Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

radium-223 dichloride 1000kBq/mL solution for injection (Xofigo®)

SMC No. (1077/15)

Bayer Pharma AG

4 September 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan process

radium-223 dichloride (Xofigo®) is accepted for use within NHS Scotland.

Indication under review: for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

In a randomised phase III study of adult men with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases, treatment with radium-223 dichloride was associated with a significant improvement in overall survival compared to placebo.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of radium-223 dichloride. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

Dosing Information

50kBq per kg body weight intravenously, given at four week intervals for six injections.

Radium-223 dichloride must be administered by slow intravenous injection (generally up to one minute). The intravenous access line or cannula must be flushed with isotonic sodium chloride 9mg/mL (0.9%) solution for injection before and after injection of radium-223 dichloride.

Radium-223 dichloride should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings and after evaluation of the patient by a qualified physician.

Product availability date

January 2014. Radium-223 dichloride meets SMC end of life and orphan equivalent criteria.

Summary of evidence on comparative efficacy

Radium-223 dichloride, hereafter referred to as radium-223, is a new medicine and the first alpha-particle emitting radiopharmaceutical to be licensed in the UK. It acts by mimicking calcium and selectively targeting bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent tumour cells, resulting in a potent cytotoxic effect. Additional effects on the tumour microenvironment, including osteoblasts and osteoclasts, also contribute to the *in vivo* efficacy. The alpha particle range from radium-223 is less than 100 micrometers (10 cell diameters) which minimises damage to the surrounding normal tissue. The half life of radium-223 is 11.4 days.[1]

The evidence to support the use of radium-223 in prostate cancer comes from the results of a phase III, randomised, double-blind study (ALSYMPCA).[2,3] Eligible patients had histologically confirmed progressive castration-resistant prostate cancer, at least two bone metastases on skeletal scintigraphy and no known visceral metastases. They had baseline prostate specific antigen (PSA) ≥5nanograms/mL and evidence of progressively increasing PSA values (two consecutive increases over the previous reference value), an Eastern Co-operative Oncology Group (ECOG) performance status score of 0 to 2 and a life expectancy of at least six months. Patients could have either received prior treatment with docetaxel or not. They also had symptomatic disease and had regularly used analgesics or received external beam radiation therapy for cancer-related bone pain in the previous 12 weeks. A total of 921 patients were randomised, in a ratio of 2:1, to radium-223 (50kBq/kg) (n=614) or placebo (n=307) by intravenous injection every four weeks for six injections. Randomisation was stratified by previous use of docetaxel, baseline alkaline phosphatase (ALP) (<220U/L or ≥220U/L) and

current use of bisphosphonates. All patients also received best local standard of care which could include local external beam radiation therapy, glucocorticoids, antiandrogens, ketoconazole or oestrogens.

The primary outcome was overall survival defined as the time from randomisation to death from any cause. At the time of the pre-planned interim analysis (based on 809 enrolled patients: 541 in the radium-223 group and 268 in the placebo group), median overall survival was 14.0 months in the radium-223 group and 11.2 months in the placebo group: hazard ratio (HR) 0.70 (95% confidence interval [CI]: 0.55 to 0.88), p=0.002. In the radium-223 group, 35% (191/541) of patients had died compared with 46% (123/268) in the placebo group. An independent data monitoring committee stopped the study early based on this significant survival benefit. In an updated analysis, performed six months later and before patients were allowed to crossover from placebo (based on 528 deaths), median overall survival was 14.9 months in the radium-223 group and 11.3 months in the placebo group: HR 0.70 (95% CI: 0.58 to 0.83), p<0.001. In the radium-223 group, 54% (333/614) of patients had died compared with 64% (195/307) in the placebo group. Patients had received a mean of 5.1 doses of radium-223 and 4.5 doses of placebo and a median of six and five doses respectively.[2,3]

Pre-specified subgroup analyses were performed and found that the survival benefit was consistent. In the subgroup of patients who had received previous docetaxel, median overall survival was 14.4 months in the radium-223 group (n=352) and 11.3 months in the placebo group (n=174): HR 0.70 (95% CI: 0.56 to 0.88), p=0.002. In the subgroup who had not received previous docetaxel, median overall survival was 16.1 months in the radium-223 group (n=262) and 11.5 months in the placebo group (n=133): HR 0.69 (95% CI: 0.52 to 0.92), p=0.01.[4]

Results of secondary outcomes significantly favoured radium-223 over placebo as detailed in table 1 below.

