies other than LHRH analogues have not been established; an increased risk of mortality and fractures is possible. The combination of radium-223 with other systemic cancer therapies other than LHRH analogues is not recommended. The use of Xofigo is not recommended for treatment of adults with CRPC and only asymptomatic bone metastases. In adults with CRPC 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. In clinical studies, patients with fewer than 6 bone metastases had an increased risk of fractures and did not have a statistically significant survival benefit. A pre-specified subgroup analysis also showed that overall survival was not significantly improved in patients with a total ALP < 220 U/L. Therefore, in patients with a low level of osteoblastic bone metastases treatment with radium-223 is not recommended. Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, have been reported in patients treated with Xofigo. Haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo. In case there is no recovery in values for absolute neutrophil count (ANC), platelets and haemoglobin 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 should be treated with caution. Safety and efficacy of Xofigo have not been studied in patients with Crohn's disease and ulcerative colitis. Due to faecal excretion of Xofigo, radiation may lead to aggravation of acute inflammatory bowel disease. Therefore, Xofigo should only be administered after a careful benefit-risk assessment in patients with acute inflammatory bowel disease. 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. Xofigo increases the risk of bone fractures, especially in patients with medical history of osteoporosis and in patients with <6 bone metastases. Prior to starting radium-223 bone status and baseline risk of fractures of patients (e.g. osteoporosis, less than 6 bone metastases, medication increasing fracture risk, low body mass index) should be carefully assessed, and closely monitored for at least 24 months. Preventive measures should be considered before starting or resuming treatment with Xofigo. In patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk. In patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo. In patients treated with bisphosphonates and Xofigo, an increased risk of development of osteonecrosis of the jaw (ONJ) cannot be excluded. Xofigo contributes to a patient's overall long-term cumulative radiation exposure which 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. Xofigo 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. This medicinal product can contain up to 2.35 mmol (54 mg) sodium per dose, depending on the required volume, and must be taken into consideration by patients on a controlled sodium diet. **Interactions:** No clinical interaction studies have been performed. Interactions with calcium and phosphate cannot be excluded. Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. **Fertility, pregnancy & lactation:** Xofigo is not indicated in women. Results from animal studies, indicate there is a potential risk that radiation from Xofigo could cause adverse effects on fertility. Male patients should seek advice on conservation of sperm prior to treatment. Due to potential effects on spermatogenesis associated with radiation, men should be advised to use effective contraceptive methods during and up to 6 months after treatment with Xofigo. **Effects on ability to drive and use machines:** There is no evidence, nor is it expected, that Xofigo will affect the ability to drive or use machines. **Undesirable effects:** *Very common*: Thrombocytopenia, diarrhoea, vomiting, nausea, bone fracture. *Common*: Neutropenia, pancytopenia, leukopenia and injection site reactions. *Uncommon*: Lymphopenia, osteoporosis. *Serious*: Thrombocytopenia and neutropenia. Prescribers should consult the SmPC in relation to other side effects. **Overdose:** No specific antidote. In the event of an inadvertent overdose, general supportive measures, including monitoring for potential haematological and gastrointestinal toxicity should be undertaken. **Incompatibilities:** Do not mix with other medicinal products. **Special Precautions for Storage:** Store in accordance with national regulation on radioactive materials. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** Single vial pack £4040. **MA Number(s):** EU/1/13/873/001 and PLGB 00010/0710. **Further information available from:** Bayer plc, 400 South Oak Way, Reading, Berkshire, RG2 6AD United Kingdom. Telephone: 01182063000. **Date of preparation: November 2022**

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