



Australian Government

Medical Services Advisory Committee

MSAC Public Summary Document

Application No. 1268 – Radium-223 for the treatment of patients with symptomatic castrate resistant prostate cancer with skeletal metastases

Sponsor/Applicant/s: Bayer Australia Pty Ltd

Date of MSAC consideration: MSAC 61st Meeting, 3-4 April 2014

1. Purpose of application

In December 2011, the Department of Health received a submission based assessment from Bayer Australia requesting the listing of a service for the administration of radium-223, an injectable radiopharmaceutical for the treatment of patients with symptomatic hormone refractory prostate cancer (HRPC) with skeletal metastases. The Protocol Advisory Sub-Committee requested that the terminology be castrate resistant prostate cancer (CRPC) rather than HRPC.

2. Background

The administration of Radium-223 is not publicly reimbursed in Australia and has not been previously considered by MSAC.

3. Prerequisites to implementation of any funding advice

At the time of MSAC's consideration Radium-223 was not registered by the Therapeutic Goods Administration (TGA). However, on 20 May 2014 Radium-223 was registered by the TGA for use in Australia for the treatment of castration-resistant prostate cancer patients with symptomatic bone metastases and no known visceral metastatic disease.

4. Proposal for public funding

Applicant Submission Proposed MBS item descriptor for radium-223

Category 3 – Therapeutic Procedure

MBS XXX

ADMINISTRATION OF RADIUM-223 for symptomatic castrate resistant prostate cancer in patients who have:

(i) ≥ 2 skeletal metastases; AND

(ii) ECOG performance status of 0-2; AND

(iii) previously failed, or are medically unsuitable for, treatment with docetaxel.

Schedule Fee: \$7,237.42

A maximum of six intravenous injections are to be administered at four week intervals.

ECOG = Eastern Cooperative Oncology Group

“Symptomatic” is defined as either regular (not occasional) use of analgesic medication for cancer-related bone pain or treatment with external beam radiotherapy (EBRT) for bone pain.

The submission based assessment (applicant’s submission) stated that access to radium-223 is intended for patients who have received docetaxel and experienced disease progression, or who are unwilling to receive docetaxel or patients in whom treatment with docetaxel is contraindicated.

5. Summary of Consumer/Consultant Feedback

Feedback suggested that the introduction of radium-223 onto the MBS would provide patients with an alternative to currently available chemotherapy and radiopharmaceuticals for palliative patients.

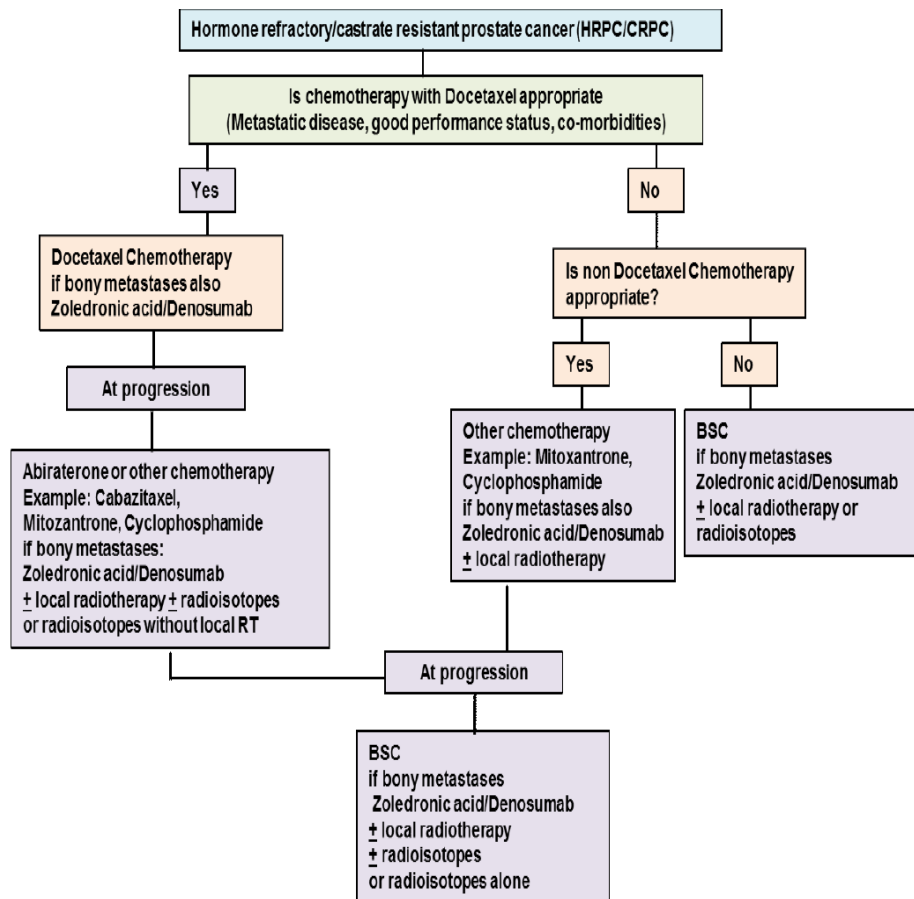
Given the availability and storage requirements of radium-223, access may be location dependent and therefore not available in many rural/remote areas.

