NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using radium-223 dichloride in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
- Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply:
  - The health technology cannot be appropriately administered until training is in place?
<p>| | |</p>
<table>
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<tbody>
<tr>
<td>o</td>
<td>The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?</td>
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<tr>
<td>o</td>
<td>The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?</td>
</tr>
<tr>
<td>o</td>
<td>The health technology is not yet available in England.</td>
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If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE’s guidance on using radium-223 dichloride in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 25 June 2015

Next Appraisal Committee meeting: 6 October 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.
1  Appraisal Committee’s preliminary recommendations

1.1 Radium-223 dichloride is recommended as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases, only if:

- they have had treatment with docetaxel, and
- the company provides radium-223 dichloride with the discount agreed in the patient access scheme.

1.2 People whose treatment with radium-223 dichloride is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2  The technology

2.1 Radium-223 dichloride (Xofigo, Bayer) is a radiopharmaceutical agent designed to deliver alpha radiation to bone metastases without affecting normal bone marrow. The marketing authorisation for radium-223 dichloride (hereafter referred to as radium-223) is ‘for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases’.

2.2 The summary of product characteristics lists the following adverse reactions for radium-223: thrombocytopenia, diarrhoea, vomiting, nausea, neutropenia, pancytopenia, leukopenia, injection-site
reactions and lymphopenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The company’s submission states that radium-223 is available at a radioactivity of 6 MBq in a 6-ml vial at a net price of £4040 (excluding VAT). It is administered by intravenous injection at a recommended dose of 50 kBq/kg body weight every 4 weeks for 6 injections (giving the average cost of a course of treatment of £24,240, estimated by the company). The company that holds the marketing authorisation for radium-223 (Bayer) has agreed a patient access scheme with the Department of Health that makes radium-223 available with a discount applied to all invoices. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company’s submission

The Appraisal Committee (section 8) considered evidence submitted by the company that holds the marketing authorisation for radium-223 and a review of this submission by the Evidence Review Group (ERG; section 9).

3.1 The company’s decision problem compared radium-223 plus best supportive care with best supportive care alone for people who have and have not had docetaxel therapy. The company also submitted additional evidence comparing radium-223 with abiraterone in people who have and have not had docetaxel therapy. The company did not present a comparison of radium-223 with docetaxel as specified in the final scope on the basis that radium-223 is not proposed to be offered to people who can have docetaxel.
Clinical effectiveness evidence

3.2 The key clinical evidence in the company’s submission came from the pivotal phase-III trial, ALSYMPCA. ALSYMPCA was an international, multicentre, randomised, double-blind, placebo-controlled trial comparing radium-223 with placebo, both in combination with best supportive care, for treating symptomatic hormone-refractory prostate cancer with bone metastases. Patients were followed-up for up to 3 years after having their first treatment.

3.3 People were eligible to participate in ALSYMPCA if they had hormone-relapsed disease with bone metastases, were aged 18 years or older, and had a life expectancy of 6 months or more. The trial included patients who had previously had docetaxel, as well as patients for whom docetaxel was unsuitable and patients who did not want to take it. Patients for whom docetaxel was available and suitable and who were willing to take it were excluded from the trial. Patients with visceral metastases were also excluded from the trial. After screening, 921 patients were randomised in a 2:1 ratio to have either 50 kBq/kg body weight of radium-223 (n=614) or placebo (n=307) by intravenous injection every 4 weeks, in addition to best supportive care. Best supportive care included local external-beam radiotherapy, corticosteroids, anti-androgens, oestrogens, estramustine and ketoconazole. Patients were allowed to take bisphosphonates during the trial if they were using them at trial entry. Patients could have up to 6 doses of trial treatment, over the 6-month treatment period, but the company designated the average number of doses as commercial in confidence. Patients stopped trial treatment if they had an adverse event with an unacceptable risk, or had any non-trial treatment, voluntarily withdrew from the trial or were taken out of the trial at the
investigator’s request. Patients who withdrew were followed up 4 weeks after the last treatment.

3.4 Baseline patient characteristics were generally similar between the treatment groups. In both treatment groups, 94% of patients were white. Approximately 87% of patients in both arms had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, and the remaining 13% had an ECOG performance score of 2. Approximately 57% of patients in each treatment group had previously had docetaxel.

3.5 The primary outcome in ALSYMPCA was overall survival, defined as the time from randomisation to the time of death. The key secondary outcomes were:

- time to occurrence of first skeletal-related event (SRE), which included pathological fracture, spinal cord compression, and radiotherapy or surgery to the bone
- changes and time to progression in prostate-specific antigen (PSA) concentration
- changes and time to progression in total alkaline phosphatase activity (a biochemical marker of bone turnover).

Quality of life was assessed using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) and EuroQoL (EQ-5D) questionnaires.

3.6 There was a statistically significant improvement of 3.6 months in the primary end point of median overall survival, which was 14.9 months in the radium-223 group compared with 11.3 months in the placebo group during the 3-year follow-up period (hazard ratio [HR] 0.70; 95% confidence interval [CI] 0.58 to 0.83; p=0.00007). For the secondary outcomes, median time to
occurrence of the first SRE was 15.6 months in the radium-223 group compared with 9.8 months in the placebo group (HR 0.66; 95% CI 0.52 to 0.83; p=0.00037). Radium-223 was also associated with statistically significant reductions in the incidence of SREs compared with placebo, except for surgery to the bone and pathological fracture, for which the reductions were not statistically significant. Time to PSA progression was 3.6 months in the radium-223 group and 3.4 months in the placebo group (HR 0.64; 95% CI 0.54 to 0.77; p<0.00001). The company designated as academic in confidence the median time to total alkaline phosphatase progression and the health-related quality of life scores.

3.7 The company presented results for the pre-planned subgroups defined by docetaxel use in ALSYMPCA. In the subgroup of people who had previously had docetaxel, there was a statistically significant improvement of 3.1 months in median overall survival; this was 14.4 months in the radium-223 group compared with 11.3 months in the placebo group (HR 0.71, 95% CI 0.57 to 0.89, p=0.003). In the subgroup of people who had not previously had docetaxel, there was a statistically significant improvement of 4.6 months in median overall survival; this was 16.1 months in the radium-223 group compared with 11.5 months in the placebo group (HR 0.75, 95% CI 0.56 to 0.99, p=0.004). The company also reported median time to occurrence of the first SRE and time to PSA progression for both of the subgroups, in which radium-223 demonstrated a benefit. However, at the time of submission the company designated the results as academic in confidence.

3.8 The company defined the safety population (n=901) as patients who had at least 1 dose of trial medication. Bone pain was the most common adverse event in both treatment groups, although it
occurred with a higher frequency in the placebo group (62%) than in the radium-223 group (50%). Adverse events leading to trial treatment discontinuation also occurred with a higher frequency in the placebo group (20.6%, compared with 16.5% in the radium-223 group). The company designated as academic in confidence the data for drug-related serious adverse events, death from conditions associated with disease progression and death because of non-prostate cancer events.

**Indirect treatment comparison with abiraterone**

3.9 To carry out an indirect treatment comparison of radium-223 with abiraterone, the company identified 2 phase III randomised controlled trials that compared abiraterone with placebo:

- **COU-AA-301** in which abiraterone plus prednisone was compared with placebo plus prednisone in people with metastatic hormone-relapsed prostate cancer who had previously had 1 or 2 chemotherapy regimens, 1 of which must have contained docetaxel.

- **COU-AA-302** in which abiraterone plus prednisone was compared with placebo plus prednisone in people with progressive metastatic hormone-relapsed prostate cancer, who had not had previous chemotherapy and who had not yet developed clinically significant, cancer-related symptoms.

In the COU-AA-301 study, people were randomly assigned to the abiraterone group (n=797) or to the placebo group (n=398). At median follow-up of 20.2 months, median overall survival for the abiraterone group was 15.8 months compared with 11.2 months in the placebo group (HR 0.74; 95% CI 0.64 to 0.86; p<0.0001). Median time to PSA progression for the abiraterone group was 8.5 months compared with 6.6 months in the placebo group (HR
In the COU-AA-302 study, people were randomly assigned to the abiraterone group (n=546) or to the placebo group (n=542). At median follow-up of 22.2 months there was a 25% decrease in the risk of death in the abiraterone group compared with the placebo group, indicating a strong trend towards improved survival. However, median survival for the abiraterone group was not reached. Median time to PSA progression for the abiraterone group was 11.1 months compared with 5.6 months in the placebo group (HR 0.49, 95% CI 0.42 to 0.57, p<0.001).

