
1268

Protocol to guide the
assessment of
radium-223 for the
treatment of patients
with symptomatic
castrate resistant
prostate cancer with
skeletal metastases

2013

Contents

MSAC and PASC 3

- Purpose of this document..... 3
- Acknowledgements 3
- Summary of matters for consideration by the applicant 4
- Purpose of application..... 6
- Background 6
 - Current arrangements for public reimbursement..... 6
 - Regulatory status..... 6
- Intervention 6
 - Description..... 6
- Medical condition 7
- Incidence 8
- Delivery of the intervention 8
- Dose, frequency of administration and duration of treatment10
- Prerequisites10
- Co-administered and associated interventions11
- Listing proposed and options for MSAC consideration14
 - Proposed MBS listing.....14
 - Population.....15
 - Clinical place for proposed intervention.....16
- Comparator21
- Clinical claim26
- Clinical outcomes affected by introduction of proposed intervention.....27
- Proposed structure of economic evaluation (decision-analytic).....28
- Health care resources34
- References38

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the question for public funding that the assessment is intended to answer:

- P**atients – specification of the characteristics of the patients in whom the intervention is to be considered for use
- I**ntervention – specification of the proposed intervention and how it is delivered
- C**omparator – specification of the therapy most likely to be replaced by the proposed intervention
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Acknowledgements

The PASC and the MSAC wish to thank Dr William Macdonald, A/Executive Director, Imaging West, Department of Health, Western Australia, for his valuable contributions to the development of this protocol.

Summary of matters for consideration by the applicant

- The likely use of radium-223 in clinical practice in Australia. More specifically, the most representative structure of the clinical algorithm for the patient group distinguishing between all treatments at each point in time. In the absence of any other information, the use of a “Treatment Survey” by the applicant, of a nationally representative sample of key healthcare providers managing CRPC patients (medical oncologists, urologists radiation oncologists and nuclear medicine specialists), would be considered appropriate by PASC to develop a clinical treatment algorithm of the likely use of radium-223. Issues to be considered:
 - Given the available chemotherapy options, conventional radiotherapy, and the currently listed radionuclides, what treatment or treatments is radium-223 likely to substitute? Should conventional radiotherapy be considered a secondary comparator in some patient groups?
 - Will radium-223 be used instead of chemotherapy options in some patients due to the claim that it prolongs survival?
 - Or will radium-223 likely be used in addition to the currently available treatments? Is it likely that patients will be eligible to receive subsequent radionuclides after treatment with radium-223? In other words, is there the possibility of patients receiving radium-223 for a course and then subsequently receiving strontium-89 (or samarium-153 lexidronam) as palliative care?
- Definition of the most appropriate patient group: should it include all of: patients who have received docetaxel and subsequently experienced disease progression, patients who are not fit enough to receive docetaxel, patients who are not willing to receive docetaxel, and patients for whom docetaxel is not available for other reasons? Should this apply to the other chemotherapy options now available on the PBS (abiraterone and cabazitaxel)?
- Three target populations for radium-223 were identified: previously received docetaxel and candidates for further active treatment; unsuitable for docetaxel (not otherwise defined) but candidates for further active treatment; and candidates not for further active treatment. Due to the limited data currently available on-line regarding the ALSYMPCA trial, the applicant will need to appropriately justify the conduct of sub-group analysis.
- In respect to the palliative care setting above (candidates not for further active treatment), it is unclear whether the full six cycles of radium-223 would be contemplated—other palliative radionuclide therapies (strontium-89 and samarium-153 lexidronam) employ one or two treatments only. This would clearly have major cost implications given the proposed fee per treatment.
- Is there likely to be a difference in the use of bisphosphonates or denosumab between patients receiving radium-223 and those who receive the comparator therapies; and whether concurrent bisphosphonate or denosumab use is likely to impact on the effectiveness of radium-223.

- Is the proposed patient population likely to receive additional diagnostic monitoring services (bone scans) as a result of treatment with the radium-223 intervention, and is this different from any of the comparators?
- Will there be other interventions claimed in association with radium-223 treatment aside from MBS items 110 or 104? Should these items not be claimable since consultation with specialists has been built into the estimate of the cost of the service?
- Are the time estimates for the administration of radium-223 consistent with the expectations for administration of strontium-89 or samarium-153 lexitronam?
- The proposed descriptor for the administration of radium-223 will require further refinement of the eligible population

Purpose of application

A proposal for an application requesting MBS listing of radium-223, a radiopharmaceutical for injection for the treatment of patients with symptomatic hormone refractory prostate cancer (HRPC) with skeletal metastases was received from Bayer Australia Ltd. by the Department of Health and Ageing in December 2011. This proposal seeks reimbursement for a new intervention not currently listed on the MBS.

Throughout the DAP, when referring to the population relevant to this application, PASC has requested that the terminology be castrate resistant prostate cancer (CRPC) rather than hormone refractory prostate cancer (HRPC).

Background

Current arrangements for public reimbursement

Radium-223 is not publicly reimbursed in Australia and it has not been previously considered by MSAC. The application states that there are currently no arrangements under which radium-223 is provided to patients. Radium-223 is not registered by the Therapeutic Goods Administration (TGA) for use in Australia at the present time.

Regulatory status

An application to the Therapeutic Goods Administration (TGA) is currently being prepared for radium-223 with July 2012 being the estimated date of submission. The proposed indication is as follows: radium-223 for the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases.

Intervention

Description

The drug substance is a radioactive solution of divalent radium-223 cations in a sodium citrate solution, containing sodium chloride and calcium chloride (CaCl₂). The intervention of radium-223 injection is a trademarked product with a trade name of Alpharadin[®].

Radium-223 is an alpha-emitting pharmaceutical (alpha-pharmaceutical), that naturally targets bone metastases due to its calcium-mimicking properties. The bone targeting property of radium-223 is similar to that of other earth alkaline elements, like strontium-89. Radium-223, with a physical half-life of 11.4 days, emits high linear energy transfer alpha radiation to destroy cancer cells, with a range limited to less than 100 micrometres. Thus it can be used to generate localised radiation zones thereby reducing exposure of surrounding normal tissues. Radium-223 that is not taken up by the bone metastases is cleared to the gut and excreted.

There are two other radiopharmaceuticals currently listed on the MBS: strontium-89 and samarium-153 lexidronam. Strontium-89 is listed for painful bony metastases from carcinoma of the prostate where hormone therapy has failed and the disease is either poorly controlled by conventional radiotherapy or conventional radiotherapy is inappropriate due to the wide distribution of sites of bone pain. Strontium-89 chloride is a radiopharmaceutical that is administered by intravenous injection and

concentrates in bone as an analogue of calcium. Strontium-89 is a radionuclide that emits beta particles, and is indicated for pain relief from painful bone metastases.

Samarium-153 lexidronam is listed on the MBS 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. Samarium-153 lexidronam is a monophosphonate radiopharmaceutical that is administered by intravenous injection and concentrates in bone as an analogue of inorganic phosphate. Samarium-153 is a radionuclide that emits beta particles and gamma rays, and is indicated for pain relief from painful bone metastases.

The main difference between radium-223 and strontium-89 and samarium-153 lexidronam is the type of radiation emitted: radium-223 emits alpha particles while strontium-89 and samarium-153 lexidronam emit beta particles. Alpha radiation consists of a helium nucleus which is a heavy, very short-range, positively charged particle (2 protons and 2 neutrons), and is not able to penetrate human skin or a piece of paper. It is only harmful to humans if the radioactive material is inhaled, swallowed, or absorbed through open wounds. In contrast, beta radiation consists of high-energy electrons which are lighter, longer-range particles. This type of radiation can penetrate human skin to the "germinal layer," where new skin cells are produced, and can be halted by a Lucite or aluminium plate.

Medical condition

The requested MBS listing is for radium-223 is for the treatment of patients with symptomatic hormone refractory prostate cancer with symptomatic skeletal metastases. The PASC requests that the wording be altered to "castrate resistant" prostate cancer rather than "hormone refractory" prostate cancer.

Prostate cancer occurs when some of the cells of the prostate reproduce far more rapidly than in a normal prostate, causing swelling or a tumour. Prostate cancer cells eventually break out of the prostate and invade distant parts of the body, particularly the bones and lymph nodes, producing secondary tumours, a process known as metastasis. Once the cancer escapes from the prostate, treatment is possible but "cure" becomes impossible.

A single protein is essential at every stage of tumour development. This protein is called the androgen receptor; it is located in the nucleus in the healthy prostate cell. The androgen receptor is responsible for binding the male hormone, testosterone, to the prostate. Prostate cancer cells also need an active androgen receptor. When the testosterone is bound to the receptor, it controls the working of the genes in the cell's nucleus that are necessary for cell growth and reproduction. This is essential for the survival of prostate cancer cells (Cancer Council Australia 2009).

Androgen deprivation therapy is considered the primary approach in the treatment of symptomatic metastatic prostate cancer to reduce levels of male hormones available to cancer cells. Androgen deprivation can be achieved surgically (castration), or medically using hormone therapy. However, androgen deprivation therapy has been found to be palliative, not curative, in metastatic disease. Ultimately, patients stop responding to hormone therapy and are then referred to as having castrate resistant or androgen-independent prostate cancer.

The most common site of distant cancer spread in men with castrate resistant prostate cancer is bone. Untreated patients face morbidity with symptoms that include bone pain, bone fracture, compression of the spinal cord and haematological consequences of bone marrow replacement. Symptoms can vary depending on the extent of the spread of the cancer. If treated successfully, these symptoms may be palliated and patients may also gain a survival benefit.

Incidence

Prostate cancer is the most common non-cutaneous cancer among males and is the second most common cause of cancer death in males (Krupski, T eMedicine). In Australia in 2007 there were 19,403 new cases of prostate cancer diagnosed. In 2008, Australia had the world's highest age-standardised incidence rate of prostate cancer (105 cases per 100,000 males) (AIHW 2010).

Predominantly a disease of elderly men, prostate cancer is rare before age of 40 but increases dramatically thereafter. The risk of prostate cancer is one in seven men before the age of 75 years and one in four men before the age of 85 years (Cancer Council Australia 2009).

People living in remote and very remote areas of Australia have lower rates of prostate cancer than those living in more urbanised areas. People living in areas with the highest socioeconomic status have significantly higher incidence of prostate cancer than people living in other areas. Because prostate cancer is primarily a disease that affects older people, the shorter life expectancy of Indigenous Australians (approximately 10 years less than that of non-Indigenous Australians) may mean that these cancers may not have presented by the time of death. Furthermore, the uptake of screening and diagnostic testing, such as prostate-specific antigen (PSA) testing, is low among Indigenous people, which may contribute to a low rate of diagnosis (AIHW 2010).

In a study performed in the USA (Crawford et al., 2003) 654 urologists completed a survey in which they were asked questions on the patients managed by the urologists. The results from this study show that just over one in five patients with prostate cancer had metastatic disease (21%) and almost one in five of these patients with metastatic prostate cancer had hormone refractory prostate cancer (HRPC) (19%). Metastatic disease does not necessarily mean bone metastases. Note that this interpretation of the results has been amended from that presented in the application.

Skeletal metastases occur in more than four out of five cases of advanced-stage prostate cancer and confer a high level of morbidity (Sturge et al., 2011). About four out of five patients with hormone refractory prostate cancer have bone metastases (Coxon et al., 2004). Estimates indicate that treatment of bone pain is required in approximately three out of ten men with hormone refractory/castrate resistant prostate cancer and associated bone metastases (Smith et al., 2009).

Delivery of the intervention

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 is administered by intravenous injection. The application states that it is envisaged that a nuclear physician or a radiation oncologist would administer radium-223 and that this would take place within a licensed nuclear medicine, radiology or radiation oncology department.