6. Proposed intervention’s place in clinical management

The identified three target populations for radium-223 treatment included patients who:

- Have previously received docetaxel and are candidates for further active treatment,
- Have not previously been treated with docetaxel, but are candidates for further active treatment,
- Are not candidates for any of the currently available active therapies.

The following diagram describes the proposed clinical algorithm, which portrays these three populations where radioisotopes are targeted.



Patients with castrate resistant prostate cancer would be in the care of a medical oncologist or urologist, who would then refer the patient to a nuclear medicine physician or a radiation oncologist to administer the radiopharmaceutical radium-223 by intravenous injection.

Radium-223 would be administered a maximum of six times per patient at regular intervals of four weeks as monotherapy. The duration of treatment is six months maximum.

The proposed intervention could be delivered within a licensed nuclear medicine, radiology or radiation oncology department. If delivery of the proposed intervention is outside of the hospital setting, it would attract additional benefits through the Extended Medicare Safety Net.

7. Comparator

There are several comparators for radium-223:

- i) abiraterone (hormone therapy) and cabazitaxel (chemotherapy), in patients who have previously failed docetaxel;
- ii) the radiopharmaceuticals, strontium-89 and samarium-153 lexidronam, and best supportive care in patients who may or may not have failed docetaxel; and
- iii) best supportive care in patients who are not candidates for any of the currently available active therapies. Best supportive care includes; local external beam radiotherapy, androgen deprivation therapy (ADT), oestrogens or ketoconazole.

Abiraterone and cabazitaxel are both listed on the PBS.

The administration of Strontium-89 was first listed on the MBS in 1997. The MBS item descriptor as at February 2014 was:

Category 3 – Therapeutic Procedures
<p>MBS 16015</p> <p>ADMINISTRATION OF STRONTIUM-89 for painful bony metastases from carcinoma of the prostate where hormone therapy has failed and either:</p> <ul style="list-style-type: none"> (i) the disease is poorly controlled by conventional radiotherapy; or (ii) conventional radiotherapy is inappropriate, due to the wide distribution of sites of bone pain <p>Fee: \$4,085.70 Benefit: 75% = \$3,064.30 85% = \$4,011.20</p>

The administration of Samarium-153 lexicidronam was listed on the MBS in 2000. The MBS item descriptor as at February 2014 was:

Category 3 – Therapeutic Procedures
<p>MBS 16018</p> <p>ADMINISTRATION OF ¹⁵³Sm-LEXIDRONAM for the relief of bone pain due to skeletal metastases (as indicated by a positive bone scan) where hormonal therapy and/or chemotherapy have failed and either the disease is poorly controlled by conventional radiotherapy or conventional radiotherapy is inappropriate, due to the wide distribution of sites of bone pain.</p> <p>Fee: \$2,442.45 Benefit: 75% = \$1,8315.85 85% = \$2,367.95</p>

MSAC considered that these were appropriate comparators and noted that, as well as replacing some use of these comparators, radium-223 may be used in addition by being used sequentially with these comparators.