3.10 The 2 abiraterone trials were compared with the corresponding subgroups in ALSYMPCA (people who had previously had docetaxel and people who had not had docetaxel). However, the company stated that the patient populations differed between the trials. It noted that alkaline phosphatase (ALP) score was higher for patients who had docetaxel in ALSYMPCA compared with patients in COU-AA-301 (the baseline ALP was not reported for the COU-AA-302 trial). Baseline PSA scores were also higher for patients who had docetaxel and patients who had not had docetaxel in ALSYMPCA compared with COU-AA-301 and COU-AA-302 respectively. Other notable differences between the trials highlighted by the company included the proportion of people with bone metastases, which were present in all people in ALSYMPCA, around 90% of people in COU-AA-301 and around half of people in COU-AA-302.

3.11 The HRs for overall survival and progression-free survival for the intervention groups compared with the placebo groups used in the indirect treatment comparison are presented in table 1 and table 2.
Table 1. Summary of the overall survival HR data for the intervention groups compared with the placebo groups that was used in the indirect analysis (company’s additional evidence submission)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSYMPCA</td>
<td>No prior docetaxel</td>
<td>Radium-223 dichloride</td>
<td>0.745</td>
<td>0.562</td>
<td>0.987</td>
<td>0.004</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>No prior docetaxel</td>
<td>Abiraterone</td>
<td>0.79</td>
<td>0.66</td>
<td>0.99</td>
<td>0.0151</td>
</tr>
<tr>
<td>ALSYMPCA</td>
<td>Prior docetaxel</td>
<td>Radium-223 dichloride</td>
<td>0.710</td>
<td>0.565</td>
<td>0.891</td>
<td>0.003</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>Prior docetaxel</td>
<td>Abiraterone</td>
<td>0.74</td>
<td>0.64</td>
<td>0.86</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio (<1 favours the intervention)

Table 2. Summary of the progression-free survival HR data for the intervention groups compared with placebo groups that was used in the indirect analysis (company’s additional evidence submission)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSYMPCA</td>
<td>No prior docetaxel</td>
<td>Radium-223 dichloride</td>
<td>0.64</td>
<td>0.54</td>
<td>0.77</td>
<td>0.004</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>No prior docetaxel</td>
<td>Abiraterone</td>
<td>0.5</td>
<td>0.42</td>
<td>0.57</td>
<td>0.0151</td>
</tr>
<tr>
<td>ALSYMPCA</td>
<td>Prior docetaxel</td>
<td>Radium-223 dichloride</td>
<td>0.64</td>
<td>0.54</td>
<td>0.77</td>
<td>0.003</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>Prior docetaxel</td>
<td>Abiraterone</td>
<td>0.58</td>
<td>0.46</td>
<td>0.73</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio (<1 favours the intervention)

3.12 The company’s indirect comparison results for overall survival and progression-free survival comparing the prior-docetaxel and no-prior-docetaxel subgroups in ALSYMPCA with data from the total populations in COU-AA-301 and COU-AA-302 respectively are
shown in table 3 and table 4. The results for overall survival marginally favour radium-223 in both subgroups compared with abiraterone but the CIs are large.

**Table 3. Indirect treatment comparison results for overall survival for abiraterone compared with radium-223 (company’s additional evidence submission)**

<table>
<thead>
<tr>
<th>Population</th>
<th>HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior docetaxel</td>
<td>1.04</td>
<td>0.79</td>
<td>1.37</td>
</tr>
<tr>
<td>No prior docetaxel</td>
<td>1.06</td>
<td>0.75</td>
<td>1.50</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio (>1 favours radium-223)

The results for progression-free survival marginally favour abiraterone in both subgroups compared with radium-223 but the confidence intervals are large.

**Table 4. Indirect treatment comparison results for progression-free survival for abiraterone compared with radium-223 (company’s additional evidence submission)**

<table>
<thead>
<tr>
<th>Population</th>
<th>HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior docetaxel</td>
<td>0.91</td>
<td>0.68</td>
<td>1.21</td>
</tr>
<tr>
<td>No prior docetaxel</td>
<td>0.78</td>
<td>0.62</td>
<td>0.99</td>
</tr>
</tbody>
</table>

CI, confidence interval, HR, hazard ratio (>1 favours radium-223)

The company used adverse event data for radium-223 from the overall safety population of ALSYMPCA, and compared this with the adverse event data for abiraterone from COU-AA-301, which it stated had the most comparable patient population to ALSYMPCA. The results of the indirect comparison for adverse events were designated academic in confidence by the company.
**Cost-effectiveness evidence**

3.13 The company carried out a de novo analysis of the cost effectiveness of radium-223 compared with placebo, both in combination with best supportive care, for treating hormone-relapsed prostate cancer with bone metastases using data from the intention-to-treat (ITT) population in ALSYMPCA. In response to the Committee’s considerations that abiraterone and docetaxel were the most relevant comparators for this appraisal, the company submitted revised economic analyses that also included a comparison with abiraterone, but not with docetaxel. For the comparison with abiraterone, the company presented 2 analyses:

- people with prior docetaxel treatment, using data from the prior-docetaxel subgroup in ALSYMPCA and the ITT population in COU-AA-301
- people without prior docetaxel treatment, using data from the subgroup who had not had docetaxel in ALSYMPCA and the ITT population in COU-AA-302.

3.14 The company developed a 5-state, semi-Markov model with time-dependent probabilities to reflect the clinical pathway of hormone-relapsed prostate cancer with bone metastases. All patients entered the model in the ‘progression-free without SRE’ health state, and in each cycle could either move to the ‘progression-free with SRE’ health state, the ‘progressed without SRE’ health state or the ‘progressed with SRE’ health state. They could then also move from the ‘progression-free with SRE’ state and the ‘progressed without SRE’ state to the ‘progressed with SRE’ state. At any time, patients could move from any of the 4 health states to the ‘death’ state, or remain in their current health states. The model had a time horizon of 5 years consisting of...
weekly cycles, and did not include a half-cycle correction. Costs and benefits were discounted at 3.5%. The analysis was performed from the perspective of the NHS and personal social services.

3.15 For the analyses comparing radium-223 with best supportive care, the proportion of patients in each state at each point in time was derived directly from parametric survival functions using patient-level time-to-event data (including overall survival, progression-free survival based on serum PSA concentration, and SRE-free survival) from the ITT population in ALSYMPCA. The company also assessed progression-free survival using alkaline phosphatase concentration and ECOG-performance status in sensitivity analyses. The company stated that the occurrence of SREs in ALSYMPCA was observed closely only for the first 6 months, and the proportion of patients in the model who were SRE-free was assumed to be constant after 6 months. The overall survival, progression-free survival and SRE-free survival curves for both treatment groups of ALSYMPCA were extrapolated beyond the trial period using the log-normal distribution, which the company considered to provide the best model fit, based on the Akaike information criterion.

3.16 For the analyses comparing radium-223 with abiraterone, the company carried out survival analyses and used regression models based on the Weibull function. The company stated that although the log-normal and log-logistic distributions provided the best fit to the trial data, the Weibull distribution makes a more conservative assumption on overall survival. This is because, unlike the log-normal and log-logistic distributions, the Weibull distribution does not have a long tail and it makes a more clinically plausible assumption of overall survival. The company assessed progression-free survival according to PSA progression only. The
company explained that there were no data on ALP progression in the abiraterone trials and that time-to-ECOG functional status deterioration was defined differently between ALSYMPCA and the abiraterone trials. The company applied HRs for overall survival and progression-free survival from the indirect treatment comparison to the curves of 1 arm to derive the corresponding curves for the other arm. The arm that formed the base varied. The company used the abiraterone curves from COU-AA-302 for the no-prior-docetaxel subgroup and the radium-223 curves from ALSYMPCA for the prior-docetaxel subgroup. The company took the SRE-free curve from the radium-223 arm of ALSYMPCA for the prior-docetaxel subgroup: at a given time point this gave the proportion of people that were SRE-free. The company then applied the proportion that were SRE-free to both the overall survival curve for radium-223 and the overall survival curve for abiraterone to estimate the SRE-free curves for radium-223 and abiraterone in the economic model for the prior-docetaxel subgroup. The company did not present an SRE-free curve for the no-prior-docetaxel subgroup.