Table 1: Results of secondary outcomes from the ALSYMPCA study[2,3]

	Radium-223 (n=614)	Placebo (n=307)	Hazard ratio (95% CI), p-value
Time to first symptomatic skeletal event[a]	15.6 months	9.8 months	0.66 (0.52 to 0.83), p<0.001
Time to an increase in ALP[b]	7.4 months	3.8 months	0.17 (0.13 to 0.22), p<0.001
Total ALP response[c]	47% (233/497)	3.3% (7/211)	p<0.001
Normalisation of total ALP level[d]	34% (109/321)	1.4% (2/140)	p<0.001
Time to an increase in PSA level[e]	3.6 months	3.4 months	0.64 (0.54 to 0.77), p<0.001

CI=confidence interval; ALP= alkaline phosphatase; PSA= prostate specific antigen

[a] Time to first symptomatic skeletal event: first use of external-beam radiation therapy to relieve skeletal symptoms; new symptomatic pathologic vertebral or non-vertebral bone fractures; spinal cord compression, or tumour-related orthopaedic surgical intervention

[b] Time to an increase in ALP level: ≥25% from baseline at week 12 (in patients with no decrease from baseline) or as an increase of ≥25% above the nadir, confirmed ≥3 weeks later (in patients with an initial decrease from baseline)

[c] A total ALP response: reduction of ≥30% from baseline value, confirmed ≥4 weeks later

[d] Normalisation of total ALP level (return to a value within the normal range at 12 weeks, confirmed by two consecutive levels ≥2 weeks apart, in patients with ALP values above the upper limit of the normal range at baseline)
[e] Time to an increase in PSA level (relative increase of ≥25% from baseline and an absolute increase of ≥2nanograms/mL at ≥12 weeks in patients with no decrease in PSA level from baseline or relative increase of ≥25% from baseline and an absolute increase of ≥2nanograms/mL above the nadir confirmed ≥3 weeks later in patients with an initial decrease from baseline)

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the European Quality of Life - 5 Dimensions (EQ-5D) questionnaire. Overall, radium-223 and placebo patients experienced loss of quality of life assessed by both measurements. However, the loss of quality of life was more pronounced in the placebo than radium-223 group.[2] During the on-treatment period, the FACT-P total score reduced by -3.88 in the radium-223 groups and by -7.65 in the placebo group (p=0.006) and the EQ-5D visual analog health status score by -2.66 and -5.86 respectively (p=0.018). However, there is limited evidence that the delay in loss of health related quality of life extends beyond the treatment period.[1]

Supportive evidence was also available from a randomised, placebo-controlled, phase II study which assessed the effects of four doses of radium-223 in 64 patients with bone metastases from hormone-refractory prostate cancer.[5,6]

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details.

Adverse events were reported in 93% (558/600) of radium-223 patients and 96% (290/301) of placebo patients, and were considered treatment-related in 63% (380/600) and 57% (171/301) of patients respectively. They were categorised as grade 3 or 4 in 56% (339/600) and 62% (188/301) of patients respectively and serious in 47% (281/600) and 60% (181/301) of patients respectively. Adverse events led to discontinuation in 16% (99/600) and 21% (62/301) of patients respectively.[3]

The most commonly reported adverse events in the radium-223 and placebo groups respectively were bone pain (50% and 62%), nausea (36% and 35%), anaemia (31% and 31%), fatigue (26% and 26%), diarrhoea (25% and 15%), constipation (18% and 21%), vomiting (18% and 14%), anorexia (17% and 18%), peripheral oedema (13% and 10%), progression of malignant neoplasm (13% and 15%), weight loss (12% and 15%) and thrombocytopenia (12% and 6%).[3] Adverse events with a notably higher incidence in the radium-223 group than the placebo group were diarrhoea (25% versus 15%), thrombocytopenia (12% versus 5.6%) and neutropenia (5.0% versus 1.0%). Adverse events led to death in 16% (96/600) of radium-223 patients and 22% (67/301) of placebo patients.[2]

Administration of radium-223 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. In particular, the risk of osteosarcoma, myelodysplastic syndrome and leukaemias may be increased. No cases of radium-223-induced cancer have been reported in clinical studies in follow-up of up to three years.[1,2]

Summary of clinical effectiveness issues

Bone is the main site of metastases in prostate cancer and depending on the site involved can result in bone pain/fractures, spinal cord compression and anaemia from affected bone marrow. Treatment aims at eradicating or limiting metastases or palliating the side effects.[2] A number of treatment options for bone metastases are noted in clinical guidelines, including external beam radiotherapy, bisphosphonates, strontium-89 and radium-223; radium-223 is the only treatment currently associated with a survival benefit.[7,8] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area for treating bone disease. Radium-223 meets SMC end of life and orphan equivalent criteria.