8. Comparative safety

The evaluation of comparative safety and effectiveness was based on:

- i) ALSYMPCA – a direct randomised comparative trial comparing radium-223 plus best supportive care (BSC) to placebo plus BSC;
- ii) an indirect comparison of radium-223 and strontium-89 based on the ALSYMPCA trial and five randomised comparative trials that compared strontium-89 and placebo or external beam radiotherapy (EBRT) with or without placebo;
- iii) an indirect comparison of radium-223 and cabazitaxel based on the ALSYMPCA trial and one randomised comparative trial comparing cabazitaxel and placebo; and
- iv) an indirect comparison of radium-223 and abiraterone based on the ALSYMPCA trial and one randomised comparative trial comparing abiraterone and placebo.

No additional samarium-153 lexicidronam trials were located beyond the two trials that were considered as part of the 1999 MSAC evaluation (#1016). The data from these trials were not included in the submission as the 1999 evaluation concluded that samarium-153 lexicidronam had similar effectiveness and no worse toxicity compared to strontium-89. Thus, the conclusions drawn in the comparison of radium-223 and strontium-89 were assumed to equally apply to samarium-153 lexicidronam.

The applicant submission concluded that radium-223 is at least as safe as alternative therapies and is superior to other bone-seeking radionuclides and best supportive care in terms of survival. There is no evidence that radium-223 is either superior or inferior to the alternative systemic therapies, cabazitaxel or abiraterone.

Based on the results of the ALSYMPCA trial, MSAC noted that radium-223 resulted in significantly fewer treatment-related adverse events (AEs) and AEs which led to discontinuation from the trial or death than placebo. The incidences of gastrointestinal disorders and thrombocytopenia were higher in the radium-223 group compared with best supportive care due to its myelosuppressive nature.

The results of the indirect comparison between radium-223 and strontium-89 showed no statistically significant differences in AEs. Radium-223 also appeared to be non-inferior in toxicity compared with abiraterone and cabazitaxel. MSAC considered that these indirect comparisons were difficult to interpret due to poor and uneven reporting across the trials and large differences in study design, dose, follow up and endpoints assessed.

Based on the results from the ALSYMPCA trial, MSAC concluded that radium-223 was associated with fewer treatment-related adverse events than placebo. However, the incidences of gastrointestinal disorders and thrombocytopenia were higher. MSAC also concluded that the indirect comparisons showed that radium-223 is probably non-inferior to strontium-89, cabazitaxel and abiraterone in terms of safety. However, MSAC noted that the indirect comparisons had low power for assessing adverse events.

9. Comparative effectiveness

The main results for comparable outcomes across the indirect comparisons are summarised in the table below.

Results for comparable outcomes across the indirect comparisons – (ITT)

Trial	Radium-223 (ALSYMPCA) trial			Comparator trials			
Event; time of ALSYMPCA analysis	Tx effect	Radium-223	Placebo	Comparator	Intervention	Tx effect	Indirect estimate of effect HR (95% CI)
	HR (95% CI)	n/N (%) Median months (95% CI)	n/N (%) Median months (95% CI)	n/N (%) Median months (95% CI)	n/N (%) Median months (95% CI)	HR (95% CI)	
				Oosterhof 2003			
				EBRT	Strontium-89		
OS; FA	0.70 (0.58, 0.83)	333/614 (54.2%) 14.9 (13.9, 16.1)	195/307 (63.5%) 11.3 (10.4, 12.8)	97/102 (95.1%) 11.0 (8.4, 15.2)	97/101 (96.0%) 7.2 (6.7, 9.6)	1.34 (1.01, 1.75)	0.52 (0.37, 0.72)
				COU-AA-301			
				Placebo	Abiraterone		
OS; FA	0.70 (0.58, 0.83)	333/614 (54.2%) 14.9 (13.9, 16.1)	195/307 (63.5%) 11.3 (10.4, 12.8)	NR 11.2 (10.4, 13.1)	NR 15.8 (14.8, 17.0)	0.74 (0.64, 0.86)	0.94 (0.74, 1.19)
Time to first SRE; IA	0.61 (0.46, 0.81)	202/614 (24.4%) 13.5 (12.2, 19.6)	116/307 (30.6%) 8.4 (7.2, NC)	93/398 (24.6%) 20.3 (16.9, NC)	180/797 (22.5%) 25.0 (25.0, NC)	0.62 (0.48, 0.79)	0.99 (0.68, 1.45)
				TROPIC			
				Mitoxantrone	Cabazitaxel		
OS; FA	0.70 (0.58, 0.83)	333/614 (54.2%) 14.9 (13.9, 16.1)	195/307 (63.5%) 11.3 (10.4, 12.8)	NR 12.7 (11.6, 13.7)	NR 15.1 (14.1, 16.3)	0.70 (0.59, 0.83)	0.99 (0.78, 1.27)

Source: Tables B(ii).6.1, B(iii).6.1 and B(iii).6.2 of Section B of the assessment report.