3.17 In its original model, the company used treatment specific EQ-5D utility values for progression-free and progressed disease derived directly from ALSYMPCA. However, in response to the Committee’s considerations that the utility estimation in the model was not robust, the company revised its utility analysis. To estimate the utility scores of the 4 main health states in the economic model (see section 3.17), the company used a repeated measures mixed-effect linear regression model to analyse the EQ-5D data collected from ALSYMPCA. The model used to estimate utilities allowed for adjustments for time from baseline (random effect within patient), baseline ALP, bisphosphonate use and prior docetaxel use. It derived separate utility estimates for radium-223 and placebo for
each health state. It assumed that the radium-223 results also applied to abiraterone. The regression model used the 3 definitions of progression (PSA, ALP and ECOG). The company repeated the overall results for the no-prior- and prior-docetaxel subgroups. When using the utility values in the economic model, the company determined whether to use an arm-specific utility value in the model or an estimate from across the arms based on statistical significance. The company estimated utilities using models including and excluding the baseline EQ-5D responses and it chose to use the model excluding the baseline EQ-5D responses. The company indicated that the quality-adjusted life year (QALY) calculation may not be robust because the significant reduction in fatigue associated with radium-223 treatment, measured using the FACT-P disease-specific measure, could not be captured with the EQ-5D.

3.18 The company stated that ALSYMPCA did not collect the disutilities from adverse events. Therefore, the company based its analysis on the adverse event disutilities for breast and non-small-cell lung cancer from external published sources (Lloyd et al. 2006, Nafees et al. 2008 and Doyle et al. 2008). The company based this on the assumption that cancer type would not influence the impact of adverse events on quality of life. The disutility estimates were then adjusted to reflect the assumption that each adverse event lasted 3 weeks, and each event was weighted by the proportion of patients who experienced it in each of the ALSYMPCA treatment arms.

3.19 The company estimated the total cost of radium-223 used in the analysis by applying the revised patient access scheme discount; designated commercial in confidence by the company. The company based the cost on the average number of injections used
in ALSYMPCA, given at a dose of 50 kBq/kg body weight every 4 weeks. It based the monitoring and administration cost of £200.92 per treatment cycle (every 4 weeks) on NHS reference costs (2012–13) for SB12Z: deliver simple/complex parenteral chemotherapy at first attendance.

3.20 The company estimated the acquisition cost for abiraterone to be £21,939 based on the list price and treatment duration of 7.4 months from COU-AA-301 for the prior-docetaxel subgroup. It estimated a cost of £42,426 based on the list price and treatment duration of 14.3 months from COU-AA-302 for the no-prior-docetaxel subgroup. Abiraterone is available to the NHS through a simple discount patient access scheme, for which the level of the discount is confidential and cannot be disclosed. The company applied assumed discounts to the list price of abiraterone in a sensitivity analysis. The company estimated an administration cost of £161.33 for abiraterone every 4 weeks.

3.21 Other cost parameters incorporated in the model included best supportive care drug costs, costs associated with the routine management of metastatic hormone-relapsed prostate cancer, costs of subsequent therapies following disease progression and costs of treating SREs and adverse events. The company based the associated cost parameters on a systematic review and a survey of oncologists and urologists in the UK. It obtained the costs estimates from the ‘British national formulary’ (BNF) edition 63, NHS reference costs for 2012–13 and unit costs of health and social care 2013. The company assumed that subsequent therapies would only be used for 3 weeks (that is, 3 model cycles). Costs of treating SREs and adverse events were weighted by the proportion of patients in each group experiencing each SRE and adverse event in ALSYMPCA and COU-AA-301. It derived a one-
off, weighted average cost of £2087 for end of life care in the last 3 months of a patient's life from Abel et al. (2013), and applied it to the death state in the model. For the analyses of progression, defined according to ECOG status deterioration, the company included costs for personal social services. The company applied the personal social services costs to the post-progression state only because it assumed that ECOG status deterioration in the pre-progression state was not likely to be as a result of metastatic hormone-relapsed prostate cancer.

Results of the company’s economic analyses

3.22 All results presented here are based on the company’s revised analyses and supersede the results of the original model. The base-case analysis for the overall population resulted in an incremental cost-effectiveness ratio (ICER) for radium-223 plus best supportive care compared with placebo plus best supportive care of £47,697 per QALY gained. The scenario analyses using ALP and ECOG as alternative measures of progression resulted in ICERs of £30,941 and £37,172 per QALY gained respectively. The company designated the incremental costs as commercial in confidence.

3.23 For the comparison of radium-223 with best supportive care, the company carried out subgroup analyses based on prior docetaxel use in ALSYMPCA. It performed survival analyses to estimate the proportion of patients in each health state in a similar way to the analysis of the ITT population used in the base case (see section 3.15). For the prior- and no-prior-docetaxel subgroups, the ICERs for radium-223 plus best supportive care compared with placebo plus best supportive care are presented in table 5. The results of the probabilistic sensitivity analysis were designated commercial in confidence by the company.
Table 5. ICERs for radium-223 compared with best supportive care for subgroups

<table>
<thead>
<tr>
<th>Progression measure</th>
<th>ICER for radium-223 versus best supportive care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-prior-docetaxel base case</td>
</tr>
<tr>
<td>PSA</td>
<td>£46,576</td>
</tr>
<tr>
<td>ALP</td>
<td>£38,182</td>
</tr>
<tr>
<td>ECOG</td>
<td>£44,724</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ICER, incremental cost-effectiveness ratio; PSA, prostate-specific antigen

3.24 In the analyses comparing radium-223 with abiraterone, radium-223 plus best supportive care dominated (that is, was less expensive and more effective than) abiraterone plus prednisone in both the prior-docetaxel and non-prior-docetaxel subgroups, using the list price for abiraterone. The company designated the incremental costs and QALYs as confidential. The company conducted sensitivity analyses by applying assumed discounts to the price of abiraterone; the results of these analyses ranged from radium-223 dominating abiraterone to an ICER of £222,224 per QALY gained.

3.25 The company provided additional analyses that applied:

- the HRs derived from indirect comparison to exponential and Gompertz survival curves from COU-AA-302 in the non-prior-docetaxel subgroup
- the inverse of the HRs derived from the indirect comparison to the exponential, Gompertz and Weibull survival curves from ALSYMPCA for the non-prior-docetaxel subgroup
- the inverse of the HRs derived from the indirect comparison to the exponential, Gompertz and Weibull survival curves from ALSYMPCA for the prior-docetaxel subgroup.
The company conducted the analyses using the list price of radium-223 only and therefore because radium-223 has a confidential patient access scheme discount the results are designated commercial in confidence.

Evidence Review Group comments

3.26 The ERG commented that the methodological quality of ALSYMPCA was good. It considered that the evidence demonstrating the clinical benefits of radium-223 plus best supportive care compared with placebo plus best supportive care in a second-line population was compelling. However, it considered that the evidence presented for first-line treatment in patients who had not had docetaxel was weak. This was because some patients in this group had refused docetaxel, or had not had access to it, and radium-223 had not been compared with first-line docetaxel, which was a valid comparator for these patients. The ERG concluded that, for the group of patients who could have taken docetaxel but had refused it or not had access to it, radium-223 had not been compared with all valid comparators, thereby limiting the interpretation of the decision problem.

3.27 The ERG commented that, without any information in the company’s submission on bisphosphonate use during the follow-up period of the trial, it was unable to assess whether the SRE results were confounded by bisphosphonate use. The ERG was concerned that excluding people with visceral metastatic disease from ALSYMPCA limited the generalisability of the results to the wider population in the scope for this appraisal. The ERG also stated that the observed effects of treatment may not be generalisable to ethnic groups who were under-represented in the trials. It stated that although the number of African–Caribbean men aged over 40 was much lower than that of white men in the trial.
they were 3 times more likely to get prostate cancer than white men of the same age (94% of patients in the trials were white; the proportion of African–Caribbean men in the trial was not reported in the company’s submission).