In the pivotal ALSYMPCA study, radium-223 achieved a statistically significant benefit over placebo in the primary outcome, overall survival, at the pre-planned interim analysis and the updated analysis (2.8 months and 3.6 months respectively).[3] The European Medicines Agency (EMA) noted that this level of benefit was clinically meaningful in patients with advanced cancer. Subgroup analyses indicated that the treatment effect was consistent in various subgroups including patients who had or had not received previous docetaxel treatment. However, the study was not powered for such subgroup analyses.[3,4] The survival benefit was supported by results of secondary outcomes including the composite of time to symptomatic skeletal event, driven by the reduced use of external beam radiation for pain relief in the radium-223 group.[2]

The updated analysis was performed six months after the interim analysis, before patients were allowed to crossover from placebo, and was considered by the EMA as more clinically relevant in view of maturity of the data. However, the data were still not fully mature and any further survival analysis would be confounded by crossover. In addition, these results should be considered descriptive and the p-values cannot formally be accepted from a statistical perspective.[2]

The comparator of placebo plus best standard care was considered appropriate at the time the study was designed. However, other agents have since been licensed for use in patients with castration-resistant prostate cancer including abiraterone and enzalutamide both after docetaxel and before docetaxel in asymptomatic or mildly symptomatic patients and cabazitaxel. To date, abiraterone and enzalutamide have been accepted for use by SMC for use in patients whose disease has progressed on or after docetaxel therapy.

During the ALSYMPCA study, concomitant medication in the form of best standard care was not standardised during the study and patients received treatment as deemed appropriate locally by their physician. Any differences between concomitant treatments used may affect the results and are difficult to differentiate from the treatment effect.[2,3]

Study patients could have received previous docetaxel therapy or not. 57% of patients received prior docetaxel. The following reasons were included for those who had not previously received docetaxel: declined to receive it; not received it as it was not available locally or not being considered fit enough to receive it. These patients may therefore form a heterogeneous group with a range of prognoses.[2]

The exclusion of patients with visceral metastases limits the generalisability of the study to the overall Scottish population with castration-resistant prostate cancer and symptomatic bone

metastases. However, the licensed indication reflects the exclusion of patients with visceral metastases, in line with the study population.[1,3]

There are no comparative data with other active agents. However, since radium-223 can be used in patients with castration-resistant prostate cancer and symptomatic bone metastases irrespective of their previous therapy, it is difficult to define appropriate relevant comparators. Clinical experts consulted by SMC considered that radium-223 is a therapeutic advancement due to the associated survival benefit and suggested that it has a potential place at various stages in the prostate cancer treatment pathway. Although the submitting company did not consider abiraterone a relevant comparator, they presented an indirect comparison of radium-223 with abiraterone, using the Bucher method, in patients who had previously received docetaxel as a scenario analysis in the economic case. This comparison included the subgroup of patients from the ALSYMPCA study and one study comparing abiraterone with placebo. The results suggested no significant difference between radium-223 and abiraterone in terms of overall survival and PSA progression free survival. However, as noted by the submitting company, important differences between the study populations and definition of PSA progression free survival limit the validity of the results. In addition, since abiraterone is not a direct comparator to radium-223, this indirect comparison has limited relevance to the current submission.

There are considerable service implications associated with the handling and administration of a radiopharmaceutical within nuclear medicine departments. Its receipt, storage, use, transfer and disposal is subject to regulations and/or appropriate licences of competent official organisations. Although these processes are likely to already be in place, there may be service implications associated with the administration of an additional agent. Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the service delivery through nuclear medicine departments.

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of radium 223, as an end of life and orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Castration resistant prostate cancer is a life threatening condition which has a major impact on patients and their families. Metastases to bone are frequent and the resulting pain can be particularly severe and difficult to control. Radium 223 has a novel mechanism of action that targets bone, alleviating symptoms whilst causing minimal damage to other cells.

- Radium 223 has been shown to delay the time to first symptomatic skeletal event which is of particular benefit to patients as these events impact on quality of life. For example, spinal cord compression is a serious and life-limiting complication that must be treated as a medical emergency to reduce or prevent loss of mobility or paralysis. Delaying the time to a major skeletal event would increase the time that a patient would remain independent and active and reduce the burden on carers.