Radium-223 is supplied in ready-to-use glass vials (Type I) of Ph.Eur./USP quality. Thus, no work-up of the product prior to administration is required, other than extracting from the vial into the syringe. The vials are closed with 20 mm, sterile Stelmi rubber stoppers of Ph.Eur./USP quality and sealed with 20 mm tear-off aluminium seals. Radioactive exposure through the container/closure system is limited to relatively low levels of radiation (<100 μ Sv/MBq radium-223 on the surface of the vial) because of the low radiation range of alpha particles, which limits the risks to persons handling the product.

Table 1 below sets out the pre-service, intra-service, and post-service time estimates compiled in the application and aggregates these for the total time required for all medical staff involved per patient per administration of radium-223.

Table 1: Estimate of pre-service time requirement for administration of radium-223 per patient

	Admin	Nursing	Radiochemist / technologist	Physician
Pre-service				
Receive and approve referral	5 min			10 min
Book appointment and organise medical record	30 min			
Order dose			10 min	
Receive and check dose			15 min	
Intra-service				
Book in	5 min			
Cannulate		20 min		
Prepare dose			20 min	
Patient consult, consent, administration and documentation				30 min
Remove cannula and post administration observation		30 min		
Post-service				
Disposal of radioactive waste				20 min
Billing patient and paying radioactive chemical invoice	20 min			
Additional labour: spill clean-up occurring approximately 1 in 50 administrations			90 min	
Total aggregated time (305 min)	60 min	50 min	135 min	60 min

There is uncertainty with the time estimates for all service components, but particularly with the post-service time requirement set aside for clearing a spill. If it is estimated that a spill would occur in one in fifty administrations then the time required on average would be one fiftieth of 90 minutes and this adjustment must be appropriately incorporated in an economic evaluation. Normally, without a spill, the time requirement estimated for post-service is 40 minutes.

Combining pre-, intra-, and post-service time estimates yields a total requirement of 305 minutes across medical staff directly associated with the delivery of radium-223 (per patient per administration

and including the full time cost of a spill). The times presented in the application relate only to medical staff involved in administration of radium-223. This is appropriate. Note that without a spill this estimate is reduced to 215 minutes.

The application asserts that the time taken for administration of radium-223 is no different than for strontium-89.

This may be true per administration although radium-223 is expected to be injected six times per course while strontium-89 is usually injected once but possibly with a repeat. Estimates of medical staff time requirements will have a direct impact on an economic evaluation of the intervention.

The PASC suggested that the table of time estimates needs to be modified as the time requirements will not be the same across the six injections. For instance the office administration costs for subsequent treatments will be reduced after the patient has been entered into the system for the first treatment. The applicant asserts in its response that the time difference between radium-223 (requiring six injections) and strontium-89 or samarium-153 lexidronam (requiring one or possibly two injections) will be adequately accounted for in the economic evaluation with financial estimates provided as part of the assessment.

Dose, frequency of administration and duration of treatment

Radium-223, if reimbursed on the MBS, would be administered 6 times per patient at regular intervals of 4 weeks as monotherapy. Duration of treatment is 6 months. Radium-223 is not a lifetime treatment and the treatment course is not repeated; patients would receive only 6 doses each. The dose of radium-223 would be 50 kilobecquerels per kilogram body weight (50 kBq/kg body weight). The application specifies that the quantity and frequency of the dose per patient is not likely to change over time.

The PASC advised that, since the dose is based on patient bodyweight, wastage of radium-223 is a relevant factor to account for in the economic evaluation. Properly incorporating wastage is important as there are specific procedures and costs associated with managing radioactive waste.

Prerequisites

Before a clinician can inject radium-223, they would have to have a relevant radiopharmaceutical licence. Patients with castrate resistant prostate cancer are mainly treated in the community by either medical oncologists or urologists. Thus, community based oncologists and urologists would have to refer patients to receive their injection at a nuclear medicine/radiology/radiation oncology facility licensed for unsealed-source therapy.

In practice reimbursement should occur only if radium-223 is administered by a physician holding a valid radiopharmaceutical licence. That is, for example, administration of the intervention should not be delegated to a technologist who does not hold a licence.

The application does not discuss whether the reimbursement for radium-223 on the MBS would require the provision of training for medical practitioners to enable administration of the intervention. No changes in staffing demand are discussed in the application.

The applicant’s response to the draft DAP states that Bayer Australia will provide training on the safe storage, handling, and disposal of the product. This training will extend to include guidance on how to handle situations such as spills. Bayer will also provide information regarding how radium-223 should be administered (IV, saline flush, etc.). Training will not be provided to nuclear medicine physicians or radiation oncologists on how to inject radium-223.

The application does not raise access to physicians with radiopharmaceutical licences or nuclear medicine/radiology facilities as an issue. The application highlights that because radium-223 will be administered in the same setting as strontium-89 it will not require additional capital investment. The PASC accepted that radium-223 would be used in the same way as strontium-89 or samarium-153 lexidronam and that any facility that can provide these treatments will also be able to provide radium-223 services.

Co-administered and associated interventions

The application states that patients eligible to receive radium-223 (if reimbursed) would be referred by a medical oncologist to a nuclear medicine physician or a radiation oncologist for consultation and administration. This is presented as the current practice in administering strontium-89.

Tables 2 and 3 below contain the MBS item descriptors pertaining to the consultation with the nuclear medicine specialist and the radiation oncologist.

Table 2: MBS item descriptor for referred consultation with a nuclear medicine physician

Category 1 – Professional Attendances
<p>MBS 101</p> <p>CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY), REFERRED CONSULTATION - SURGERY OR HOSPITAL</p> <p>Professional attendance at consulting rooms or hospital by a consultant physician in the practice of his or her specialty (other than in psychiatry) where the patient is referred to him or her by a referring practitioner.</p> <p>INITIAL attendance in a single course of treatment</p> <p>Fee: \$148.10 Benefit: 75% = \$111.10 85% = \$125.90</p>

Table 3: MBS item descriptor for referred consultation with a radiation oncologist or radiologist

Category 1 – Professional Attendances
<p>MBS 104</p> <p>SPECIALIST, REFERRED CONSULTATION - SURGERY OR HOSPITAL</p> <p>Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her.</p> <p>INITIAL attendance in a single course of treatment, not being a service to which ophthalmology items 106, 109 or obstetric item 16401 apply</p> <p>Fee: \$83.95 Benefit: 75% = \$63.00 85% = \$71.40</p>

It is uncertain whether the application intends that these MBS items would apply once per patient per course of radium-223 treatment (six injections at four week intervals over six months) or once per dose.

The application notes that zoledronic acid is commonly prescribed as supportive medicine for patients with bone metastases. Zoledronic acid is listed on the PBS for (among other indications) bone metastases from hormone-resistant prostate cancer.

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates which act primarily on bone. Bisphosphonates aim to prevent the loss of bone mass and reduce the risk of fracture; they are often used in patients with osteoporosis and similar diseases. In oncology bisphosphonates are used to reduce the risk of skeletal complications in patients with bone metastases. Other bisphosphonates listed on the PBS include alendronate, risedronate, ibandronate, pamidronate, etidronate, clodronate, and tiludronate. Various authorities are required such as a diagnosis of osteoporosis, Paget disease, multiple myeloma, bone metastases from breast cancer, and hypercalcaemia resulting from a malignancy refractory to antineoplastic therapy. Of the PBS-listed bisphosphonates, only zoledronic acid, pamidronate and clodronate are approved for use in patients with bone metastases.

Expert advice received during DAP development indicated that, while there are theoretical grounds to suspect that bisphosphonates and radium-223 might compete with each other, the risk does not appear to be significant with the other therapeutic radionuclides (strontium-89 and samarium-153 lexidronam). In all likelihood, many patients treated with radium-223 will be prescribed bisphosphonates.

Even if the bisphosphonate dose is unlikely to change across patients receiving radium-223, strontium-89, or samarium-153 lexidronam, the treatment durations and the difference in survival that radium-223 may confer could have an impact on the total use of bisphosphonates per patient. These factors have implications for an economic evaluation.

The PASC considered that zoledronic acid and other bisphosphonates approved for use in patients with bone metastases are likely to be prescribed concurrently in some patients who are administered radium-223. It is uncertain whether this co-administration of bisphosphonates will have an impact on the efficacy of radium-223.

The applicant presents a subgroup analysis in its response to the draft DAP of the overall survival of patients in the ALSYMPCA trial who received bisphosphonates and those that did not. This information is reproduced in Table U1 below.

Table U1: Subgroup analysis of OS for patients receiving radium-223 with versus without bisphosphonates

Use of Bisphosphonates	N	Hazard Ratio [95% CI]
Yes	331	0.582 [0.397 – 0.854]
No	478	0.752 [0.567 – 0.999]

OS=Overall Survival; 95% CI=Confidence Interval at the 95% level of confidence

The applicant claims that this information demonstrates that it is unlikely concurrent bisphosphonate use will impact the efficacy of radium-223. It is stated that there is no difference in the survival benefit of radium-223 as the confidence intervals are observed to overlap.

It is unknown whether this subgroup analysis is appropriately powered to detect a difference. The confidence intervals do overlap but this may be largely due to the fact that they are relatively wide confidence intervals to begin with, which indicates a high level of uncertainty of effect. There is a considerable numeric difference in the hazard ratios between groups, which raises some doubt as to whether bisphosphonate use does affect the efficacy of radium-223. Of note, the hazard ratios appear to show a stronger effect on overall survival for patients that are co-administered bisphosphonates, which may run against the intuition that these treatments could compete with each other. The applicant suggested that this issue of bisphosphonate use and the efficacy of radium-223 could be addressed as a research question. This is appropriate.

The PASC advised that the concurrent use of bisphosphonates be incorporated in the clinical algorithm and the economic evaluation of radium-223.

Denosumab is raised in the application as having been recently listed on the PBS for the treatment of bone metastases from hormone resistant prostate cancer. Denosumab is a fully human monoclonal antibody with high affinity and specificity for RANK ligand, a protein that acts as the primary signal to promote bone removal in the body. Denosumab binds to and inhibits RANK ligand to protect bone from degradation. At the July 2011 meeting, the PBAC noted that denosumab treatment was associated with a statistically significant reduction in the risk of developing a first on-study skeletal related event (SRE), both asymptomatic and symptomatic, compared with zoledronic acid in prostate cancer patients (HR 0.82; 95% CI 0.71, 0.95). Denosumab treatment also significantly reduced the risk of developing first and subsequent SREs. The PBAC noted that denosumab treatment was not associated with any improvement in survival or disease progression compared with zoledronic acid and although pain and quality of life outcomes generally favoured denosumab the differences between treatments were small and did not reach statistical significance for most outcomes.

In the same manner as for bisphosphonates the PASC considered that patients administered radium-223 could also receive denosumab although it is unclear whether the use of denosumab would be likely to have an impact on the effectiveness of radium-223.

Other drugs affecting bone mineralisation and structure listed on the PBS include calcitriol and teriparatide although the authority required for reimbursement is primarily osteoporosis and does not mention prostate cancer. It is not clear whether these drugs are prescribed in the eligible patient population but expert advice highlights that many patients with advanced prostate cancer are also osteoporotic. Consequently, there may be potential for these drugs to be used in combination with radium-223.

The application does not identify a change in the use of diagnostic or monitoring procedures associated with the use of radium-223. In an economic evaluation of radium-223 compared with strontium-89, the overall number of monitoring procedures may increase in the radium-223 patient group if radium-223 provides an advantage in overall survival in the model.