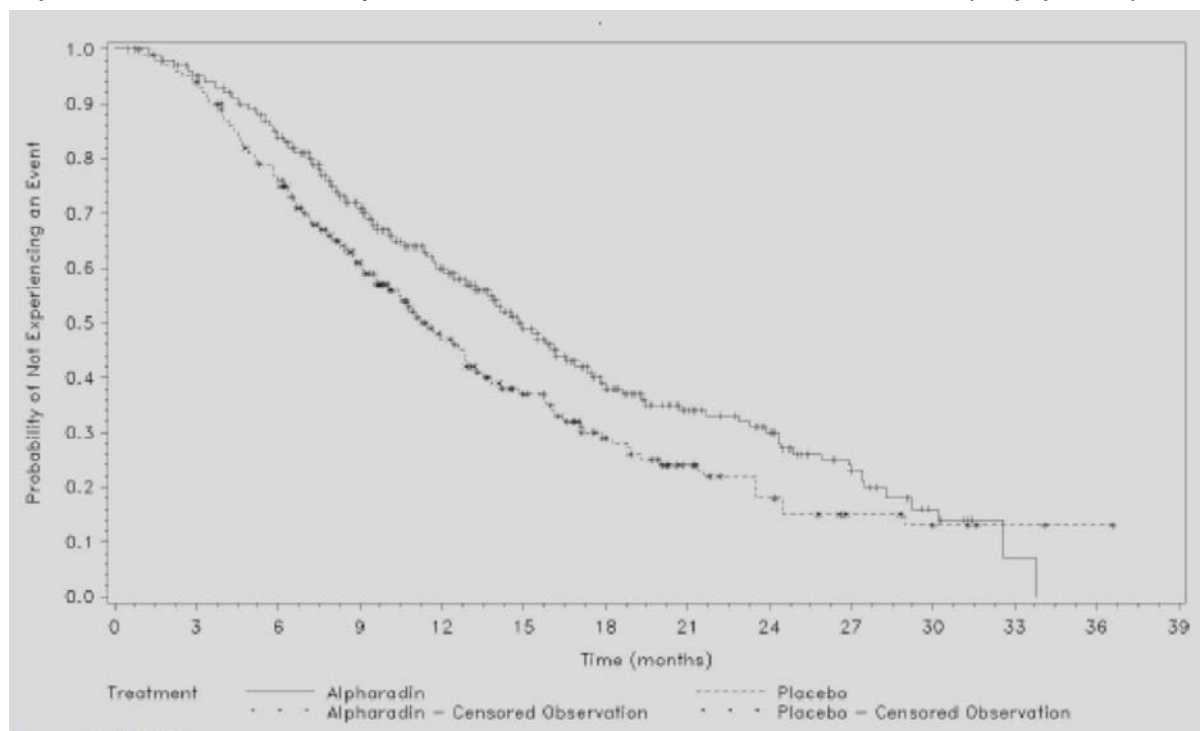
CI = confidence interval; EBRT = external beam radiotherapy; FA = final analysis; HR = hazard ratio; IA = interim analysis; ITT = intention to treat; NC = not calculated; NR = not reported; OS = overall survival; SRE = skeletal-related event; Tx= treatment, **Bold** = statistically significant

Radium-223 versus BSC (ALSYMPCA TRIAL)

The applicant submission concluded that radium-223 is superior to BSC in terms of overall survival and ‘time to first skeletal-related event (SRE)’ compared to placebo plus BSC, with or without prior docetaxel use. Radium-223 was associated with significantly less bone pain compared with placebo (interim analysis OR 0.54, 95% CI: 0.39, 0.73). Similarly, generic and cancer-specific quality of life scores were significantly better in patients treated with radium-223 compared with placebo plus BSC.

The overall survival benefit shown in the final analysis of the ALSYMPCA trial was 14.9 months with radium-223 compared to 11.3 months with placebo. This is illustrated in the Kaplan Meier curves below.