3.28 The ERG stated that one of its main concerns related to how comparable the populations and outcomes of the abiraterone studies and ALSYMPCA were, particularly for the no-prior-docetaxel groups (see section 3.10). The ERG noted that although the HRs for overall survival from the trials were similar, the median survival was considerably longer in COU-AA-302 (35.3 months) than the corresponding subgroup in ALSYMPCA (16.1 months). It also highlighted that the median time to progression for the abiraterone trials (COU-AA-301, 8.5 months; COU-AA-302, 16.5 months) was also considerably longer than for the ITT population in ALSYMPCA (3.6 months). The ERG noted that there was inconsistent handling of censored data; ALSYMPCA treated death as a censored event, while COU-AA-302 counted death as an event. The ERG commented that this introduced further uncertainty that the HRs in the no-prior-docetaxel subgroups were comparable. The ERG stated that an indirect comparison needs a similarity assumption and a consistency assumption when comparing direct and indirect estimates. It stated that for both subgroups, the patient populations between the radium-223 and abiraterone studies were heterogeneous and the similarity assumption may have been violated. The ERG noted that because no direct randomised evidence comparing radium-223 and abiraterone existed there was no way to check the appropriateness of the consistency assumption. The ERG concluded that the results of the indirect comparison needed to be treated with caution.
3.29 The ERG considered that the model structure was broadly reasonable. However, it was concerned that log-normal curves were used in all cases in the company’s model for comparing radium-223 with best supportive care, even though the log-logistic curve provided the best fit for SRE-free survival, and overall survival in the radium-223 arm. Although it understood the appeal of using the same distribution to model both arms for overall survival, the ERG considered the log-logistic curve to be more appropriate to model SRE-free survival, because it provided the best model fit for both treatment arms. It explored the impact of using the log-logistic curve to model SRE-free survival, but this had little impact on the base-case ICER. The ERG noted that the company did not provide any justification for choosing the log-normal curve over the log-logistic curve for overall survival. The ERG understood that a 5-year time horizon was used in the model for all base-case analyses. It understood that this was because the log-normal distribution used in the base case for the comparison of radium-223 with best supportive care may result in unrealistic extrapolations as a result of its long tail, if taken too far beyond the trial data. In the company’s original analysis, the ERG noted that some patients in both arms remained alive at the end of the 5-year period in the model, and that the model did not apply end-of-life costs for these patients. The patients in the radium-223 arm survived longer in total than the patients in the placebo arm; this resulted in an underestimate of the incremental costs associated with radium-223 because of the net additional survival in this arm at 5 years. The ERG stated that the reasonable assumption should be for the overall survival curve to fall to 0 at the end of the time horizon, given that all patients are expected to die of their disease eventually. However, it noted that excluding end-of-life costs for patients still surviving after 5 years had minimal impact on the ICER.
in the original model. It further noted that limiting the time horizon to 5 years resulted in cost-effectiveness estimates that were less favourable for radium-223 compared with best supportive care.

3.30 The ERG noted that alongside the results for disease progression assessed by PSA and ALP, the company presented additional evidence for progression according to ECOG deterioration. The ERG stated that it was not surprising that ECOG performance status may be a better predictor of quality of life when compared with PSA and ALP because it measures ability to perform usual activities and how often patients are confined to bed, concepts which the ERG noted are also captured by the EQ-5D utility instrument. The ERG commented however, that this does not necessarily mean that ECOG deterioration is an adequate measure of disease progression compared with other objective markers such as PSA, radiological criteria or symptomatic markers.

3.31 The ERG noted that analyses comparing radium-223 with abiraterone only considered PSA as a measure of progression. The ERG agreed with the company’s reason for not presenting alternative analyses based on ALP or ECOG progression (see section 3.16). The ERG noted that the company did not present clinical evidence suggesting there would be a difference between radium-223 and abiraterone because of SREs. Despite this, the ERG noted that the modelling approaches that had been adopted resulted in SRE curves for radium-223 that were superior to those for abiraterone. It commented that this was not justified and that the more reasonable assumption would have been to apply the absolute radium-223 SRE curve to the abiraterone arm.

3.32 The ERG commented that the company’s revised utility analysis was a considerable step forward from that in the company’s original
submission. The ERG stated that using a repeated-measures, mixed-effect, linear-regression analysis was a sensible approach, noting that there were a variable number of utility measurements per person in the ALSYMPCA trial. It stated that the method selected by the company of excluding the baseline values may overestimate the effect of treatment because the model assumes that treatment effects apply from the first cycle of treatment. Although the ERG preferred the approach selected by the company, it indicated that the company should have explored the effect of including the baseline utility values in sensitivity analyses. The ERG noted that in some cases the company had used an arm-specific utility, and in other cases it used estimates that were pooled across arms, depending on whether the estimate was statistically significant. It commented that this approach was not adequately documented and lacked consistency and a clear justification. It stated that a consistent approach should have been used when selecting whether the same or different utilities were used for the active comparators and best supportive care. The ERG noted that the company had applied a constant value for time in each health state. However, it noted that the company’s regression analyses showed that time was a statistically significant determinant of quality of life, even in the presence of the other variable factors, such as the health states of the model. The ERG considered that there may be an argument for a more explicit consideration of time as a determinant of quality of life, although it noted that extrapolations taking this into account might be equally as uncertain as the current analyses.

3.33 The ERG noted that the number of abiraterone doses for the subgroups with prior docetaxel and no prior docetaxel was assumed to be that reported for COU-AA-301 (7.4 months’ treatment duration) and COU-AA-302 (14.3 months’ treatment duration).
duration). It noted that the number of administrations of radium-223 was based on ALSYMPCA trial data, but unlike the analysis of abiraterone this was not differentiated by patient subgroup for the docetaxel-subgroup modelling. The ERG stated that the large difference between the treatment durations in the abiraterone trials raises the possibility that the mean number of radium-223 injections might differ between the docetaxel subgroups of ALSYMPCA. The ERG suggested that it may also have been appropriate to use the average number of courses started for abiraterone because this is how the dosing of radium-223 was estimated and that using the average treatment duration of abiraterone may have biased the analysis against radium-223. The ERG explored the impact of this in sensitivity analyses by assuming 15.9 doses of abiraterone for the no-prior-docetaxel subgroup and 8.0 doses for the prior-docetaxel subgroup.

3.34 The ERG noted that, in addition to routine follow-up visits, the company assumed that abiraterone needed an additional £161 monthly administration cost. This was based on the weighted average of the NHS reference costs for delivering exclusively oral chemotherapy. The ERG considered that it was possible that abiraterone would be prescribed during the follow-up visits and stated that it may be questionable to apply an additional administration cost every month.

3.35 The ERG noted that during the first Appraisal Committee meeting there were some concerns about drug waste, and that the company had assumed no waste for either radium-223 or abiraterone. It stated that waste may occur if patients stop treatment or if they die between radium-223 being ordered and it being administered. The ERG stated that it was likely there would be some waste associated with abiraterone because not all tablets in a pack would
be consumed, but the impact of this was unknown. For the comparison of radium-223 with best supportive care, the ERG noted that including an allowance for drug waste would worsen the cost-effectiveness estimates.

3.36 The ERG noted that in the company’s response to its request for clarification, the company stated that the ALSYMPCA resource-use questionnaire was protocol driven rather than a representation of clinical practice. The ERG did not consider this to be a satisfactory justification for not presenting any analysis of the resource-use data collected during the trial, especially because the company presented data on the proportion of adverse events treated as inpatient episodes. The ERG considered that the additional resource use for a patient who experienced an SRE, or whose disease progressed, may not have been captured by the questionnaire. However, it was unable to confirm this because the company did not provide the questionnaire in response to the request for clarification.

3.37 The ERG was concerned that the respondents to the resource-use questionnaire commissioned by the company may have included the resource-use associated with SREs and adverse events in their response. This would result in double counting of these costs, given that the company estimated them separately in the model. In the original analysis, the ERG explored the impact of this in sensitivity analyses, by equalising the routine ongoing costs between the treatment arms for the pre-progression health states and equalising the routine ongoing costs across all health states (the impact on the ICER was minimal).