In response to the draft DAP the applicant comments that there is no evidence to support the notion that radium-223 would accelerate osteoporosis and require additional surveillance thereof. Further the applicant states that:

“Bone scanning using radionuclide scintigraphy is routinely used to assess progression and response of metastatic bone disease and would be routinely done in these patients. There is no reason to suspect that use of therapy to alleviate symptoms would increase the use of these techniques and it is conceivable that the beneficial symptomatic responses seen with this therapy would decrease since bone scans are done to assess bone pain in patients with advanced prostate cancer (Bayer Australia Response to draft DAP).”

There is some uncertainty related to how radium-223 will be used in clinical practice; if some patients are able to access radium-223 and then, following a treatment course, also access strontium-89 and/or samarium-153 lexitronam, the economic evaluation will have to capture the full cost to government health budgets including the costs of additional scans. It is uncertain whether, in practice, radium-223 will replace other radionuclides or be used in addition to them. This uncertainty will have major implications for the comparator and the economic evaluation.

In its table of costs proposed for inclusion in an economic analysis of radium-223 the application lists pain medications such as analgesics, anti-inflammatory medication, and corticosteroids as examples that may be prescribed concurrently with radium-223. The actual medications expected to be prescribed are not identified.

Listing proposed and options for MSAC consideration

Proposed MBS listing

Table 4 below sets out the MBS listing as proposed in the application by the sponsor of radium-223 and amended in response to PASC requests for clarity.

Table 4: Proposed MBS item descriptor for radium-223

Category 3 – Therapeutic Procedure
<p>MBS XXX</p> <p>ADMINISTRATION OF RADIUM-223 for symptomatic castrate resistant prostate cancer in patients who have:</p> <ul style="list-style-type: none"> (i) ≥ 2 skeletal metastases; AND (ii) ECOG performance status of 0-2; AND (iii) Previously failed, or are medically unsuitable for treatment with docetaxel. <p>Fee: \$5,000-10,000</p> <p>A total of six intravenous injections are to be administered at four week intervals.</p>

ECOG = Eastern Cooperative Oncology Group

The MBS fee presented in the descriptor excludes other costs such as that of administration. The applicant further states that this price reflects the cost of one administration of radium-223 (not a course of six administrations). The PASC noted that the whole proposed benefit (fee) may range from \$30,000 to \$60,000.

The PASC considered that the wording in the proposed MBS item descriptor requires further definition. In particular there needs to be a clear understanding of the definition of ‘symptomatic.’ The MBS item descriptor for strontium-89 requires painful bony metastases and for samarium-153 lexitronam

requires bone pain; this is acknowledged in the applicant response, which states that to some extent a combination of the current samarium-153 lexidronam and strontium-89 descriptors would provide a reasonably close description of the ALSYMPCA trial population because it requires the presence of "painful bony metastases from carcinoma of the prostate." Similar wording on the radium-223 listing may be required. Additionally, ALSYMPCA defined "symptomatic" as, "either regular (not occasional) use of analgesic medication for cancer related bone pain (level 1; WHO ladder for cancer pain), or treatment with EBRT for bone pain (the EBRT should be within the last 12 weeks before randomisation)." It is proposed in the applicant's response that the wording of the listing includes description of "symptoms" in line with the trials evidence. This would position the use of radium-223 after radiotherapy.

The PASC suggested that the wording castrate resistant prostate cancer be used rather than hormone refractory prostate cancer as was initially proposed.

Population

It is stated in the application that the patient population who would benefit from radium-223 are similar to those recruited in the Phase III pivotal clinical trial (ALSYMPCA), as follows:

- i. Histologically or cytologically confirmed adenocarcinoma of the prostate
- ii. Castrate resistant prostate cancer defined as:
 - a. Castrate serum testosterone level: ≤ 50 ng/dL (1.7 nmol/L)
 - b. Bilateral orchidectomy or maintenance on androgen ablation therapy
- iii. Serum prostate specific antigen (PSA) value ≥ 5 ng/mL ($\mu\text{g/L}$)
- iv. Multiple skeletal metastases (≥ 2 hot spots) on bone scintigraphy
- v. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

In addition patients in ALSYMPCA were:

- patients who had received docetaxel,
- patients who were not fit enough to receive docetaxel,
- patients who were not willing to receive docetaxel, or
- patients for whom docetaxel was not available for other reasons.

It is proposed in the application that radium-223 be used in patients who have tried docetaxel and experienced disease progression, or who have failed docetaxel treatment, or who are not eligible or unwilling to take docetaxel, or patients in whom treatment with docetaxel is contraindicated.

PASC considered that the population group that will gain access to radium-223 requires better definition. In particular, clarification is required as to whether the eligible patient group is post-systemic treatment, or patients in whom treatment with docetaxel has failed due to disease progression, or patients in whom treatment with docetaxel (and other chemotherapies) is contraindicated. The characteristics of the patients in the ALSYMPCA trial must be made clear and apparent in the inclusion and exclusion criteria. The PASC also indicated that the terminology, patients with castrate resistant prostate cancer, should be used when describing the population instead of the term 'hormone refractory' prostate cancer.

The applicant in response to questions posed in the Consultation DAP, identified three target populations for radium-223 treatment:

- i. Previously received docetaxel and candidates for further active treatment;
- ii. Unsuitable for docetaxel (not otherwise defined) but candidates for further active treatment;
- iii. Not candidates for further active treatment (palliative care).

Due to the limited data currently available on-line regarding the ALSYMPCA trial, PASC was concerned that the applicant will need to appropriately justify conduct of sub-group analysis.

With specific referenced to the palliative care setting (iii above), PASC is unclear whether the full six cycles of radium-223 would be contemplated—other palliative radionuclide therapies (strontium-89 and samarium-153 lexidronam) employ one or two treatments only. This would clearly have major cost implications given the proposed fee per treatment.

Further, to restrict the patient group accessing radium-223 to those most likely to benefit, some additional clinical assessments may be required such as bone scintigraphy, serum PSA test, and application of ECOG test or similar. The costs of these services if applied would need to be included in the economic evaluation.

Current clinical practice in Australia is to refer for external beam radiotherapy (EBRT) in this patient group prior to the use of radionuclides, although comparative research has not established the superiority of EBRT. In addition there is some indication that the use of EBRT produces greater patient inconvenience compared with radionuclides. Radium-223 is different to the other currently listed radionuclides of strontium-89 and samarium-153 lexidronam in that it will be prescribed as an active, anti-cancer therapy, while the latter two are for end-of-life pain relief only. The clinical expert has indicated that the ability to prolong life means that it is likely patients will want the treatment and their doctors will be more likely to refer them. Including a requirement for patients to have attempted EBRT or that EBRT be clinically inappropriate would bring the listing of radium-223 into line with other radionuclides but potentially does not address the 'active cancer therapy' difference of radium-223.

The PASC considered that conventional radiotherapy may be an appropriate comparator to radium-223 in some circumstances. The most representative clinical management algorithm for these patients must be determined before EBRT requirements are included as restrictions on the MBS item descriptor.

There is currently no registered or approved indication as the TGA application has not yet been submitted.

Clinical place for proposed intervention

As mentioned earlier, the application states that access to radium-223 is intended for patients who have tried docetaxel and experienced disease progression, or who are unwilling to take docetaxel or patients in whom treatment with docetaxel is contraindicated.

Figures 1 and 2 below detail the current clinical algorithm and how it is anticipated that this will change with the listing of radium-223 on the MBS.

Figure 1: Current clinical algorithm (without radium-223)

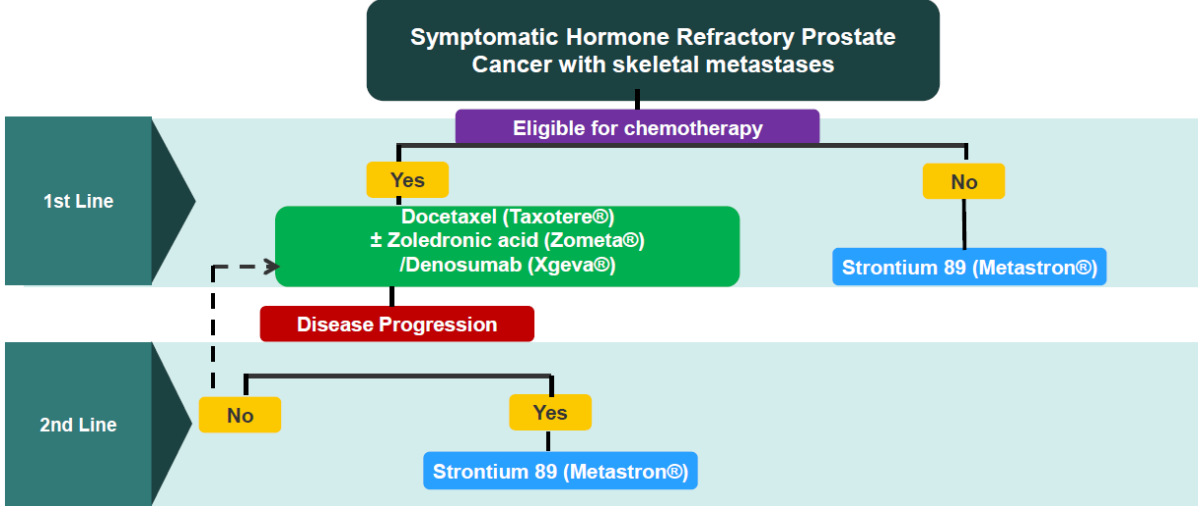
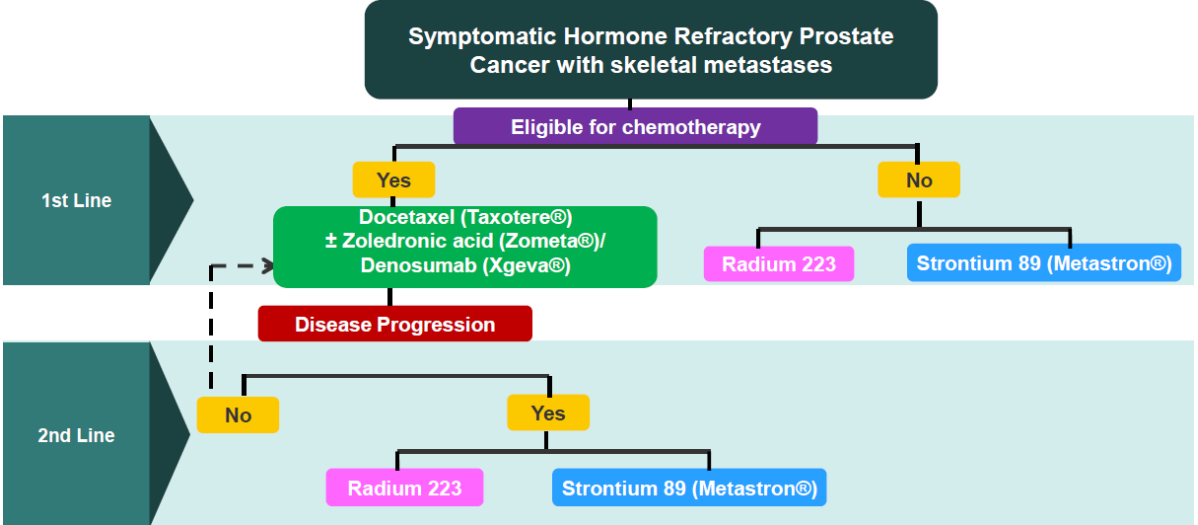


Figure 2: Proposed clinical algorithm with radium-223 reimbursed on the MBS



The clinical management algorithms presented in the application apply to patients who have already progressed to the stage of castrate resistant prostate cancer with skeletal metastases. The application notes that once metastases are diagnosed, the patient would initially be asymptomatic but as time goes by symptoms (e.g. bone pain) would develop.