- Clinicians indicated that the side effects of radium 223 are very mild, which contrasts with the high burden of side effects associated with chemotherapy.

- Clinicians would expect to use radium 223 in the full licensed population and they consider it a valuable addition to other treatments. They expect a limited number of patients to be eligible as the licence excludes patients with visceral metastases.

- The additional requirements for delivery of a radiopharmaceutical were recognised but clinicians considered there would not be significant additional work for centres that had been involved in clinical trials. They did not feel there would be difficulties in treatment centres meeting the necessary requirements for radiopharmaceuticals.

- The PACE group felt that radium 223 can reduce the risk of spinal cord compression and pathological fractures which are particularly important due to high morbidity and associated costs, and radium 223 is considered a therapeutic advancement. This medicine shows overall survival benefit which other treatments do not.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis which compared radium-223 plus best supportive care (BSC) to BSC alone in the licensed population. A Markov modeling approach was chosen to assess the cost-effectiveness of radium-223 versus the comparator. The analysis used a 10 year time horizon.

In terms of model structure, patients entered the model in the progression-free without SSE (symptomatic skeletal event) health state where patients were assumed to be treated with radium-223 plus BSC or BSC. Patients could then either remain in this health state or transition to the progression-free with SSE health state, the progressed without SSE state, or the progressed with SSE state. Patients who were in the progression-free with SSE and the progressed without SSE states could also move to the progressed with SSE state. Patients could also die throughout the model.

The source of the clinical data used in the analysis was primarily the ALYSMPCA study.

Baseline utility estimates and a utility increment for radium-223 were taken from the ALYSMPCA study using EQ-5D data. Disutilities relating to adverse events were taken from the published literature.

Medicines and administration costs were included in the analysis, as were the costs of background disease management, medical resource usage, adverse events, SSE management, subsequent lines of treatment and end of life care.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was given on the price of the medicine.

With the PAS, the result indicated that the incremental cost-effectiveness ratio (ICER) for radium-223 plus BSC versus BSC was £20,583 per QALY gained. It is SMC policy to include the estimated QALY gain in the detailed advice document for all submissions. The PAS for radium-223 includes a discount to the NHS that is commercial in confidence and the submitting company has advised that publication of the QALY gain, when considered with other cost-effectiveness data in the public domain, could reveal the level of discount. For this reason, SMC

has agreed not to publish the estimated QALY gain for radium-223. The economic analysis was most sensitive to increasing the monthly price of radium-223, reducing the length of stay in hospital in the progressed without SSE health state for BSC, increasing the number of cycles of radium-223, reducing the length of stay in hospital for the progression with SSE health state for BSC and increasing the length of stay in hospital for the progression free without SSE health state for radium-223. When these variations were applied to the analysis, the ICER increased to £29,086, £27,183, £26,373, £23,411 and £22,997 per QALY gained respectively.

The company also provided a subgroup analysis which compared radium-223 against BSC in patients who were unsuitable for docetaxel. The results of this analysis generated an ICER of £26,607 with PAS. In addition, the company provided subgroup analyses that compared radium-223 against BSC and abiraterone respectively in patients who had prior exposure to docetaxel. For the comparison against BSC, the results generated an ICER of £23,168 with PAS. In relation to the comparison against abiraterone, the results indicated that radium-223 was dominant (i.e. less costly and more effective) with PAS. A PAS is in place for abiraterone and this was included in the analysis by using an estimate of the relevant price of abiraterone.

The main weaknesses were as follows:

- The base case analysis compared radium-223 versus BSC. However, as radium-223 is licensed for use in patients irrespective of their previous therapy, other comparators such as enzalutamide or abiraterone which are accepted for use post-docetaxel, may also be relevant to the evaluation. SMC clinical expert responses did appear to support BSC as a comparator; however, one SMC clinical expert response has indicated that it may displace enzalutamide or abiraterone. The company did provide subgroup analyses which compared radium-223 against abiraterone. Following discussion at the New Drugs Committee, the base case analysis which compared radium-223 against BSC in the intention to treat population of the ALSYMPCA study was considered to be the most appropriate analysis for consideration.