3.38 The ERG stated that it would be more appropriate to estimate the average cost per SRE using data for any SRE rather than first
SRE. It stated that this should apply to both arms of the model for the comparison with best supportive care and to the radium arm for the comparison with abiraterone. For the comparison with abiraterone, the ERG considered the data for any SRE for radium-223 to be more in line with those for abiraterone. It considered that this ensured a consistent approach for estimating the average cost per SRE for the 2 arms of the model. The ERG explored the impact of estimating the costs associated with each SRE based on all SREs experienced by a patient rather than the first SRE only. This increased the average SRE costs estimated by the company for the radium-223 and best supportive care arms in the original model and the radium-223 arm for the comparison with abiraterone. In the original analysis, the ERG stated that it could not verify the assumption in the model that all pathological fractures were either non-vertebral fractures of the arm, rib, or leg, and that there was an equal balance between these. It stated that there was a likelihood that other pathological fractures may have been recorded in ALSYMPCA. The ERG stated that the average cost per pathological fracture of £189 applied in the model (£233 in the revised model) was much lower than the average cost of £1581 estimated for non-vertebral fractures in the health technology assessment of denosumab for bone metastases from solid tumours by Ford et al. (2013). The ERG applied the costs used by Ford et al. in an exploratory analysis for the company’s original analysis, and this had a minimal impact on the ICER.

3.39 In the original analysis, the ERG noted that in order to cost second-line therapies it was necessary to calculate the incidence of progression for each cycle in both arms and that the company used Kaplan–Meier curves to do this. The ERG considered it more appropriate to calculate the incidence of progression using the parametric curves. It also noted that the additional incidence of...
PSA progression in the radium-223 arm was not accounted for in the model, because the company used the Kaplan–Meier data for placebo for both treatments. To correct for this, the ERG revised the costs of subsequent therapies to include the additional incidence of progression within the radium-223 arm. The ERG made a number of revisions to the company’s base case in the revised model:

- It revised the utility inputs to be point estimates rather than the average between the arms, where there was no statistically significant difference between these.
- For the comparison of radium-223 with abiraterone, it revised the HR for progression-free survival in the no-prior-docetaxel subgroup from 0.77 to 0.78 and in the prior-docetaxel subgroup from 0.91 to 0.89 as a result of an error in the company’s submission.
- It removed the administration cost for abiraterone.
- It set the cost of end of life care to 0 to avoid improper modelling effects as a result of the shortening of the overall survival curves by the time horizon of 5 years.
- It corrected a referencing error in the overall survival curve for radium-223 in the comparison of radium-223 with abiraterone for the no-prior-docetaxel subgroup.
- It corrected an error in the calculation of the personal social services costs and applied the personal social services costs to both the progression-free and progressed health states.
- The ERG’s revisions to the base case ICERs for radium-223 compared with best supportive care are presented alongside the company’s base-case estimates in table 6.
Table 6. ICERs for radium-223 compared with best supportive care (whole population)

<table>
<thead>
<tr>
<th>Progression measure</th>
<th>Company base case ICER</th>
<th>Base case ICER with ERG revisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>£47,697</td>
<td>£41,419</td>
</tr>
<tr>
<td>ALP</td>
<td>£30,941</td>
<td>£32,825</td>
</tr>
<tr>
<td>ECOG</td>
<td>£37,172</td>
<td>£53,349</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; ICER, incremental cost-effectiveness ratio; PSA, prostate-specific antigen

3.40 The ERG noted the improved ICER for the analyses that used PSA as the measure of progression was largely as a result of changing the utility inputs to point estimates. The ICER for the analyses that used ALP as the measure of progression was not particularly affected by any of the changes. The ICER for the analysis that used ECOG as the measure of progression increased, mainly as a result of the revisions to the ECOG cost calculations and applying the relevant values to the pre-progression and the post-progression health states.

3.41 The base-case ICERs with the ERG’s revisions for the subgroups of people with and without prior docetaxel use in the analyses comparing radium-223 with best supportive care are presented alongside the company’s estimates in table 7. The ERG noted that the patterns observed for the whole patient population analyses were broadly repeated for the subgroup analyses.
Table 7. ICERs for radium-223 compared with best supportive care (subgroups)

<table>
<thead>
<tr>
<th>Progression measure</th>
<th>No prior docetaxel</th>
<th>Prior docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Company base case</td>
<td>With ERG revisions</td>
</tr>
<tr>
<td>PSA</td>
<td>£46,576</td>
<td>£39,612</td>
</tr>
<tr>
<td>ALP</td>
<td>£38,182</td>
<td>£40,721</td>
</tr>
<tr>
<td>ECOG</td>
<td>£44,724</td>
<td>£63,140</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; PSA, prostate-specific antigen

3.42 For the analyses comparing radium-223 with abiraterone, the ERG presented results using the list price for abiraterone and several assumed discounts to reflect the patient access scheme for abiraterone. The base-case ICER with the ERG’s revisions in the subgroup that had previously used docetaxel showed that radium-223 dominated abiraterone. This happened when abiraterone was supplied at the list price and when it applied all assumed discounts, with the exception of the highest assumed discount; this resulted in an ICER of £62,496 per QALY gained. The base case ICER with the ERG revisions in the subgroup that had not previously used docetaxel showed that radium-223 dominated abiraterone. This happened when all assumed discounts were applied to abiraterone, with the exception of the 2 largest discounts; these discounts resulted in ICERs of £58,478 and £293,167 per QALY gained.

3.43 The ERG conducted a number of univariate sensitivity analyses around the revised base-case ICERs. For the comparison of radium-223 with best supportive care in the no-prior-docetaxel group, the effect of equalising quality-of-life values between the arms after week 24 increased the ICERs to £106,560, £57,208 and £63,864 per QALY gained using PSA-, ALP- and ECOG-
progression respectively. The effect of this analysis in the prior-docetaxel group increased the ICERs to £88,179, £46,302 and £56,121 per QALY gained using PSA-, ALP- and ECOG-progression respectively. In the no-prior-docetaxel group, the use of the Weibull function to model the trial outcomes to be consistent with the comparison with abiraterone increased the ICERs to £49,180, £67,532 and £76,460 per QALY gained using PSA-, ALP- and ECOG-progression respectively. The effect of this analysis in the prior-docetaxel group increased the ICERs to £49,118, £50,902 and £57,544 per QALY gained using PSA-, ALP- and ECOG-progression respectively.

3.44 For the comparison of radium-223 with abiraterone among the no-prior-docetaxel subgroup, the ERG’s sensitivity analyses showed that radium-223 dominated abiraterone at all times except at the highest assumed discount for abiraterone. For the prior-docetaxel subgroup, radium-223 dominated abiraterone (that is, radium-223 was more effective and associated with fewer costs than abiraterone) in most scenarios. The ERG noted that the ICERs were mostly sensitive to the various assumptions around abiraterone treatment costs (that is, when the monthly drug cost for abiraterone was based on 4 weeks rather than 4.33 weeks and including an administration cost for abiraterone). The ICERs for these scenarios ranged from radium-223 dominating abiraterone to £311,220 per QALY gained across the various abiraterone discounts.

Additional evidence following consultation on the second Appraisal Consultation Document

3.45 The company submitted additional evidence for the no-prior-docetaxel population on the parametric distributions used to model the survival data, duration of utility benefits with radium-223 and...
medical resource use from ALSYMPCA. The company’s additional evidence was based on the ERG’s previous revisions to the model, which resulted in an ICER for radium–223 compared with best supportive care of £40,721 per QALY gained for the ALP-based progression.

3.46 The company maintained that the log-normal distribution offered the best fit to the overall survival data from the ALSYMPCA study. To address the Committee’s concerns about the face validity of the long-term extrapolation and to provide a more conservative analysis, the company presented an analysis using the log-normal distribution. However, after 3 years (156 weeks), it doubled the weekly mortality rate for the best supportive care and the radium-223 arms of the trial. This resulted in lower overall survival estimates (data are academic in confidence) at 5 years, and increased the ICER for radium–223 compared with best supportive care from £40,721 to £42,170 per QALY gained. The company explored the effect of extending the time horizon to 10 years. Doubling the weekly mortality rate and increasing the time horizon to 10 years resulted in an ICER of £40,076 per QALY gained. The company stated that this analysis reduces the uncertainty around the extrapolation of data.