Upon development of CRPC with skeletal metastases, if the patient is considered eligible, treatment with docetaxel chemotherapy is pursued. If the patient is not deemed eligible for chemotherapy, radium-223 would be an option for 'first line' treatment, potentially directly substituting for strontium-89.

It is uncertain from the clinical management algorithm what constitutes eligibility for chemotherapy. This issue relates to the detail included in the proposed MBS item descriptor for radium-223 (ECOG performance status of 0-2). Note that docetaxel is listed on the PBS for treatment of androgen independent (castrate resistant) metastatic carcinoma of the prostate in a patient with a Karnofsky performance-status score of at least 60%. This criterion could imply that treatment will not be available until the patient reaches a threshold in symptoms although it is somewhat unclear as to the precise threshold (a Karnofsky score of 100 = no evidence of disease while a Karnofsky score of 0 = dead; the wording 'at least 60%' is likely to refer to a score of 60 or higher however it is not clearly defined).

An additional factor related to the clinical management algorithm is that the March 2012 meeting of the PBAC considered two separate re-submissions for treatments to be used after docetaxel. The PBAC recommended abiraterone for authority required listing on the PBS for the initial and continuing treatment, in combination with prednisone or prednisolone, of patients with metastatic advanced prostate cancer (castration resistant prostate cancer) in whom disease progression has occurred following treatment with docetaxel. The PBAC also recommended cabazitaxel for authority required listing on the PBS for treatment of hormone refractory metastatic carcinoma of the prostate in patients previously treated with a docetaxel containing regimen. Either of these treatments must be included in the clinical management algorithm and the economic model of radium-223. Patients failing docetaxel would have the option of attempting therapy with these agents before or instead of receiving radium-223.

The management algorithm details that patients treated with chemotherapy may or may not receive zoledronic acid or denosumab as additional or concurrent treatment. These interventions are not available in the algorithm for patients ineligible for chemotherapy. Patients administered docetaxel can continue to receive repeats (up to a maximum specified on the PBS of 10 cycles) provided the disease has not progressed. Once disease has progressed for patients treated with docetaxel the option of radium-223 or strontium-89 would become available as 'second line' treatment. Again in this instance the clinical management algorithm describes radium-223 as an option alongside strontium-89.

Samarium-153 leixidronam does not feature in the clinical management algorithm submitted with the application; however, it is available for use in the relevant patient group. The PASC determined that samarium-153 leixidronam is an appropriate comparator for radium-223 in the same manner as strontium-89. This still depends on the structure of the clinical management algorithm representing practice in Australia.

Although not an option in the presented algorithm, there may be the possibility of patients receiving radium-223 for one course as per the restriction and then subsequently receiving strontium-89 (or samarium-153 leixidronam) as palliative care. The implication for an economic evaluation would be that radium-223 would not substitute directly for strontium-89 or samarium-153 leixidronam and the cost offsets and quality of life benefits of these radionuclides would not apply.

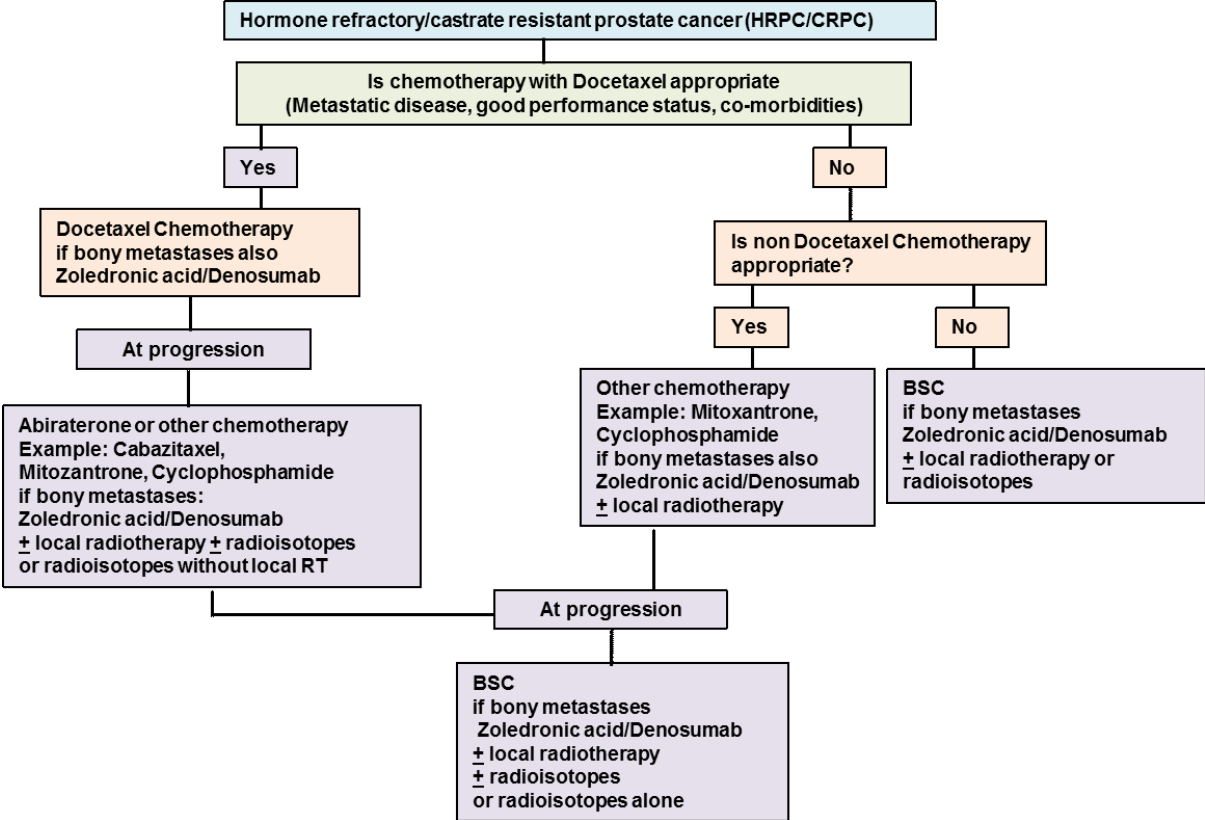
Neither of the clinical management algorithms presented in the initial application identify where EBRT fits in the treatment process.

The algorithm shows that radium-223 potentially addresses an unmet clinical need in patients who cannot access chemotherapy. Previously the options available included strontium-89 and samarium-153 lexidronam (which does not appear in the algorithm provided) both palliative, end of life treatments for bone pain, and without clinically demonstrated survival benefit. However, no comparative evidence is presented examining the relative efficacy of radium-223, strontium-89, samarium-153 lexidronam, and placebo.

The application does not attempt to estimate the proportions of patients in each branch of the algorithm although it is clear that all patients alive when disease has progressed and docetaxel treatment is discontinued will at least have the option to receive radium-223. As mentioned in the application, at some point in time, docetaxel treated patients will experience disease progression. These patients would then be prescribed strontium-89 (or samarium-153 lexidronam but this does not feature in the algorithm presented), or should radium-223 be listed, patients may be eligible for treatment with radium-223.

In response to the draft DAP the applicant provided an updated version of the clinical algorithm for Australian practice that includes radionuclides but does not distinguish between the agents (radium-223, samarium-153 lexidronam, and strontium-89). This is presented below in Figure U1.

Figure U1: Updated proposed clinical algorithm for patients with castrate resistant prostate cancer



The algorithm in the figure above also includes the chemotherapy agents of abiraterone and cabazitaxel considered and recommended for use in this patient group by the PBAC at its April 2012 meeting. The applicant had previously stated that it is likely that the radioisotopes will end up in the same position in the algorithm irrespective of the PBAC decisions on abiraterone and cabazitaxel.

Further changes from the initial algorithm include that zoledronic acid and denosumab are shown as available for concurrent use in patients receiving radioisotopes. External beam radiotherapy is also identified as an option at the same point in the algorithm as radioisotopes.

The updated algorithm includes the additional treatment options, which is appropriate but a weakness is that it is not clear on the likely ordering of the treatments in practice. A flow diagram may go some way to resolving this although it is acknowledged that there is a high level of complexity involved (stemming from the large number of choices of therapies) that may make a flow diagram difficult to create while maintaining representativeness and accuracy. Some uncertainties with clinical management of these patients include:

- The likely ordering of chemotherapies is unclear (both following docetaxel treatment and in patients who are not eligible for docetaxel treatment). With the recent acceptance of abiraterone to the PBS it may be reasonable to expect that this will be the first alternative choice in most cases given that it is relatively new and that the PBAC noted that abiraterone has a better safety profile and is more convenient to administer (oral administration) than cabazitaxel. Cabazitaxel may be the second alternative choice.
- For patients receiving chemotherapy, it is unclear when the decision is made to discontinue with chemotherapy rather than try alternative chemotherapy. There are several potential chemotherapies available as options for this patient group and it is uncertain how many will be used in succession before switching to a treatment such as radium-223. If this decision is made earlier than normal (i.e. while there are still alternative chemotherapy options available) due to radium-223 being listed on the MBS then this raises the question of whether chemotherapy is a comparator to radium-223 in some situations.
- The submitted algorithm does not answer the question of whether radium-223 will supplant the other available radioisotopes or whether it will be used as an additional treatment. It is reasonable to assume that radium-223 will be used before its counterparts of strontium-89 and samarium-153 lexidronam as there may be a survival advantage attributable to radium-223. The applicant stated in its response to the DAP that the restriction for radium-223 will not explicitly prohibit the use of subsequent radioisotopes although the efficacy and safety of subsequent radioisotopes after a course of radium-223 is unknown.
- In some circumstances radium-223 may replace conventional radiotherapy (if there is no restriction in place). External beam radiotherapy (EBRT) is likely to be used before the radioisotopes of strontium-89 and samarium-153 lexidronam due to the restrictions in place; however, there is no restriction yet placed on radium-223. Again the impact on survival that radium-223 may have will be a factor in its use relative to EBRT.

In response to the points raised above about the uncertainties in the application of the likely use of radium 223 in clinical practice in Australia, and the structure of the clinical algorithm, the applicant, Bayer requested that the PASC consider providing them access to the proposed clinical treatment algorithm for CRPC that was accepted by the PBAC, at the March 2012 meeting. At this meeting the PBAC made a positive recommendation for the reimbursement of abiraterone onto the PBS for the initial and continuing treatment, in combination with prednisone or prednisolone, of patients with

metastatic advanced prostate cancer (castration resistant prostate cancer) in whom disease progression has occurred following treatment with docetaxel. The PBAC also recommended cabazitaxel for listing on the PBS for treatment of hormone refractory metastatic carcinoma of the prostate in patients previously treated with a docetaxel containing regimen. Failing access to the requested clinical algorithm considered by PBAC when deciding on the reimbursement of abiraterone and cabazitaxel onto the PBS, the applicant suggested they would conduct a "Treatment Survey" of a nationally representative sample of key healthcare providers managing CRPC patient to construct a treatment algorithm which best reflects clinical practice.

The request for access to the clinical algorithm considered by PBAC when deciding on the reimbursement of abiraterone and cabazitaxel onto the PBS was denied. This was because, firstly, the discussions about the clinical algorithm occurred only a few months after the listing of cabazitaxel and prior to abiraterone being listed, and did not involve an algorithm available in a discrete form that could be shared and secondly, the listing of both abiraterone and cabazitaxel, would likely have altered this clinical algorithm and it may no longer reflect contemporary practice. The applicant was encouraged to make use of whatever sources of advice are available to develop an algorithm that reflects current practice. The use of a "Treatment Survey" of nationally representative sample of medical oncologists, urologists and radiation oncologists who manage CRPC patients to derive a current clinical management algorithm would be appropriate.