Kaplan Meier curve for final analysis overall survival in the ALSYMPCA radium-223 trial (ITT population)



Radium-223 versus strontium-89/samarium-153 lexidronam

The applicant submission concluded that, compared with strontium-89 (and samarium-153 lexidronam), radium-223 is superior in terms of overall survival in patients with or without prior docetaxel use.

This conclusion was based on the indirect comparison of the ALYSMPCA trial with a single trial of strontium-89 versus EBRT (Oosterhof 2003), in which the strontium-89 arm had poorer survival than the EBRT group. Comparisons with other strontium-89 trials were not included in the submission as the survival in the comparator arms was different to that in the placebo arm of the ALSYMPCA trial.

The applicant submission also concluded that radium-223 offers similar efficacy to strontium-89 in terms of time to first SRE. However, no indirect comparison was performed.

No quality of life data were provided in the applicant submission for the strontium-89 trials.

Radium-223 versus abiraterone (COU-AA-301 trial) and cabazitaxel (TROPIC trial)

The applicant submission concluded that, compared with abiraterone and cabazitaxel, radium-223 is non-inferior in terms of overall survival, the proportion of patients experiencing SRE, bone pain and quality of life. However, no evidence for quality of life and time to first SRE was presented for cabazitaxel.

Summary: Therapeutic conclusions for radium-223 versus the relevant comparators

Comparator	Overall survival	Time to first SRE	Bone pain	Quality of life	Adverse events	Economic evaluation
Abiraterone	Non-inferior	Non-inferior	Non-inferior	Non-inferior	Non-inferior	CMA
Cabazitaxel	Non-inferior	Non-inferior	Non-inferior	Non-inferior	Non-inferior	CMA
Strontium-89	Superior	Assume non-inferior	Assume non-inferior	Non-inferior	Non-inferior	CEA
Samarium-153 lexidronam	Superior	Assume non-inferior	Assume non-inferior	Non-inferior	Non-inferior	CEA
BSC	Superior	Superior	Superior	Superior	Non-inferior	CEA

BSC = best supportive care; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; SRE = skeletal-related event

MSAC considered that, based on the ALSYMPCA trial, radium-223 is superior to best supportive care in terms of overall survival, time to first skeletal-related event and improvement in bone pain.

MSAC considered that radium-223 is probably superior to strontium-89 in terms of overall survival. Based on its previous conclusion of the therapeutic similarity of samarium-153 lexidronam and strontium-89, MSAC did not object to extending this comparison of radium-223 with strontium-89 to include samarium-153 lexidronam.

MSAC considered that radium-223 is probably non-inferior to cabazitaxel and abiraterone in terms of overall survival, time to first skeletal-related event and improvement in bone pain. The committee noted that its conclusions of non-inferiority involving abiraterone and cabazitaxel were supported by the evidence in the presented indirect comparisons.

10. Economic evaluation

The applicant submission presented a cost-minimisation analysis comparing radium-223 with (i) cabazitaxel and (ii) abiraterone, based on the non-inferiority claim on effectiveness and safety.

The average course of radium-223 was 5.1 injections per patient as observed in the ALSYMPCA trial. The estimated price per administration of radium-223 that achieves parity with the cost of a course of treatment with cabazitaxel (**\$redacted**) was **\$redacted**. The corresponding result to achieve parity with the cost of a course of treatment using abiraterone (**\$redacted**) was **\$redacted**.

MSAC noted that at the time of its assessment of Radium-223 its comparators abiraterone and cabazitaxel were subject to PBS special arrangements. Refer to www.pbs.gov.au

The applicant submission also presented a cost-utility analysis comparing radium-223 with (i) best supportive care (BSC), (ii) strontium-89 and (iii) samarium-153 lexidronam, based on the superiority claim of effectiveness and similar safety.

The comparison of radium-223 versus samarium-153 lexidronam was based on the assumption that strontium-89 and samarium-153 lexidronam have a similar mechanism of action, efficacy and toxicity (previously determined by MSAC 1016). The applicant submission did not present any comparative evidence of radium-223 versus samarium-153 lexidronam. Subsequently, all the model inputs for samarium-153 lexidronam were identical to those for strontium-89, except for the MBS fee.

The cost-utility analysis was based on a Markov cohort model with 4-week cycles, five health states and 10-year duration. The model inputs relied heavily on the ALSYMPCA trial results and utilities. The main costs used in the model were for health care resource use and included drug acquisition costs, costs of managing adverse events and SREs, on-going pain control and end-of-life-care. The key component driving the model was radium-223 acquisition costs.