3.47 Noting the Committee’s view that the quality-of-life benefits with radium-223 could extend beyond 24 weeks but would not extend over a person’s lifetime, the company presented sensitivity analyses assuming a differential benefit being maintained for 26, 52, 78 or 104 weeks, compared with best supportive care. These results are presented in table 8. The model was varied by changing utilities in the radium-223 arm to be the same as the best supportive care arm after these time periods. The company highlighted that these results indicated that assuming a continued
quality of life benefit for radium-223 compared with best supportive care over a period of 52 weeks resulted in an ICER of £46,278 per QALY gained, and over 104 weeks the ICER was £43,194 per QALY gained.

Table 8. Impact of duration of quality of life benefit with radium-223 on the ICER

<table>
<thead>
<tr>
<th>Duration of quality of life benefit</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime (base case)</td>
<td>£40,721</td>
</tr>
<tr>
<td>26 weeks</td>
<td>£49,692</td>
</tr>
<tr>
<td>52 weeks</td>
<td>£46,278</td>
</tr>
<tr>
<td>78 weeks</td>
<td>£44,390</td>
</tr>
<tr>
<td>104 weeks</td>
<td>£43,194</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio

3.48 The company submitted an additional analysis using data on medical resource use in the ALSYMPCA study, which was presented at the annual conference for the American Society of Clinical Oncology in 2014. This showed fewer hospital days with radium-223 compared with best supportive care in the ALSYMPCA study (14.6 compared with 8.1 hospital days per year, p<0.001; based on pooled data from all patients whether they had prior docetaxel treatment or not), resulting in a saving of £2955 per patient, based on a daily cost of £450.61. This analysis was not incorporated into the company model. The company highlighted that applying this benefit reduces the incremental cost of radium-223 and therefore estimated that the ICER reduced from £40,721 to £30,214 per QALY gained for the no prior docetaxel group.

**ERG critique of the additional evidence**

3.49 The ERG highlighted that the company’s additional evidence was based on the model revisions suggested in the second ERG report only and had not taken into account revisions suggested by the
ERG in its original report. The revisions in the original ERG report included recalculating the cohort flow as a result of death being treated as a censored event, rather than an event for the PFS curve and the SRE curve. The revision to the cohort-flow calculation applied the formula as described in the company’s submission (figure 27 of the company’s original submission), but because this was not implemented correctly in the company’s model, the ERG corrected this in its explorations. Another amendment that was included in the original ERG report revised the costs of second-line care to include all data within the radium-223 arm (although this had a minor impact on the ICER). When the ERG applied the revisions as described in both ERG reports, these increased the ICER for radium-223 compared with best supportive care for the no-prior-docetaxel subgroup (using ALP as the measure of progression) from £40,721 to £56,479 per QALY gained for the 5-year time horizon, and from £35,306 to £48,808 per QALY gained for the 10-year time horizon.

The ERG cross-checked the company’s ICER of £42,170 per QALY gained as a result of doubling the weekly mortality rate from 156 weeks and produced an ICER of £42,184 per QALY gained. The ERG commented that the company’s reason for selecting the 156-week point to double the weekly mortality rate was not clear. It stated that the Kaplan–Meier curves are not defined at this point, and even at 104 weeks, very few patients remain at risk in either Kaplan–Meier curve (these data are academic in confidence). The ERG commented that this suggests that the point at which the weekly probability of death doubles in the sensitivity analysis should be before 156 weeks, for example, 104 weeks (2 years) or earlier. The ERG conducted an exploratory analysis using a time-point of 104 weeks, which increased the ICER from the ERG’s estimate of £42,184 to £45,395 per QALY gained. When the ERG
applied the revisions as described in both ERG reports together with doubling the weekly probability of death from 156 weeks, the ICER increased from £42,184 to £58,983 per QALY gained. Applying the revisions as described in both ERG reports together with doubling the weekly probability of death from the ERG’s preferred time point of 104 weeks, the ICER increases to £63,381 per QALY gained.

3.51 The ERG agreed with the company that the quality-of-life benefit of radium-223 is likely to last longer than 24 weeks, but suggested that a more sophisticated analysis of time trends could have been used to model the effects over time. Furthermore, the ERG highlighted that the company had applied utility values derived from all patients in the ALSYMPCA study rather than those derived specifically from the no-prior-docetaxel group. The ERG presented exploratory analyses that applied utility values from the no-prior-docetaxel group and stated that it had previously contended that these values should have been used for the company’s base case. This amendment increased the base-case ICER from £40,721 to £49,625 per QALY gained. This was based on the suggested revisions from the second ERG report, a 5-year time horizon and the assumption that the quality-of-life benefit of radium-223 compared with best supportive care continued for life, even after treatment had stopped. If a 104-week quality-of-life benefit for radium was applied, the ICER increased to £52,431 per QALY gained. When the ERG applied the revisions as described in both ERG reports in addition to 104-week quality-of-life benefit for radium, this increased the ICER to £63,492 per QALY gained.

3.52 The ERG highlighted that the company’s additional data on medical resource use was based on pooled data from all patients, whether they had prior docetaxel treatment or not. However, among those
who had not had prior docetaxel the estimate was only 4.58 days compared with 6.56 days presented by the company. Using 4.58 days, the ERG estimated that this reduced the base-case ICER from £40,721 to £33,382 per QALY gained, compared with the company’s estimate of £30,214 per QALY gained (see section 3.48). When incorporating the ERG’s suggested amendment from the original ERG report as well, the ICER of £56,479 per QALY gained decreased to £46,607 per QALY gained.

Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of radium-223, having considered evidence on the nature of hormone-relapsed prostate cancer with bone metastases and the value placed on the benefits of radium-223 by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee considered the clinical need for treatment in people with hormone-relapsed prostate cancer with bone metastases. It heard from the patient experts that bone metastases are very distressing for patients and their families, particularly as a result of bone pain and fatigue, which have a profound impact on patients’ quality of life. It also noted the comments from consultees that bone metastases affect mobility and that full-time care would often be needed for people to carry out daily activities. The patient experts stressed the need for a treatment option that could potentially provide relief from bone pain and other effects of bone metastases, thereby significantly improving quality of life. They also emphasised that radium-223 would target the specific part of the body where
bone metastases have occurred, unlike chemotherapy, and this was considered to outweigh the potential adverse events associated with treatment. The Committee recognised the need for alternative treatment options with the potential to improve quality of life in people with bone metastases associated with hormone-relapsed prostate cancer, and concluded that radium-223 could potentially be a treatment option.

4.2 The Committee discussed the relevant comparators for this appraisal, noting that the final scope specified abiraterone and best supportive care (for people who have and have not had docetaxel), and docetaxel (for people who have not had docetaxel) as comparators. The Committee heard from the clinical experts that abiraterone is not an appropriate comparator for people who have not had docetaxel because the people who would have radium-223 were distinct from those who would be considered for abiraterone. This is because the marketing authorisation for abiraterone in this setting is for people with asymptomatic or mildly symptomatic disease in whom chemotherapy is not yet clinically indicated; the marketing authorisation for radium-223 is for people with symptomatic disease. The Committee concluded that abiraterone was not an appropriate comparator for radium-223 for people who have not had docetaxel. The Committee understood that the company had not presented a comparison of radium-223 with docetaxel for people who have not had previous docetaxel therapy on the basis that radium-223 is not proposed to be used in people for whom docetaxel would be suitable. It heard from the clinical experts that people for whom docetaxel is suitable would not be offered treatment with radium-223 because docetaxel would always be the preferred treatment option. However, in response to consultation it was highlighted that this was not the case because in the ALSYMPCA trial, patients could be offered radium-223 if they
declined to take docetaxel. The Committee noted that this was in line with the trial exclusion criteria of ALSYMPCA, which excluded those who were eligible for docetaxel defined as people who were willing to have docetaxel, in addition to those fit enough and where docetaxel is available. The Committee also noted that radium-223 is available through the Cancer Drugs Fund for people who declined to have docetaxel in addition to people for whom it is not suitable. The Committee considered this to mean that people for whom docetaxel is suitable can decide whether to have docetaxel or radium-223, and therefore docetaxel is an appropriate comparator for this group of people. The Committee heard from clinical experts that there are people for whom docetaxel is contraindicated or unsuitable, and who would typically have best supportive care in clinical practice. The clinical experts stated that this group of people could be considered for treatment with radium-223. However, they emphasised that people in this group are difficult to define and that making such a treatment decision needed an assessment of multiple factors such as age, wellbeing and comorbidities. For people who have not had previous docetaxel therapy and for whom docetaxel is suitable, the Committee concluded that docetaxel is the appropriate comparator. It accepted the views of the clinical experts that there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable. It concluded that for this group of people, best supportive care is the most relevant comparator.