Comparator

Strontium-89 is proposed as the most appropriate comparator for radium-223 in the application. As detailed earlier, strontium-89 is currently listed on the MBS and restricted to a subset of the patient group relevant to the radium-223 application (EBRT experienced or EBRT inappropriate).

Table 5 below contains the MBS item descriptor for strontium-89.

Table 5: MBS item descriptor for strontium-89

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> <p style="padding-left: 40px;">(i) the disease is poorly controlled by conventional radiotherapy; or</p> <p style="padding-left: 40px;">(ii) conventional radiotherapy is inappropriate, due to the wide distribution of sites of bone pain</p> <p>Fee: \$4,009.50 Benefit: 75% = \$3,007.15 85% = \$3,935.80</p>

The application notes that strontium-89 is a beta emitter but presents a number of similarities between radium-223 and strontium-89 as rationale for the nomination. Both products:

- are radiopharmaceuticals,
- have to be administered in an appropriately licensed nuclear medicine/radiology/radiation oncology facility,
- require a suitably licensed nuclear medicine physician or a radiation oncologist to administer the product, following referral from a medical oncologist ? or urologist,

- the administering physician must have a licence to administer unsealed-source therapy,
- are indicated for use in patients with castrate resistant prostate cancer with bone metastases,
- have affinity for bone, and
- are concentrated in the bone at the site of metastases when administered.

According to the clinical management algorithms presented above the comparator may be appropriate although there are a number of uncertainties associated with the algorithm such as:

- samarium-153 lexidronam is an additional radiopharmaceutical not previously mentioned in the application,
- it is uncertain whether patients administered radium-223 will be eligible for other palliative radiopharmaceuticals later in treatment,
- it is uncertain whether radium-223 will be prescribed, in some patients, as an alternative to chemotherapy in which case docetaxel or another chemotherapy (potentially abiraterone or cabazitaxel) would be the most appropriate comparator,
- it appears that some patients administered radium-223 will receive co-administered bisphosphonates and it is uncertain whether this will impact on the efficacy of radium-223,
- it appears that some patients administered radium-223 will receive co-administered denosumab and it is uncertain whether this will impact on the efficacy of radium-223, and
- expert advice and the MBS listings for strontium-89 and samarium-153 lexidronam indicate that EBRT is prescribed before radionuclides in current clinical practice although it is uncertain whether this will apply to radium-223 given the potential impact on survival of the therapy.

The application for radium-223 states that the resources required for administration of radium-223 are the same as for strontium-89 and the interventions are delivered in the same clinical setting.

However, it is uncertain whether some additional diagnostic services will be required such as bone scintigraphy, serum PSA test, and application of the ECOG test or similar (especially if the patient group is to be restricted to those most likely to benefit from access to radium-223). These services would need to be included in the economic evaluation.

Data are presented in the application on the number of Medicare services of strontium-89 reimbursed between July 2000 and June 2011. These data are reproduced below in Figure 3.

Figure 3: Medicare services processed for strontium-89

Requested Medicare items processed from July 2000 to June 2011										
		State (Services)								Total (services) Services
		NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
Item Number 16015	2000/2001	118	85	80	43	23	15	4	0	368
	2001/2002	114	89	101	33	6	9	2	0	354
	2002/2003	91	86	98	35	13	15	1	0	339
	2003/2004	67	77	63	33	8	6	1	0	255
	2004/2005	43	84	49	22	8	9	0	1	216
	2005/2006	37	71	30	18	13	5	0	0	174
	2006/2007	27	67	39	7	18	9	0	0	167
	2007/2008	21	51	41	14	16	4	0	0	147
	2008/2009	11	60	16	7	2	8	0	0	104
	2009/2010	16	52	19	1	3	6	0	0	97
	2010/2011	10	29	21	2	4	2	0	0	68
	Total		555	751	557	215	114	88	8	1

The data show a substantial drop in the number of strontium-89 services processed over the 10 years from July 2000 in Australia. Expert advice obtained during the development of the DAP suggested that this reduction in strontium-89 use may be a combination of prescribers shifting towards samarium-153 leixidronam and a general decline in radionuclide bone therapy.

Samarium-153 leixidronam is listed on the MBS with the item descriptor provided below in Table 6.

Table 6: MBS item descriptor for samarium-153 leixidronam

Category 3 – Therapeutic Procedures
<p>MBS 16018</p> <p>ADMINISTRATION OF 153 SM-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: \$2,396.90 Benefit: 75% = \$1,797.70 85% = \$2,323.20</p>

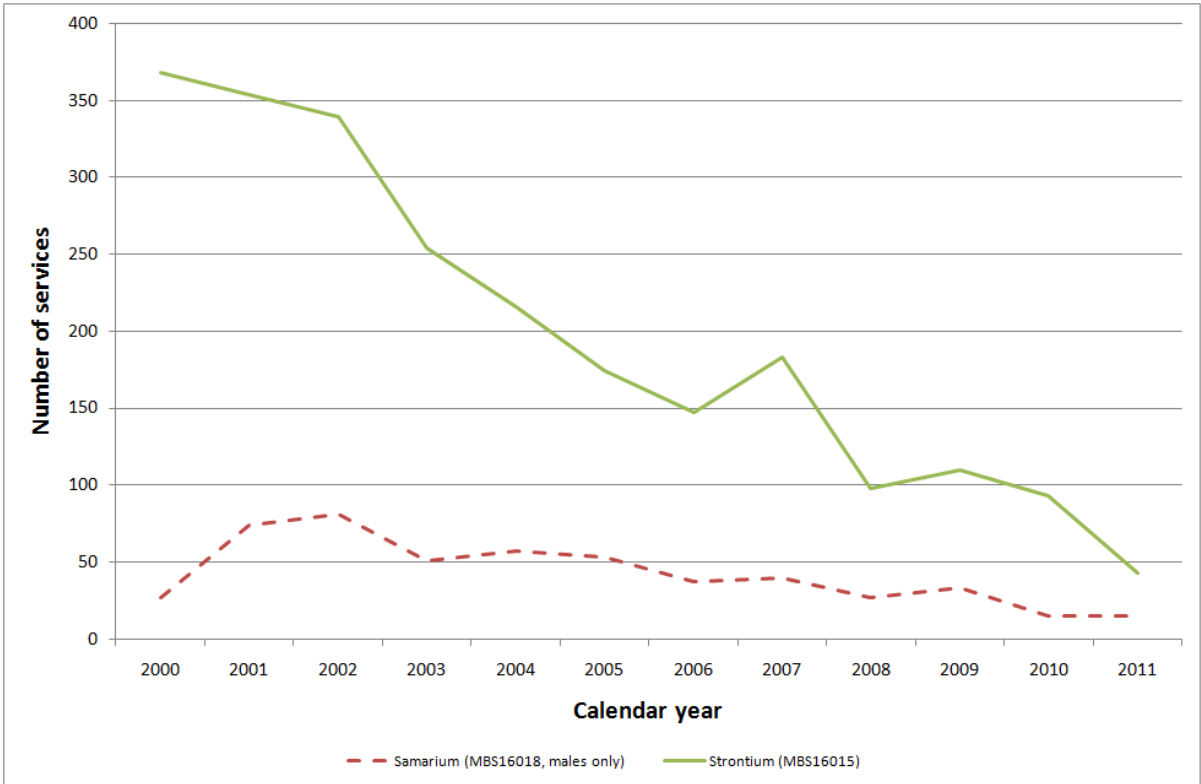
The application does not discuss the use of samarium-153 leixidronam as an intervention in the proposed patient population. It is uncertain exactly how the use of samarium-153 leixidronam would change if radium-223 were to be reimbursed on the MBS although radium-223 has the potential to substitute for samarium-153 leixidronam. Expert advice obtained during development of the draft DAP highlights that the prostate cancer patients in whom samarium-153 leixidronam is used are the same as those in whom radium-223 would be used (the same is true of strontium-89). It is unclear what proportion of samarium-153 leixidronam therapy is directed at prostate cancer (compared with other cancers) but it is likely to be the vast majority. In this sense radium-223 would be a substitute for

both samarium-153 lexidronam and strontium-89 in prostate cancer. Expert advice further indicated that, at the expert's clinic, samarium-153 lexidronam is used in preference over strontium-89 due to the lower cost and lack of established clinical advantage for strontium-89.

The PASC considers that both strontium-89 and samarium-153 lexidronam are potential comparators for radium-223. The subcommittee requests further investigation of the Medicare data to clarify the current usage in Australian practice of strontium-89 and samarium-153 lexidronam.

In its response to the draft DAP for item 1268, Bayer Australia included the following graph presented in Figure U2.

Figure U2: Medicare items processed from 2000 to 2011 for samarium-153 lexidronam and strontium-89.



The applicant notes the decrease in services recorded for both radionuclides and concludes that this is due to a general decline in the use of radionuclides for bone pain rather than a switch from strontium-89 to samarium-153 lexidronam. The applicant states that this graph demonstrates that strontium-89 remains the most appropriate comparator as it has significantly higher usage than samarium-153 lexidronam.

From the data above it does appear that radionuclide therapy is declining in use in Australia. Although properly taking into account the trend over time for strontium-89 services reinforces the PASC advice that both strontium-89 and samarium-153 lexidronam would be equally appropriate comparators for radium-223. The PASC acknowledged, however, that a comparison of radium-223 with these agents is complicated by the fact that strontium-89 and samarium-153 lexidronam are used primarily as palliative care, while radium-223 may provide greater time to a skeletal-related event and possibly prolonged survival.

The PASC also viewed conventional external beam radiotherapy (EBRT) as a potential comparator to radium-223. This relates to the extent of skeletal metastatic disease. The ALSYMPCA study enrolled patients who had 2 or more skeletal metastases, which is different from the strontium-89 or samarium-153 lexidronam population, who have disseminated disease which is not readily amenable to EBRT. There is little doubt that palliative, "single-shot" EBRT is a very effective option for isolated symptomatic metastases. The PASC is of the opinion that the role of EBRT remains vaguely defined.

The applicant states that it is not the intention of the MSAC submission for radium-223 to replace docetaxel in this setting and it asserts that chemotherapy is not an appropriate comparator to use. Justification is based on the recommendation of the Australian Cancer Network Guidelines, which indicate first line treatment of this patient group with docetaxel in combination with prednisone and that the ALSYMPCA trial evaluated patients who had tried and failed docetaxel or those in whom treatment with docetaxel was not appropriate.

This justification does not provide certainty that radium-223 will not be used, at least in a subgroup of patients, as a replacement or alternative to chemotherapy. Proper restriction on the MBS may be required due to the perception that radium-223 presents an option to extend life possibly with less toxicity compared with chemotherapy.

Another issue raised by the applicant in its response to the draft DAP is that there is a perception that the MBS fees for services with strontium-89 (\$4,009.50) and samarium-153 lexidronam (\$2,396.90) are not sufficient to cover the purchase price of the radiopharmaceuticals. This is suggested as a further reason for the reduction in the use of these treatments shown in the graph above. The applicant comments that a comparison of radium-223 with strontium-89 or samarium-153 lexidronam as represented by their respective MBS fees is inappropriate.

This issue is important and requires confirmation; however, until it is clear that the MBS fees for treatments with currently listed radiopharmaceuticals are inadequate, and a course of action to correct the issue is taken, the most appropriate cost to use in an economic model will continue to be the MBS item fee.

On the basis of the above discussion, the following potential comparators have been suggested by the applicant and agreed to by PASC:

For patients with symptomatic castrate resistant prostate cancer who have received prior docetaxel treatment, radium 223 treatment to be compared to:

- strontium-89 or samarium -153 lexidronam;
- Cabazitaxel;
- Abiraterone;
- Best supportive care (including external-beam radiotherapy).