Redacted paragraph

The fee proposed in the applicant submission was derived from the cost of the five comparators. The applicant submission presented five different prices (or MBS fees) at which radium-223 was either considered to be cost neutral – i.e. cost minimised against administration of cabazitaxel and abiraterone – or acceptably cost-effective compared with BSC, strontium-89 and samarium-153 lexidronam. The proposed radium-223 price per injection (i.e. effective MBS fee; **\$redacted**) was the result of a weighted average across these prices, where the weights represented the expected extent of substitution away from each of the five comparators. This proposed fee included a notional **\$redacted** drug acquisition and administration component. The weights were obtained from a survey of 986 Australian specialists (medical oncologists, urologists, radiation oncologists) commissioned by the applicant.

The applicant submission requested a special pricing arrangement, which would represent a new type of funding arrangement for the MBS.

In the applicant submission, a patient contribution of \$74.50 was set, which assumed services are performed out of hospital and patients are charged the schedule fee. \$74.50 represented the maximum gap between the MBS 85 per cent patient out-of-hospital rebate and the schedule fee current at the time the assessment report was submitted.

The service would be eligible for safety net benefits when performed out of hospital. However, as the MBS comparators currently have minimal out-of-pocket costs, capping of safety net benefits may not be required.

11. Financial/budgetary impacts

The applicant submission estimated that over the next five years (2014-2018) **redacted** patients would receive treatment with radium-223. The estimates of patient numbers were based on AIHW 2009 incidence data and the commissioned survey of Australian specialists described above.

It was anticipated that patients would only receive one course of treatment comprising up to six radium-223 injections in a lifetime. The applicant submission assumed that, on average,

5.1 injections per person would be administered. However, the MBS item would allow for six injections per patient, per course of treatment.

Department modelling, based on the proposed listed price of \$7,237.42 and patients receiving an average 5.1 injections per person, estimated an increase in MBS expenditure of \$3.4 million in 2014-15 rising to \$13.4 million in 2018-19. There would also be a corresponding saving to the Pharmaceutical Benefits Scheme (PBS) because of substitution.

12. Other significant factors

Nil

13. Summary of consideration and rationale for MSAC's advice

MSAC considered the application for MBS listing of the radiopharmaceutical radium-223 for the treatment of certain patients with prostate cancer.

Radium-223 is an intravenously administered radiopharmaceutical that specifically targets bone metastases due to its calcium mimicking properties. There are currently two other radiopharmaceuticals listed in the MBS for use in treating bone metastases, strontium-89 and samarium-153 lexidronam. In contrast to these radiopharmaceuticals, radium-223 releases ultra-short range alpha particles which may lead to less bone marrow toxicity.

The proposed eligible population for MBS funding is patients with symptomatic castrate resistant prostate cancer and at least two skeletal metastases, who have good performance status but have failed or are medically unsuitable for docetaxel.

MSAC agreed that there are several comparators for radium-223 treatment for these patients:

1. best supportive care: in patients who are not candidates for any of the currently available active therapies including local external beam radiotherapy, androgen deprivation therapy, oestrogens or ketoconazole
2. strontium-89, samarium-153 lexidronam or best supportive care: in patients who may or may not have failed docetaxel
3. abiraterone (hormone therapy) or cabazitaxel (chemotherapy): in patients who have previously failed docetaxel.

MSAC noted that, as well as replacing some use of these therapies, radium-223 may be used sequentially in addition to these therapies.

MSAC considered comparative clinical evaluations of radium-223 based upon one direct randomised trial comparison with best supportive care alone and three indirect comparisons with currently available treatments for hormone refractory prostate cancer patients:

1. ALSYMPCA trial – direct randomised trial comparing radium-223 plus best supportive care with placebo plus best supportive care
2. indirect comparison with strontium-89 based on the ALSYMPCA trial and five randomised trials comparing strontium-89 and placebo or external beam radiotherapy with or without placebo (MSAC agreed with ESC that the main trial by Oosterhof 2003 used in the indirect comparison had been a comparison of strontium-89 with radiotherapy rather than with best supportive care, which biased the indirect

comparison against strontium-89 to the extent that radiotherapy is more effective than best supportive care)

3. indirect comparison with cabazitaxel based on the ALSYMPCA trial and one randomised trial comparing cabazitaxel and mitoxantrone (MSAC accepted that mitoxantrone had not been demonstrated to improve progression-free or overall survival over placebo)
4. indirect comparison with abiraterone based on the ALSYMPCA trial and one randomised trial comparing abiraterone to placebo.