4.3 The Committee went on to discuss the relevant comparators for people who have had docetaxel therapy. The Committee heard from the clinical experts that abiraterone was used when the disease has progressed and that radium-223 would be an alternative option to abiraterone in people who have had prior
docetaxel therapy. However, the clinical experts explained that the number of people who could have radium-223 may be limited, given the complexities associated with administering a radioactive treatment, in which case abiraterone would be considered instead. The clinical experts also stated that in clinical practice the choice of whether to use radium-223 rather than abiraterone depends on whether the bone metastases were symptomatic and whether the alkaline phosphatase level was increasing, given that radium-223 specifically targets areas of bone metastases. The Committee acknowledged that radium-223 would be an alternative option to abiraterone in people who have had prior docetaxel therapy and concluded that abiraterone is the relevant comparator for radium-223 in this group of people.

**Clinical effectiveness**

4.4 The Committee considered the clinical effectiveness of radium-223 and noted that the key clinical evidence in the company’s submission came from the ALSYMPCA trial, which compared radium-223 plus best supportive care with placebo plus best supportive care. The Committee discussed the characteristics of the patients in ALSYMPCA and the generalisability of the results to UK clinical practice. It noted that people with visceral metastases were excluded from ALSYMPCA and that people of African–Caribbean origin, in whom the risk of developing prostate cancer is higher, were under-represented in the trial. It heard from the clinical experts that the trial was generalisable to the wider UK population because visceral metastasis was rare among patients with bone metastases. The clinical experts also stated that people with visceral metastases were excluded from the trial because they have a worse prognosis than people with bone metastases alone, and the survival benefit with treatment in patients with visceral
metastases would be minimal. The clinical experts stated that people of African–Caribbean origin may have been under-represented because they have a higher incidence of visceral and lymph node metastases, and would not have been eligible to participate in the trial. The Committee also heard from the clinical experts that there was no plausible reason why the drug would work differently in people of different ethnic origins. The Committee concluded that ALSYMPCA was relevant to UK clinical practice for patients without visceral metastases.

4.5 The Committee noted that patients in the ALSYMPCA trial comprised people who had previously had docetaxel and people who had not. It further noted that the group who had not had docetaxel included people who had refused docetaxel or who had not had access to it, in addition to patients for whom docetaxel was unsuitable. It was aware that approximately 87% of people in the trial had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, indicating that they would have been fit enough to have docetaxel. The Committee heard from clinical experts that assessment of ECOG status was subjective and that there were people in the trial for whom docetaxel was not suitable regardless of their performance status. The Committee heard from the clinical experts that uptake of docetaxel at the time of ALSYMPCA was variable and that clinical practice has changed in the last 5 years. The clinical experts explained that most people in ALSYMPCA had docetaxel because it was one of the few treatments available at the time, and that some of those people would not have docetaxel in clinical practice now. They also explained that patients who were not treated with docetaxel at that time may now be able to have docetaxel in clinical practice. The Committee considered that a significant proportion of the patients in the group who did not have docetaxel would now be eligible for
docetaxel in clinical practice, and thus docetaxel is a relevant comparator. However, the company had not submitted evidence comparing radium-223 with docetaxel for people who have not had previous docetaxel therapy and for whom docetaxel is suitable. Therefore, the Committee concluded that any discussion on the group of people who have not previously had docetaxel would be limited to those for whom docetaxel is contraindicated or unsuitable.

4.6 The Committee examined the clinical effectiveness data from ALSYMPCA for radium-223 plus best supportive care compared with placebo plus best supportive care. It noted that radium-223 was associated with a statistically significant median overall survival benefit of 3.6 months across all patients, and that the median overall survival benefit in the subgroups who had and who had not had prior docetaxel were 3.1 months and 4.6 months respectively. However, noting that not all patients in ALSYMPCA who had not had prior docetaxel were genuinely unable to have it, the Committee questioned whether the 4.6 months overall survival gain in the trial could be generalised to the population in UK clinical practice for whom docetaxel is contraindicated or unsuitable. It noted the company’s response to consultation that site-specific data from ALSYMPCA suggested that most patients would have had access to docetaxel and so the reason for not having docetaxel would have been as a result of it being unsuitable for them. The Committee also noted that across all patients, radium-223 was associated with statistically significant reductions in median time to first skeletal-related event (SRE), median time to prostate-specific antigen (PSA), and total alkaline phosphatase progression. The Committee considered the Evidence Review Group’s (ERG’s) comment that the SRE results could have been confounded by bisphosphonate use during follow-up in ALSYMPCA. However, it
accepted the views of the clinical experts that radium-223 and bisphosphonates had different mechanisms of action, and that people would be expected to benefit from radium-223 treatment regardless of the use of bisphosphonates. The Committee also noted that radium-223 was associated with health-related quality of life benefits compared with placebo. The Committee concluded that radium-223 plus best supportive care was more effective in treating hormone-relapsed prostate cancer with bone metastases compared with best supportive care alone.

4.7 The Committee considered the adverse event profile associated with radium-223 plus best supportive care compared with placebo plus best supportive care in ALSYMPCA. It noted that bone pain was the most common adverse event in the trial, occurring with a higher frequency in the placebo group than in the radium-223 group. It also noted that the most frequently observed adverse reactions in the radium-223 group, occurring in 10% of patients or more, were diarrhoea, nausea, vomiting and thrombocytopenia. However, the Committee was aware that the incidence of treatment-emergent adverse events leading to trial discontinuation or death was consistently higher in the placebo group than in the radium-223 group. The Committee noted the statements submitted by consultees that evidence from ALSYMPCA showed that radium-223 has a low risk of adverse effects compared with current radiopharmaceuticals such as strontium-89. The Committee concluded that the current evidence indicates that radium-223 has an acceptable adverse event profile.

4.8 The Committee considered the company’s indirect comparison of radium-223 and abiraterone. Having previously concluded that abiraterone was only an appropriate comparator for people who have had prior docetaxel therapy, the Committee did not consider it
relevant to discuss the indirect comparison for people who had not had prior docetaxel therapy. The Committee noted that the network of evidence in the post-docetaxel setting was limited to 2 trials, the abiraterone trial COU-AA-301 and the subgroup of people who had had docetaxel in ALSYMPCA; each provided direct comparisons with best supportive care. The Committee noted that there were some differences between the trials, particularly in the definitions of progression, median PSA scores and the statistical handling of censored data. The Committee commented that despite these differences, the patient populations across the prior-docetaxel populations were more similar in terms of ECOG status, bone metastases and median overall survival, than those across the no-prior-docetaxel populations. The Committee also heard from clinical experts that although few patients in COU-AA-301 had visceral metastases compared with no patients in ALSYMPCA, the patient populations in the trials for the prior-docetaxel populations were generally similar. On the balance of the available evidence, the Committee concluded that it was appropriate to compare radium-223 with abiraterone in people who have previously had docetaxel using the indirect comparison.

4.9 The Committee examined the results of the indirect treatment comparison in the prior-docetaxel group. It noted that the point estimates for the hazard ratios were 1.04 for overall survival and 0.91 for progression-free survival, suggesting that radium-223 was more effective in prolonging overall survival and less effective in delaying disease progression compared with abiraterone. However, it noted that the differences were not statistically significant. The Committee, while recognising the uncertainty around using the point estimates of the hazard ratios, and while acknowledging the ERG’s comments to treat the results with caution, concluded that it would be reasonable to assume that radium-223 and abiraterone
had similar effectiveness in delaying disease progression and prolonging survival.