For patients with symptomatic castrate resistant prostate cancer with no prior docetaxel treatment, radium treatment to be compared to:

- strontium-89 or samarium -153 lexidronam;
- Best supportive care (e.g. radiotherapy, mitozantrone)

Potential comparators relevant to an assessment of treatment with radium 223 will be confirmed through a "Treatment Survey", which has been proposed by the applicant. This survey will include key health care providers managing CRPC patients (medical oncologists, urologists, radiation oncologists) where available.

Clinical claim

The application makes the clinical claim that radium-223 is superior in terms of efficacy and safety compared with strontium-89. Based on the results of the phase III clinical trial, ALSYMPCA, radium-223 has shown an improvement in overall survival and median time to first skeletal related event. The application further adds that radium-223 is well tolerated while the toxicity associated with strontium-89 treatment limits its use.

The PASC advised that the safety profile of radium-223 must be clearly provided by the applicant to enable a judgement on whether the clinical claim is justified and supported.

Of note, it is uncertain whether the toxicity associated with strontium-89 treatment limits its use as claimed in the application. Adverse events associated with strontium-89 include bone marrow toxicity, renal impairment, and transient increases in pain although the frequency of these events is not established (eMedicine, strontium-89 chloride). Figure 3 above makes it is clear that strontium-89 use in Australia is decreasing and has been for 10 years. Expert advice indicates that referring habits may play an important role in this decrease (patients are generally referred for EBRT in preference to strontium-89, even though comparative research has clearly established no superiority of EBRT and greater patient inconvenience). There is limited understanding among referring doctors of radionuclides and the patients that tend to be referred are those, often in severe pain, for whom all other options have failed – no treatment works well in this group and the lack of success contributes to a perception of radionuclides as having limited value and discourages further referrals. Furthermore, clinical expert advice indicates that there have historically been recurring supply problems with both strontium-89 and samarium-153 lexidronam in Australia, sometimes with delays of weeks between patient assessment and delivery of the drug. On occasions, manufacturing issues have meant the drugs are not available at all. On the basis of the claim for superiority in both safety and efficacy, an appropriate economic evaluation would be a cost-effectiveness/cost-utility analysis should be presented in the application.

Table 7 below presents the clinical claims for radium 223 compared to the potential comparators (that are yet to be determined but may result from the proposed "Treatment Survey") for the population with prior docetaxel treatment and with **no** prior docetaxel treatment. The proposed economic evaluations are also included.

Table 7: potential comparators and clinical claim

Patient population	Comparator	Therapeutic claim		Economic evaluation
		Overall survival	Skeletal related events	
Prior Docetaxel	Strontium-89/Samarium-153 leixidronam	Superior	Non-inferior	Cost utility
	Cabazitaxel	Non-inferior	Non-inferior	Cost minimisation
	Abiraterone	Non-inferior	Non-inferior	Cost minimisation
	BSC (e.g. radiotherapy)	Superior	superior	Cost utility
No prior Docetaxel	Strontium-89/Samarium-153 leixidronam	Superior	Non-inferior/superior	Cost utility
	BSC (e.g. Radiotherapy, Mitoxantrone*)	Superior	Superior	Cost utility

*ERBT is currently used for pain relief of skeletal metastases in patients who have localised bone lesions but not for extensive bone lesions.

Indirect comparison with mitoxantrone could be performed independently, however PBAC accepted that mitoxantrone is equivalent to placebo and this it is represented here as BSC (Abiraterone PSD November 2011) but mitoxantrone is not TGA registered for use in CRPC

Clinical outcomes affected by introduction of proposed intervention

The application states that there are no head to head, double-blind, randomised trials which directly compare radium-223 with strontium-89, Samarium-153 leixidronam, Cabazitaxel or Abiraterone in patients with castrate resistant prostate cancer with prior docetaxel treatment. The comparison of radium-223 to these comparators (if deemed to be relevant based on the proposed "Treatment Survey") will be made indirectly via the common comparator of placebo. There is a head to head, double-blind, randomised trial which directly compare radium-223 with BSC in this population.

There is no head to head, double-blind, randomised trials which directly compare strontium-89 or Samarium-153 leixidronam in patients with castrate resistant prostate cancer with **no** prior docetaxel treatment. The comparison of radium-223 to strontium-89 or Samarium-153 leixidronam will be made indirectly via the common comparator of placebo. There is a head to head, double-blind, randomised trial which directly compare radium-223 with BSC in this population

Taking the approach of an indirect comparison is appropriate given that there is no direct trial evidence available. However, including samarium-153 leixidronam is necessary since this is also a radionuclide intervention used in the patient group.

Outcomes to be considered are (as listed in the application):

- overall survival,
- time to first skeletal related event (SRE),
- quality of life, and
- safety.

PASC stated that these outcomes are appropriate.

Overall survival is an appropriate outcome to use given that radium-223 is claimed to prolong life.

It is suggested that public funding of radium-223 will result in a reduction in the number of hospitalisations and medication used to treat the skeletal related events (SRE). The use of time to first SRE as an outcome is acceptable and this outcome is relatively common in the literature. Some detail will be needed on the medication used to treat SREs in clinical practice. Further to this,

hospitalisations and the reason for their occurrence could be an outcome measured directly to underpin the claim of a reduction in hospitalisations attributable to radium-223.

Quality of life is best measured using an instrument that converts Health-Related Quality of Life (HR-QoL) information to utilities such as the EuroQoL 5D (EQ-5D) or the Assessment of Quality of Life instrument (AQoL). In order for these instruments to produce reliable and relevant output the patient groups in the trials would have to be comparable and all use the same HR-QoL instrument. Quality of life would also have to be measured at consistent time points across the trials. Failing this a search of the clinical literature for relevant utilities in patients with advanced symptomatic castrate resistant prostate cancer with skeletal metastases may be acceptable.

The application indicates that public funding of radium-223 will lead to a reduction of medication used to treat the adverse events arising due to the comparator (strontium-89).

In terms of the outcome of safety, all relevant adverse events (AEs) ought to be captured in the trials. These include but are not limited to: bone marrow toxicity, renal impairment, and transient increases in pain (eMedicine, strontium-89 chloride). Of particular importance are AEs that can be categorised as grade 3 or 4 or are judged to be serious. If the application is to make the claim for a reduction in the medication used to treat the adverse events then information must be presented detailing the likely treatment pathways and costs for patients in Australia experiencing these AEs. If a quality of life impact is quantified then appropriate utilities from HR-QoL instruments must also be presented for assessment. The PASC considered that the applicant should provide clinical evidence concerning the safety and toxicity of radium-223. This would be useful both to justify the clinical claim of superiority compared with strontium-89 in terms of safety and to inform the economic evaluation of radium-223.

Proposed structure of economic evaluation (decision-analytic)

Table 8 sets out a summary of the extended PICO for the comparison of radium-223 with the potential comparators (not all are yet to be determined but may result from the proposed "Treatment Survey") presented in the application.

Table 8: Summary of extended PICO to define the question for public funding that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered*
Symptomatic CRPC in patients with bone metastases, who received prior docetaxel;	Radium-223 is a radiopharmaceutical, which is administered intravenously six times at four week intervals	-Strontium-89 is a radiopharmaceutical, administered IV once per course with the potential for repeat courses. -Samarium-153 lexidronam is radiopharmaceutical administered IV once per course with potential for repeat courses -Cabazitaxel is a antineoplastic agent administered IV every 3 weeks with potential for repeat courses -Abiraterone is an androgen inhibitor administered orally once daily with potential for repeat courses -BSC	Improvement in overall survival (OS) Increased time to first skeletal related event (SRE) Impact on quality of life Improved safety Reduced bone pain	Cost of intervention and comparator Costs of medical staff time for tasks and consultation Cost of consumables per administration of intervention and comparator Cost of co-administered interventions Costs of scans and lab tests Cost of management of AEs Costs of follow-up
Symptomatic CRPC in patients with bone metastases, who received no prior docetaxel;	Radium-223 is a radiopharmaceutical, which is administered intravenously six times at four week intervals	-Strontium-89 is a radiopharmaceutical, administered IV once per course with the potential for repeat courses. -Samarium-153 lexidronam is radiopharmaceutical administered IV once per course with potential for repeat courses -BSC	Improvement in overall survival (OS) Increased time to first skeletal related event (SRE) Impact on quality of life Improved safety Reduced bone pain	Cost of intervention and comparator Costs of medical staff time for tasks and consultation Cost of consumables per administration of intervention and comparator Cost of co-administered interventions Costs of scans and lab tests Cost of management of AEs Costs of follow-up

* Not included in application; added during DAP development; BSC=best supportive care; IV=intravenous

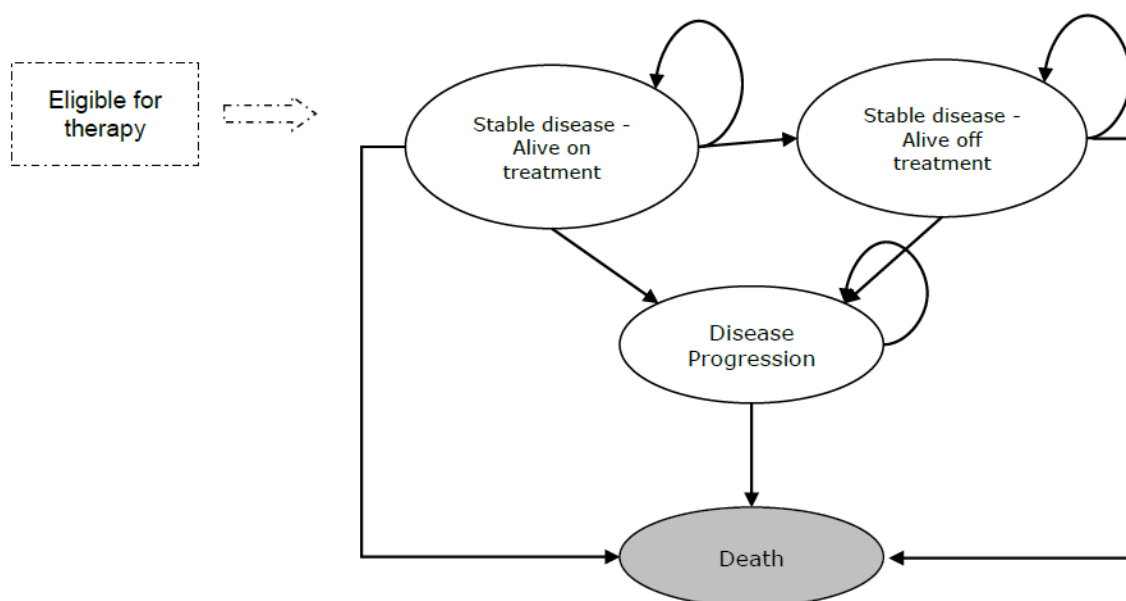
Symptomatic CRPC is defined in the application as either regular (not occasional) use of analgesic medication for cancer-related bone pain or treatment with external beam radiation therapy (EBRT) for bone pain. The extended PICO table presented in the application includes the outcome of reduced bone pain but this outcome is not presented explicitly under the health outcomes heading above. Reduced bone pain could be captured under the quality of life outcome as pain can factor in to the calculation (and be translated to utility).

The application indicates that a health state transition model would be developed in Microsoft Office Excel 2007. The model would consist of four health states as follows:

- Stable disease - Alive on treatment
- Stable disease - Alive off treatment
- Disease progression
- Death

Figure 4 below illustrates the model health states and the flow of patients between the health states as presented in the application.