MSAC also noted that the indirect comparisons were based on comparing across trials with large differences in time since the trial was conducted, design, dose, follow-up and endpoints assessed.

Based on the results from the ALSYMPCA trial, MSAC noted that radium-223 was associated with fewer treatment-related adverse events than placebo. However, the incidences of gastrointestinal disorders and thrombocytopenia were higher. The indirect comparisons showed that radium-223 is probably non-inferior to strontium-89, cabazitaxel and abiraterone in terms of safety. However, MSAC noted that the indirect comparisons had low power for assessing adverse events.

MSAC also considered the evidence for clinical effectiveness based on the above comparisons. Based on the final analysis of the ALSYMPCA trial, radium-223 is superior to best supportive care in terms of overall survival (median 14.9 months vs 11.3 months [HR 0.7; 95% CI: 0.58 – 0.83]), time to first skeletal-related event (median 15.6 months vs 9.8 months [HR 0.66; 95% CI: 0.52-0.83]) and improvement in bone pain (OR 0.61; 95% CI: 0.46-0.81).

MSAC considered that radium-223 is probably superior to strontium-89 in terms of overall survival, noting that this required accepting weak evidence in the form of a potentially biased indirect comparison involving the ALSYMPCA trial for radium-223 and the Oosterhof 2003 trial for strontium-89. Based on its previous conclusion of the therapeutic similarity of samarium-153 lexidronam and strontium-89, MSAC did not object to extending this comparison of radium-223 with strontium-89 to include samarium-153 lexidronam. MSAC noted that this uncertainty had little impact on its overall advice because only 4% of the projected use of radium-223 is assumed to replace these radiopharmaceuticals.

MSAC considered that radium-223 is probably non-inferior to cabazitaxel and abiraterone in terms of overall survival (indirect HR 0.99; 95% CI: 0.78, 1.27 for cabazitaxel and indirect HR 0.94; 95% CI: 0.74, 1.19 for abiraterone), time to first skeletal-related event (indirect HR 0.99; 95% CI: 0.68, 1.45 for abiraterone) and improvement in bone pain (indirect OR 0.61; 95% CI: 0.30, 1.24 for cabazitaxel and indirect OR 0.69; 95% CI: 0.47, 1.01 for abiraterone). The committee noted that its conclusions of non-inferiority involving abiraterone and cabazitaxel were supported by the evidence in the presented indirect comparisons.

MSAC noted that five economic evaluations were presented: three involving acceptance of therapeutic superiority to support cost-utility analyses against best supportive care, strontium-89 and samarium-153 lexidronam; and two involving acceptance of therapeutic non-inferiority to support cost-minimisation analyses against cabazitaxel and abiraterone. MSAC considered that this approach favoured radium-223 to the extent that it is used in sequence with its comparators rather than to replace them.

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MSAC reached the following conclusions in its appraisal of this approach.

- The nominated acceptable incremental cost-effectiveness threshold or willingness-to-pay of \$75,000 per QALY gained was unacceptably high and did not reflect contemporary PBAC-decision making in the context of cabazitaxel and abiraterone as claimed in the application. The basis for the applicant's claim was a publication that relied on the ICER ranges (e.g. \$45,000 to \$75,000) currently required for publication of PBAC decisions rather than an analysis across particular ICERs.
- MSAC questioned the use of a 10-year cost-utility model for patients with a median overall survival time of 1.3 years (based on the ALSYMPCA results for radium-223), but noted that reducing the time horizon to a more clinically acceptable 5-year model did not substantially change the results and so this was not a pivotal matter for its advice to the Minister.
- MSAC advised that the cabazitaxel price be used in the abiraterone cost-minimisation analysis, noting that PBAC's reasons for supporting a price advantage for abiraterone over cabazitaxel (being an oral therapy rather than an injected therapy resulting in reduced costs of administration and greater patient convenience) did not apply to radium-223.