- The company's approach to modelling survival was inconsistent and other relevant curves were not used in the analysis. The company provided analyses which used the Gompertz, lognormal, Weibull and exponential curves which generated ICERs with PAS of £44,099, £23,818, £37,066 and £17,484 per QALY gained respectively. This variation suggested a degree of uncertainty around the estimates. The company also provided the PFS plots of the Kaplan-Meier curve and the parametric functions used in the analysis. The fit of the survival curves to the Kaplan-Meier data was good up to 30 weeks; however, the curves diverged from this point onwards. Visual inspection of the curves suggested that the Gompertz curve is the closest to the actual data and therefore relying on the Akaike Information Criteria (AIC) was misleading due to the dramatic drop in progression-free survival (PFS) for radium-223 after 30 weeks. In addition, when the Gompertz curve was used in the analysis, the ICER increased to £44,099 per QALY gained.

- The results of the overall survival (OS) and PFS modelling raised some issues in terms of face validity. The company provided the median OS and PFS estimates generated by the model and compared this against the ALSYMPCA study. The results suggested that median OS in the study and in the model were similar. However, median PFS for radium-223 was three months higher in the model than in the study, and was one month lower for BSC. Therefore, the difference in median PFS between radium-223 and BSC in the model was 7.6 months while in the study it was only 3.6 months, so the model has doubled the PFS benefit from the study. SMC expert responses regarding the plausibility of the model outputs

were limited. The company has subsequently provided an analysis which used the Kaplan-Meier data where available and the extrapolation thereafter and this increased the ICER to £22,159. The company also provided an analysis which compared the PFS benefit for radium-223 from the model using the Kaplan-Meier curves and the extrapolation at different time points. This analysis reported that the model did not substantially or systematically overestimate PFS benefit and was therefore helpful in providing reassurance.

- The economic model was sensitive to the length of stay of hospitalisation due to disease progression and duration in hospital differed for radium-223 and BSC. The company response highlighted that an analysis of medical resource use data reported significantly fewer hospital bed days per year for patients treated with radium-223 versus BSC. In addition, radium-223 was also associated with a significant extension of time to first SSE and disease progression, which also impacted on hospital care. However, SMC expert responses had questioned the validity of the figures used in the analysis. The company provided an analysis with differences in length of stay removed which increased the ICER with PAS to £26,507 per QALY gained.

The Committee considered the benefits of radium-223 in the context of its decision modifiers that can be applied when encountering high cost-effectiveness ratios and where there is increased uncertainty due to the orphan status of the medicine and concluded that the criteria for a substantial improvement in survival had been met.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate modifiers, the Committee was able to accept radium-223 for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Tackle Prostate Cancer, Prostate Scotland and Prostate Cancer UK, which are all registered charities.

- Tackle Prostate Cancer and Prostate Cancer UK have received pharmaceutical company funding in the past two years but not from the submitting company. Prostate Scotland has not received any funding from pharmaceutical companies in the past two years.

- Advanced prostate cancer can be an extremely painful and debilitating condition. Men are often bed-ridden and unable to perform day-to-day activities, many experience pain and fatigue. A significant number of men develop bone metastases. Bone metastases are one of the most painful conditions to endure and can cause spinal cord compression leading to weakness and numbness in the legs. This can impact on personal mobility, impacting on both quality of life and also for some men on employment. There can also be significant emotional and personal difficulties for men and their families' outlooks and lives.

- These men face an extremely limited range of treatment options to extend their lives and ease the symptoms of advanced disease, especially in the chemotherapy naïve setting.

- Radium 223 would provide men who have limited treatment options with an option that may give increased survival time and alleviate symptoms from bone metastases which are very impactful on their quality of life. The possible life extension is particularly important to patients and their families.

Additional information: guidelines and protocols

The European Association of Urology updated its prostate cancer management guidelines, in 2014.[7] The defining characteristics of castration-resistant prostate cancer are:
Castrate levels of serum testosterone (<50 nanograms/dL or <1.7 nanomol/L) plus either

1. Biochemical progression: Three consecutive increases in PSA (7 days apart) resulting in two 50% increases over the nadir, with PSA >2nanograms/mL or
2. Radiological progression: The appearance of at least two bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST.

The gold-standard treatment outcome in castration-resistant prostate cancer is overall survival, with other commonly used outcomes of improvements in quality of life, progression free survival and prostate cancer specific survival. Nearly all studies of treatments for castration-resistant prostate cancer have been conducted with ongoing androgen suppression, which should be continued in these patients. In patients with metastatic castration-resistant prostate cancer, good performance status, mildly symptomatic or asymptomatic with no evidence of visceral disease, the following are suggested as first-line non-chemotherapy-based therapeutic options: abiraterone, Sipuleucel T (not available in the UK), and enzalutamide. The guidance notes that common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. It notes several treatment options for painful bone metastases but that the only bone-specific drug associated with a survival benefit is radium 223, an alpha-emitter.