Figure 4: Economic model health states and transitions



The diagram shows the four health states with arrows indicating the possible transitions patients can make between the states. Beginning in the health state entitled "Stable disease – Alive on treatment," the patient may move to the states of "Stable disease – Alive off treatment," "Disease progression," and "Death." The looped arrow also indicates that patients may remain in "Alive on treatment" for more than one cycle. From the health state of "Stable disease – Alive off treatment," patients transition to the state of "Disease progression" after a median progression-free survival. It is also possible to transition to "Death" from this health state. The only transition from "Disease progression" is to "Death" although the arrows indicate that multiple model cycles can be spent in the progressed disease health state.

These transitions appear appropriate and take account of the realistic possibility of death at any point in the model. There is no transition from "Alive off treatment" to "Alive on treatment" indicating that repeat treatments with radionuclides are not an option in the model. Whether or not this is the case in practice is uncertain (for instance it may be possible for patients to receive radium-223 for six months and then later receive strontium-89 or samarium-153 leixidronam as part of palliative care). The cycle length in the model will have to be chosen carefully – it needs to be short enough to be able to capture appropriate changes in patient quality of life and costs while long enough to properly account

for durations of treatment (for instance treatment with radium-223 will last for six months while treatment with strontium-89 will be much shorter).

The PASC noted that it is unclear whether the health state of "Alive – Off Treatment" refers to patients having completed the treatment course with radium-223 or whether it indicates that patients are not receiving active treatment at all. This issue requires clarification.

One concern is that there appears to be no health state representing the impact of adverse events, which is an area where radium-223 is asserted to be superior to the nominated comparator of strontium-89 (improved safety with reduced costs and increased quality of life resulting). Note though that this may be captured in a more general way through the utilities and costs assigned to the health states presented. The application recognises that the model structure does not explicitly include quality of life and cost implications of skeletal-related events but states these will be included as the model is developed. The PASC considered that clinical evidence on the safety and toxicity of radium-223 should be incorporated in the economic model.

Figure 5 below illustrates the decision tree for the economic evaluation of radium-223 presented in the application.

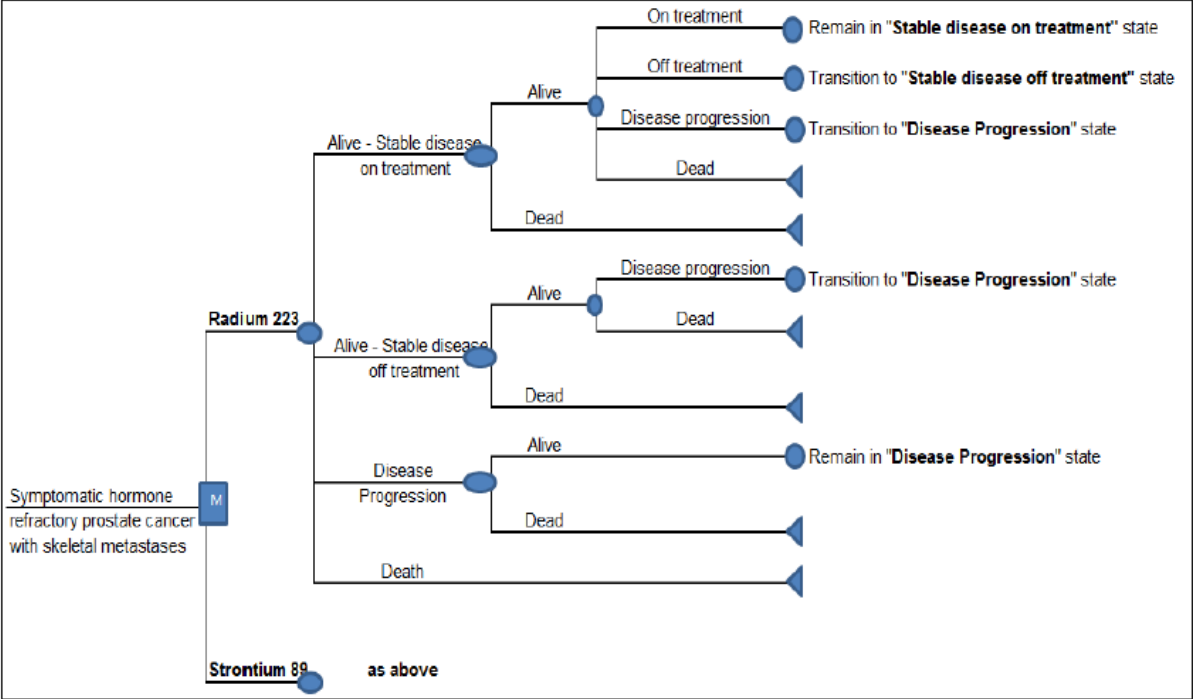


Figure 5: Radium-223 cost-effectiveness model decision tree

Patients entering the Markov model are those who have symptomatic castrate resistant prostate cancer with skeletal metastases as defined above. The model focuses on overall survival as the primary patient relevant endpoint. In this way, a direct link to the main outcome in the cost-effectiveness analysis, quality-adjusted life years (QALYs), can be achieved. In addition to QALYs, the economic evaluation will measure life years as an outcome.

The model will include the following treatment arms for castrate resistant prostate cancer with skeletal metastases:

- radium-223, and
- strontium-89.

The outcome of life years or life years gained is useful in an economic model; however, its importance is not as high as QALYs since life years gained do not contain as much information as QALYs. The primary measure of health impact should be QALYs. If radium-223 is able to extend life then this is likely to be the key driver of the model.

The proposed structure of the economic model is mostly consistent with the clinical treatment algorithm presented in the application, that is, radium-223 is compared with strontium-89 in the appropriate patient group and this is the final treatment option for these patients. There are a number of uncertainties with the algorithm though and these uncertainties flow through to the structure of the economic evaluation.

The main concern is the possibility that the radionuclide samarium-153 lexidronam is also an option in these patients but does not feature in the model. An extra treatment arm may be added to the decision tree to capture patients treated with samarium-153 lexidronam. The structure of the economic evaluation will require amending if, in practice, it may be possible for patients to access radium-223 and then, later, either strontium-89 or samarium-153 lexidronam or both. A transition pathway from the health state "Alive – Stable disease, off treatment" back to "Alive – Stable disease, on treatment" will be necessary.

The clinical management algorithm identifies a group of patients who will experience disease progression (after chemotherapy) and then have the option for either strontium-89, or radium-223 if it is reimbursed. The model structure presented above does not appear to account for these patients as in the health state of "Disease progression" no transition to treatment is possible. Properly correcting the structure for this possibility could add substantial complexity to the model.

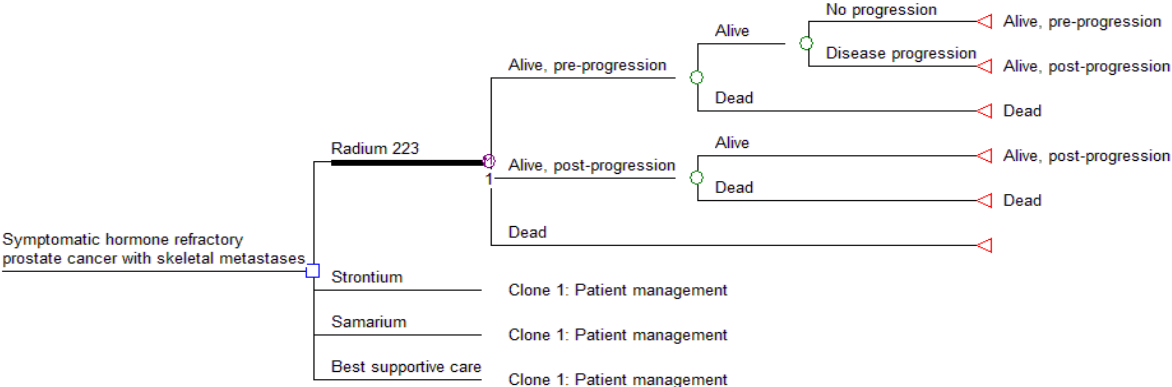
Another uncertainty arises with medications potentially co-administered with radiopharmaceuticals. This isn't identifiable from the diagram of the economic structure although costs and benefits would need to account for the proportions of patients receiving bisphosphonates such as zoledronic acid or human monoclonal antibodies such as denosumab. The PASC considers that this patient group is likely to access bisphosphonates or denosumab and as such these additional treatments will need to be costed into the economic evaluation (if it is identified that the co-administration of bisphosphonates or denosumab may affect radium-223 efficacy then this will need to be accounted for as well).

Again it might not be visible in the model structure but EBRT may need to be factored in to the model at some point. The interventions of strontium-89 and samarium-153 lexidronam require conventional radiotherapy to be inappropriate or for the disease to be poorly controlled by conventional radiotherapy. The same criteria is not proposed for radium-223 at this stage (doing so would bring the intervention in to line with other radionuclides but may ignore the potential for radium-223 to prolong life) and so there is the possibility that some patients will be administered EBRT after having accessed radium-223.

After consideration of the model structure the PASC advises that it is potentially over simplified and requires adjustment to better reflect the costs and outcomes for patients with CRPC in Australia.

In response to these issues raised by PASC the applicant has adjusted the structure of the model to be used for the economic evaluation. Unlike Figure 5, there is no "off treatment" health state included. Figure 6, presents this "adjusted" cost-effectiveness decision tree.

Figure 6: Radium-223 "adjusted" cost-effectiveness model decision tree



The adjusted cost effectiveness model, presented in Figure 6 now includes additional treatment arms for CRPC. In addition to strontium-89, samarium-153 lexidronam and best supportive care (including external-beam radiotherapy) are included. If the clinical treatment algorithm developed via the proposed "Treatment Survey" show that cabazitaxel and abiraterone are also relevant comparators, these will need to be incorporated into the model. A cost utility analysis comparing strontium-89, samarium-153 lexidronam and best supported care will be presented. It is assumed that strontium-89 and samarium-153 lexidronam offer the same clinical benefits but different treatment costs which the model will capture. The cost-effectiveness of radium-223 compared to BSC, will be informed by clinical data available from the ALSYMPCA trial.

A key change between Figure 6 and Figure 5 is the removal of the "off treatment" health state. The inclusion of an "off treatment" health state in Figure 5 was questioned as it seemed to exclude the possibility of repeat treatment with radionuclides and it was unclear which patients were included.

According to the applicant, the modelling approach will primarily be in line with what is described above (for Figure 5), however the adjusted model (Figure 6) will take a form of 'partitioned' survival analysis. The applicant states that the survival analysis can be built in a simpler structure and is typically associated with less data requirement (when compared with a Markov model or microsimulation), offering greater modelling transparency but that strictly speaking, it does not take the form of a decision tree analysis (although presented as a decision tree structure in Figure 6). Partitioned survival analysis, is a technique for quality adjusted survival analysis, and has been recommended as an approach (Glasziou et al., 1990), where there are a variety of clinical trial endpoints (e.g. disease progression, survival and degree of toxicity), and where treatment may show an advantage in some end points (e.g. improved response) but a disadvantage in other endpoints (e.g. more toxic). Patients may experience several health states which differ in their quality of life.

Health care resources

In the information request documents the application states that it is envisaged that no additional healthcare resources would be required up to the point at which the product is administered in comparison with strontium-89. Rather the application expects that healthcare resources associated with managing skeletal related events and adverse events in general would reduce with the availability of radium-223.

Table 9 lists the resources to be considered in the economic evaluation of radium-223 as presented in the application. Detailed disaggregated cost information is not provided at this stage.