The cost-minimisation analyses by the applicant used the PBS published price of abiraterone and cabazitaxel rather than the effective price of these medicines to the government. MSAC noted that the Department would have to manage a process through which the applicant could be advised of these effective prices and thus their consequence for reducing the applicant's back-calculated fee.

- MSAC accepted the proportions of substitutions used to calculate the weighted proposed fee whilst noting their reliance on an applicant-commissioned survey of 986 Australian specialists (medical oncologists, urologists, radiation oncologists) with a response rate of 8.1%.

Based on the responses in this survey, the applicant also estimated that over the next 5 years (2014 – 2018) 1,251 patients would receive treatment with radium-223 if listed in the MBS. MSAC noted issues with this assessment, in particular the low response rate in the survey and incidence data on estimated patient numbers based on 2005 and 2009 AIHW data. The assessment did not allow for uncertainty in these measures. Further, by limiting its estimates to incident patients expected to become eligible for radium-223 in each year of listing, the assessment did not also estimate the initial use of radium-223 in the prevalent pool of patients who would already be eligible for this use at the time of listing. In addition, the assessment was based on an average number of 5.1 injections of radium-223 per patient. The proposed MBS item would allow for up to six injections per patient's lifetime.

MSAC noted that utilisation of radium-223 would depend on a number of issues including the uptake of the new medications listed on the PBS (abiraterone and cabazitaxel), improved supportive care, clinician choice, cost and access. MSAC noted that estimated reductions in utilisation of comparator therapies would depend on the extent to which radium-223 would

supplement rather than substitute for them. For these reasons, MSAC indicated that the government should give consideration to including radium-223 in the risk-share arrangements that apply to cabazitaxel and abiraterone in prostate cancer.

MSAC observed that the decision of whether to accept the applicant’s proposal for a hidden pricing arrangement behind the published fee with payment of rebates in arrears was a policy matter for the government. It is difficult to predict any consequence of the hidden pricing arrangement on patient out of pocket expenses.

14. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of radium-223 for the treatment of patients with symptomatic castrate resistant prostate cancer with skeletal metastases, MSAC supported public funding via a new MBS item. This support acknowledged the applicant’s intention to negotiate a hidden arrangement to rebate the government in order to reflect a cost-effective price below the published fee. MSAC therefore advised that this price be recalculated based on the following modifications to the approach presented in the application:

- the cost-utility analyses should use a lower threshold ICER ; and
- the cost-minimisation analyses should use the effective price of cabazitaxel to the government rather than the price published in the Pharmaceutical Benefits Schedule.

In relation to the MBS item descriptor, MSAC advised:

<p>MSAC’s Proposed MBS item descriptor for radium-223 Category 3 – Therapeutic Procedure</p>
<p>MBS XXX ADMINISTRATION OF ONE INJECTION OF RADIUM-223, where referred by a specialist in medical oncology, radiation oncology or urology, for symptomatic castrate resistant prostate cancer in patients who have: (i) two or more skeletal metastases (as indicated by a positive bone scan); AND (ii) ECOG performance status of 0-2; AND (iii) previously failed, or are medically unsuitable for, treatment with docetaxel. (Published) Fee: \$7,237.42 A maximum of six intravenous injections are to be administered at four week intervals.</p>

ECOG = Eastern Cooperative Oncology Group
“Symptomatic” is defined as either regular (not occasional) use of analgesic medication for cancer-related bone pain or treatment with external beam radiotherapy (EBRT) for bone pain.

MSAC noted that implementation of its advice would be subject to TGA registration of radium-223.

15. Applicant’s comments on MSAC’s Public Summary Document

Bayer welcomes MSACs decision to support the funding of Xofigo (radium-223) for listing on the MBS, however Bayer is concerned regarding the advice to decouple accepted clinical comparators and claims with the presented economic analyses. MSAC advice to use the cabazitaxel effective price within the abiraterone cost minimisation analysis component is not representative of the presented clinical evidence and justified economic analyses. Hence does not seem to be supported by the Health Technology Assessment process set out by draft MSAC guidelines as well as sponsor engagement through advice received from the

Evaluation Sub-Committee (ESC). Bayer hopes to continue working with the MBS branch to resolve these issues as part of the listing process and provide Australian patients with access to Xofigo (radium-223) in a timely manner.

16. Linkages to other documents

Further information is available on the MSAC Website at: www.msac.gov.au.