The National Institute for Health and Care Excellence (NICE) published clinical guideline number 175: Prostate cancer; diagnosis and treatment in January 2014.[8] The goals of treatment in hormone-relapsed disease are: improvement of survival and quality of life with control of symptoms. Chemotherapy is usually given to men with symptomatic progression but asymptomatic men with metastatic disease and a rapidly rising PSA may also benefit from chemotherapy. The combination of docetaxel and prednisolone is the only first-line chemotherapy regime licensed for use in hormone-relapsed prostate cancer. The guideline recommends docetaxel, within its licensed indication, as a treatment option for men with hormone-refractory prostate cancer only if their Karnofsky performance status score is 60% or more. Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy. The document states that men with prostate cancer may benefit from bone targeted therapies such as bisphosphonates, strontium-89 and radium-223 dichloride to suppress the metastases or to manage symptomatic bone metastases. The guideline recommends that bisphosphonates should not be offered to prevent or reduce the complications of bone metastases in men with hormone-relapsed prostate cancer but may be considered for pain relief in men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. Strontium-89 should be considered for men with hormone-relapsed prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy.

The European Society for Medical Oncology published; Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, in 2013.[9] It recommended that patients who develop castration-resistant prostate cancer should continue androgen suppression and be considered for further hormone treatments. In those with poor initial hormone response or severe symptoms, chemotherapy may be preferable. Patients who progress following docetaxel should be considered for treatment with abiraterone or enzalutamide. For patients with bone metastases the guideline makes a number of recommendations:

- external beam radiotherapy should be offered for those with a moderate number of painful bone metastases
- bone targeted therapy with one of the beta particle emitting radionuclides should be considered for patients with painful bone metastases
- denosumab or zoledronic acid can be recommended for patients with bone metastases at high risk for clinically relevant SREs but neither agent has been shown to prolong survival.

Additional information: comparators

Since radium-223 can be used in patients with castration-resistant prostate cancer and symptomatic bone metastases irrespective of their previous therapy, it is difficult to define directly relevant comparators. Other agents that may be used include docetaxel, cabazitaxel (not recommended by SMC), abiraterone, enzalutamide and strontium-89.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Radium-223	50kBq per kg body weight intravenously, given at 4 week intervals for 6 injections	4,040*	24,240
Abiraterone (plus prednisolone)	1,000mg orally once daily Prednisolone 10mg orally daily	2,738*	35,594
Enzalutamide	160mg orally once daily	2,735*	35,555
Docetaxel (plus prednisolone)	75 mg/m^2 intravenously every 3 weeks Prednisolone 5mg orally twice daily	723**	7,230

Doses are for general comparison and do not imply therapeutic equivalence. Costs for enzalutamide from eVadis on 4 May 2015; costs for abiraterone, cabazitaxel and docetaxel from MIMs online accessed 4 May 2015. Costs are based on an adult with a weight of 70kg or a body surface area of 1.8m^2. Costs do not take account of any patient access schemes.

* Abiraterone and enzalutamide are given continuously but costs have been calculated as a 28-day cycle to allow comparison with radium-223. Cost per course is based on six injections for radium-223 and in one year for abiraterone and enzalutamide** costs for docetaxel are based on the 21-day cycles for 10 cycles.

Additional information: budget impact

The company estimated there to be 104 patients eligible for treatment with radium-223 in year 1, rising to 106 patients in year 5 and that 9 patients would be treated in year 1, rising to 42 patients in year 5.

Without PAS
The company estimated that the gross budget impact was expected to be £193k in year 1, rising to £870k in year 5. As no medicines were assumed to be displaced, the net medicines budget impact was expected to be £193k in year 1, rising to £870k in year 5.

The company estimated additional costs associated with administration of the radiopharmaceutical and savings related to medical resource use, subsequent treatment and adverse events. The net total budget impact was estimated as £175k in year 1, rising to £792k in year 5.

In addition to budget implications for the radiopharmaceutical, there will be associated service cost implications for nuclear medicine departments.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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4. Hoskin P, Sartor O, O'Sullivan JM et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate canecr and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol2014;15:1397-406.

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This assessment is based on data submitted by the applicant company up to and including 1 July 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and

NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.