Table 9: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Funding
Resources provided to identify eligible population (Please note, that at the time of the initial consultation, a bone scan has already been done to identify metastases by the Urologist who then referred the patient to the Medical Oncologist.)				
<i>Medical consultation</i>				
- Initial consultation	Medical Oncologist	Outpatient	1	MBS
- Hospital/specialist initial consultation (planning consent, ordering laboratory tests, reviewing scans etc.) Please note: only one of the specialists would be applicable.	Nuclear Medicine Physician Radiation Oncologist	Outpatient	1	MBS
<i>Laboratory and other tests</i>				
- PSA level	Pathologist (ordered in the initial consultation with Nuclear Medicine Physician/ Radiation Oncologist)	Outpatient	1	MBS
- Haematology (Hematocrit, haemoglobin, platelet counts, red + white blood cells counts, white blood cell differential)	Pathologist (ordered during initial consultation)	Outpatient	1	MBS
- Clinical chemistry (Sodium, potassium, chloride, calcium, phosphate, AST, ALT, total ALP, γ GT, creatinine, urea, total bilirubin, albumin, total protein)	Pathologist (ordered during initial consultation)	Outpatient	1	MBS
Resources provided to deliver proposed intervention				
- Hospital/specialist visit Please note: only one of the specialists would be applicable	Nuclear Medicine Physician Radiation Oncologist	Outpatient	6*	MBS
Resources provided in association with proposed intervention				
<i>Pre- and concomitant medications</i>				
- Continued pain medication is to be given with radium-223, according to ALSYMPCA study and clinical expert advice (e.g. analgesics, anti-inflammatory, corticosteroids etc)	Medical Oncologist	Outpatient		PBS
<i>Laboratory and other tests</i>				
- PSA level	Pathologist	Outpatient	1	MBS
- Haematology	Pathologist	Outpatient	1	MBS
- Clinical chemistry	Pathologist	Outpatient	1	MBS
Resource provided following the proposed intervention				
<i>Follow up</i>				
- Hospital/specialist visit (short exit consultation: response and toleration of treatment, side effects etc) Please note: only one of the specialists would be	Nuclear Medicine Physician Radiation Oncologist	Outpatient	1 (2-4 weeks after the treatment cycle)	MBS

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Funding
applicable				
- Follow up visits (dependent on the outcome of treatment)	Referral to medical oncologist	Outpatient	Once every 2 months in first year after last injection, then once every 4 months between 1-3 years.	MBS
<i>Laboratory and other tests</i>				
- PSA level	Pathologist	Outpatient	1	MBS
- Haematology	Pathologist	Outpatient	1	MBS
- Clinical chemistry	Pathologist	Outpatient	1	MBS
<i>Continued pain medication</i>				
- Continued pain medication (e.g. analgesics, anti-inflammatory, corticosteroids etc)	Medical Oncologist	Outpatient		PBS
<i>Management of adverse events/downstream conditions in patients administered radium-223</i> (Please note that the following procedures are dependent on severity of adverse events and all may not apply. Also, hospitalisation can occur due to several adverse events, such as skeletal-related adverse events.)				
- Analgesics, Corticosteroids, Antibiotics	Medical Oncologist	Outpatient		PBS
- Recombinant G-CSF (neutropenia)	Medical Oncologist	Outpatient/inpatient		PBS
- Blood transfusion (anemia)	Medical Oncologist	Inpatient		MBS
- Hospitalisation	Medical Oncologist	Inpatient		MBS (AR-DRG)
Resources provided to deliver comparator				
- Hospital/specialist visit Please note: only one of the specialists would be applicable	Nuclear Medicine Physician Radiation Oncologist	Outpatient	1-2 (Often more than one strontium-89 injection – dependent on symptom response and blood counts)	MBS
Resources provided in association with comparator				
<i>Pre- and concomitant medications</i>				
- Continued pain medication is to be given with strontium-89, according to ALSYMPCA study and clinical expert advice	Medical Oncologist	Outpatient		PBS
<i>Laboratory and other tests</i>				
- PSA level	Pathologist	Outpatient	1	MBS
- Haematology	Pathologist	Outpatient	1	MBS
- Clinical chemistry	Pathologist	Outpatient	1	MBS
Resource provided following the proposed intervention (Please note there is no difference in the follow up management of patients treated with radium-223 or its comparator strontium-89)				
<i>Follow up</i>				
- Hospital/specialist visit (short exit consultation: response and toleration of treatment, side effects etc) Please note: only one of the specialists would be applicable	Nuclear Medicine Physician Radiation Oncologist	Outpatient	1 (2-4 weeks after the treatment cycle)	MBS
- Follow up visits (dependent on the outcome of treatment)	Referral to medical oncologist	Outpatient	Once every 2 months in first year after last injection, then once every 4 months between 1-3 years.	MBS
<i>Laboratory and other tests</i>				
- PSA level	Pathologist	Outpatient	1	MBS
- Haematology	Pathologist	Outpatient	1	MBS
- Clinical chemistry	Pathologist	Outpatient	1	MBS
<i>Continued pain medication</i>				

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Funding
- Continued pain medication (e.g. analgesics, anti-inflammatory, corticosteroids etc)	Medical Oncologist	Outpatient		PBS
<i>Management of adverse events/downstream conditions in patients administered strontium-89</i>				
- Analgesics, Corticosteroids, Antibiotics	Medical Oncologist	Outpatient		PBS
- Recombinant G-CSF (neutropenia)	Medical Oncologist	Outpatient/inpatient		PBS
- Blood transfusion (anemia)	Medical Oncologist	Inpatient		MBS
- Hospitalisation	Medical Oncologist	Inpatient		MBS (AR-DRG)

* This information (6 specialist visits for delivery of a course of radium-223) was not presented in the application but has been added during DAP development.

The cost items presented in the application are appropriate for inclusion in the economic model. Cost items associated with the additional comparators, samarium-153 lexitronam and best supportive care (e.g. radiotherapy), presented in the model (Figure 6) are not provided. These treatments attract different treatment costs which will need to be captured. As noted by the applicant, if the proposed "Treatment Survey" shows that cabazitel and abiraterone are also relevant comparators, they, with their associated treatment costs will also need to be included in the model.

Also in the application but not included in the table are detailed costs of consumables required per delivery of the intervention. Table 10 sets out the cost estimates of the consumables required per administration of radium-223 as sourced from the Royal Brisbane Hospital.

Table 10: Consumable component of direct costs for delivery of intervention

Consumable items per administration	Number of units	Cost per unit	Total
20 g Cannula	1	\$1.08	\$1.08
3 way with 10 cm extension	1	\$1.30	\$1.30
Injection caps	3	\$1.40	\$4.20
IV administration set	1	\$2.82	\$2.82
Dressing	1	\$1.83	\$1.83
Clinical waste bags	2	\$0.33	\$0.66
Impermeable absorbent cloths	2	\$0.92	\$1.84
Sealable thick walled waste bags	1	\$1.00	\$1.00
P3 masks	2	\$1.28	\$2.56
20 mL Syringe	1	\$0.31	\$0.31
10 mL Syringe	2	\$0.12	\$0.24
5 mL Syringe	1	\$0.10	\$0.10
Total			\$17.94

While these consumable costs are relatively low (and do not include the direct cost of the radiopharmaceutical) there will be a difference in the number of administrations per course between the proposed intervention and its nominated comparator/s. For example, this consumable cost will be incurred six times for a course of radium-223 while only once or twice for a course of strontium-89 or Sm-153 lexitronam. This should be incorporated in the economic evaluation and could be included in Table 10 above.

The application lists equipment costs associated with the administration of radiopharmaceuticals sourced from an expert at the Department of Nuclear Medicine at the Royal Brisbane Hospital. This information is reproduced below:

- Dose calibrator: Purchase price approximately \$8,000. Used in most of all nuclear medicine procedures (typically 20 per day (20*5*50) = \$5,000 per annum).
- Specialised spill cleanup materials: dedicated \$400.
- Radiation survey meter: purchase price approximately \$1500, used rarely in spills but essential. Shared with Nuclear Medicines procedures.
- Fume hood: \$10 000. Potentially dedicated.
- Maintenance and calibration: \$500.
- Alternative air extraction system: \$3000.

The sponsor indicates that, because the equipment is used for several radiotherapies in a hospital, it is difficult to estimate the proportion of use for administration of a radiopharmaceutical. In addition, equipment costs would be amortised after purchase. For these reasons the sponsor has not included equipment costs in its calculation of service costs. This is acceptable.

Other costs that could be included in Table 9 are those of:

- Bone scans and monitoring costs. Strontium-89 and samarium-153 leixidronam therapy requires a bone scan before treatment is initiated and expert advice indicated that patients administered radium-223 will continue to be monitored with PSA, imaging studies (nuclear bone scans, CT and/or MRI).
- External beam radiotherapy (EBRT). Depending on how this is likely to be used in practice there may be a difference between the intervention and comparators in the use of EBRT. Particularly because the radiopharmaceuticals call for EBRT to be inappropriate or not effective at controlling the disease.
- If the proposed "Treatment Survey" shows that cabazitel and abiraterone are also relevant comparators, resources used to deliver them will need to be included.
- Bisphosphonates and denosumab. There is some uncertainty whether bisphosphonates and denosumab will be prescribed in patients receiving the intervention or its comparators. If these treatments are co-administered in practice then there may be a difference in their use between treatment arms particularly if radium-223 extends life.
- Pain medications. Table 9 describes analgesics, anti-inflammatories, and corticosteroids as being part of continued pain medication prescribed during treatment with the intervention and its comparator and as part of management of AEs. It will be necessary to distinguish and cost the particular medicines expected to be administered in this capacity in the economic analysis.

The application provides detailed estimates of the time required from a variety of medical staff for tasks associated with delivering radium-223. Information is also available on the cost of staff time. While these costs are not included in Table 9, they will be useful estimates to apply in any economic evaluation of radium-223.

The applicant has proposed a survey of three nuclear medicine physicians or radiologists from different states and centres to address resource utilisation and costing information. This is agreeable to PASC. The survey will need to address issues raised by the DAP such as:

- Is the proposed patient population likely to receive additional diagnostic monitoring services (bone scans) as a result of treatment with the radium-223 intervention, and is this different from any of the comparators?
- Will there be other interventions claimed in association with radium-223 aside from MBS items 110 or 104?
- Are the time estimates for the administration of radium-223 consistent with the expectations for administration of strontium-89 or samarium-153 lexitronam?

References

- Cancer Council Australia (2009). *Advanced Prostate Cancer: A Guide for Men and Their Families*. Retrieved February 2012 from: http://www.cancer.org.au/File/HealthProfessionals/Advanced_Prostate_Cancer_Guide_2009_BOOKMARKS.pdf
- Krupski, T. Theodorescu, D. eMedicine, Medscape (updated February 2012). *Prostate Cancer*. Retrieved February 2012 from: <http://emedicine.medscape.com/article/1967731-overview>
- Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2010. Cancer in Australia: an overview, 2010. Cancer series no. 60. Cat. no. CAN 56. Canberra: AIHW.
- Crawford et al., (2003): The role of the Urologist in treating patients with hormone refractory prostate cancer. *Reviews in Urology*. VOL. 5 SUPPL. 2; p48-52.
- Sturge et al., (2011): Bone metastasis in prostate cancer: emerging therapeutic strategies, *Nature Reviews Clinical Oncology* 8, 357–368; 2011.
- Coxon et al., (2004): Kirby RS. Advances in the use of bisphosphonates in the prostate cancer setting. *Prostate Cancer and Prostatic Diseases*; 7:99–104.
- Smith et al., (2009): New opportunities for the management of cancer-related bone complications. *Clinical Advances in Hematology and Oncology*. May; 7(5 Suppl 11):1-30; quiz 31.
- eMedicine, Medscape. *Strontium-89 chloride (Rx) – Metastron*. Retrieved February 2012 from: <http://reference.medscape.com/drug/metastron-strontium-89-chloride-342189>
- Glasziou et al. (1990): Quality Adjusted Survival Analysis. *Medical Statistics*. 9:1259-1276