**Cost effectiveness**

4.10 The Committee considered the company’s economic analysis and the ERG’s critique of the analysis. The Committee had previously concluded that abiraterone was an appropriate comparator only in people who had previously had docetaxel, and that best supportive care was the only relevant comparator for people in whom docetaxel is contraindicated or unsuitable. It had also concluded that docetaxel was a relevant comparator for people who can have it. However, given that the company did not submit evidence comparing radium-223 with docetaxel, the Committee could only consider the cost-effectiveness of radium–223 compared with abiraterone and best supportive care for the relevant populations stated.

4.11 The Committee discussed the assumptions used to model the clinical outcomes. It noted that for the comparison of radium-223 with best supportive care, the company presented analyses using PSA, ALP and ECOG as the measure of disease progression. The Committee heard from the clinical experts that, although PSA concentrations are related to tumour burden, they do not necessarily correlate well with the presence or extent of bone metastases. The Committee also heard that ECOG was a crude and subjective assessment of disease progression that did not reflect disease progression well. The Committee understood that ECOG status has an impact on quality of life, but not on the natural history of disease or resource use, and that ECOG status may deteriorate because of comorbidities rather than just prostate cancer. The clinical experts indicated that because the level of alkaline phosphatase activity is associated with bone turnover, it is
the most appropriate biochemical measure of disease progression and correlates better with progression of bone metastases and their symptoms. The Committee noted that the company had assessed progression-free survival for the comparison with abiraterone according to PSA progression only. The Committee understood that there were no data reported on ALP progression in the abiraterone trials and that time to ECOG deterioration was defined differently between ALSYMPCA and the abiraterone trials. The Committee accepted PSA progression for the comparison with abiraterone, but concluded that ALP progression was the most appropriate method that it would consider in its decision-making for analyses comparing radium-223 with best supportive care.

4.12 The Committee considered the appropriateness of the 5-year time horizon used in the economic model. It noted that some patients were still alive in the model at the end of the 5-year time horizon, particularly for the comparison of radium-223 with best supportive care, even though the Kaplan–Meier data showed that the number of people surviving at the end of the 3 year follow-up period in ALSYMPCA was 0 for the radium-223 arm and 2 people for the placebo arm. The Committee heard from the company that clinical advice suggested that about 5% of patients would still be alive after 3 years, and that it had extrapolated from this to 5 years. It also heard from the clinical experts that although average life expectancy would be around 18 months, it was not unreasonable to assume that some people with bone metastases would survive up to 5 years, particularly people who have had docetaxel. The Committee understood that the survival figures from the trial could reflect loss to follow-up as well as death, and it was possible that some patients were alive at the end of the trial. The Committee noted that the NICE guide to the methods of technology appraisal indicates a preference for a lifetime time horizon when alternative
technologies lead to differences in survival or benefits that persist for the remainder of a person's life. It also noted the ERG’s comment that overall survival should fall to 0 at the end of the time horizon, given that all patients are expected to die eventually, and it was concerned that the company’s analysis excluded terminal care costs in the radium-223 arm, because a greater proportion of people were still alive after 5 years than in the placebo arm. The Committee concluded that the company’s choice of a 5 year time horizon was not in line with the NICE reference case and that a lifetime time horizon would have been more appropriate in order to capture all relevant costs and benefits. It also concluded that appropriate modelling of a lifetime time horizon would need careful consideration of the face validity of any methods used to extrapolate survival, and that truncation of the model time horizon may not be needed if more appropriate methods for extrapolation were used.

4.13 The Committee discussed the parametric distributions used by the company to model the survival data. The Committee understood from the company that it had used the lognormal distribution based on the best fitting approach for the best supportive care comparison because all the data came from ALSYMPCA, for which it had patient-level data and because the survival data were relatively mature. However, it noted that although the log-normal distribution provided the best fit for the analyses comparing radium 223 with abiraterone, the company used the Weibull distribution on the basis that it provided a more conservative assumption of survival (see section 3.16). The company also explained that, because the abiraterone data were based on hazard ratios derived from published studies and because the indirect comparison used hazard ratios, it considered it more appropriate to use a proportional hazards model. The Committee understood that the
The number of people surviving after 5 years, predicted by the Weibull distribution, was more in line with estimates from the clinical experts, although it also considered the argument for using a log-normal distribution to be valid. The Committee previously concluded that the company’s approach was inconsistent and that both the log-normal and Weibull distributions should be considered in its decision making. However, the Committee noted that as part of its additional analysis for the prior-docetaxel group, the company used the log-normal distribution to model survival for both the trial and extrapolation period, and after 3 years (156 weeks; the trial observation period) the weekly mortality rate was doubled increasing the base case ICER from £40,700 to £42,200 per QALY gained. The Committee noted that only 1 person was at risk after 3 years, and it considered that doubling the weekly probability of mortality at a time-point when more people were at risk would be more informative. It noted that when the ERG used a time-point of 2 years (104 weeks) in an exploratory analysis, the ICER increased from £42,200 to £45,400 per QALY gained. The Committee concluded that the ERG’s approach of doubling the probability of mortality after 2 years was more reasonable than extrapolation at a time point when virtually no person was at risk.

4.14 The Committee considered the ERG’s critique of the company’s additional evidence submitted in response to consultation. It noted the ERG’s comments that the company’s additional evidence overlooked the revisions specified in the original ERG report relating to the correction of the cohort flow calculation and revising the costs of second-line care to include all data within the radium-223 arm (see section 3.49). The Committee understood that the ERG’s correction used the formula as described in the company’s original submission (figure 27 of its appendix) because this was not implemented correctly in the model. The Committee
noted that these changes increased the base-case ICER for radium-223 compared with best supportive care for the no-prior-docetaxel subgroup (using ALP as the measure of progression) from £40,700 to £56,500 per QALY gained, mostly because of the correction of the cohort flow calculation. The Committee heard from the company that it did not agree with the ERG’s approach to correcting the cohort flow calculation. The company accepted that there were some missing data; it was therefore difficult to know when disease progression occurred in the trial. The Committee considered that there were a range of issues involved, not just the uncertainty relating to the cohort flow calculation, such as how the survival curves were modelled (see section 4.13). The Committee agreed that the calculation of the cohort flow was an important issue and while there was uncertainty relating to the most appropriate approach, the Committee noted the significant effect on the ICER when applying the company formula to model cohort flow.

4.15 The Committee considered the utilities applied by the company in the economic model. It was aware that in response to consultation, the company had re-analysed the EQ-5D data for its revised economic analysis. The Committee noted that the company’s method excluded the baseline EQ-5D responses. It understood from the ERG that although excluding the baseline values was reasonable, this method may overestimate the effect of treatment as the model assumes that treatment effects apply from the first cycle of treatment. The Committee noted from the ERG’s sensitivity analyses that including baseline EQ-5D responses worsened the cost-effectiveness estimate. The Committee heard from the clinical experts that if quality of life is different for each treatment arm, then it is reasonable to adjust for baseline values and this can be done by excluding them. The Committee noted that in some cases the company had used an arm-specific utility, and in other cases it
used estimates that were pooled across arms, depending on whether the estimate was statistically significant. The Committee agreed with the ERG’s approach to use point estimates, rather than the average between the arms, where there was no statistically significant difference between these. It noted that this had only a modest effect on the cost-effectiveness estimate.

4.16 The Committee considered the duration of the quality-of-life benefit associated with radium-223 compared with best supportive care. It had some concerns about the company’s assumption that a quality of life increment from radium-223 over best supportive care for a given health state would continue indefinitely. The Committee heard from the clinical experts that it is not implausible for the quality of life benefit to extend over a long period of time as a result of suppressing the disease with radium-223. Despite this, the Committee considered that the company’s assumption of a lifetime benefit was unlikely and that the benefit probably diminished over time. However, it also considered that the ERG’s assumption of a 24 week point was arbitrary and may be conservative. It noted the company’s additional analysis for the comparison of radium-223 with best supportive care for people who have not previously had docetaxel, where quality-of-life values were equalised between the arms after week 26 and up to 104 weeks. The Committee was aware that the company had used utility values based on data from all patients in the ALSYMPCA study, rather than from the no-prior-docetaxel group. It agreed with the ERG that utility values from the no-prior-docetaxel group were the most appropriate to use, and when applied to the base case (using ALP-defined progression and incorporating a lifelong quality-of-life increment from radium-223 over best supportive care) increased the ICER from £40,700 to £49,600 per QALY gained. The Committee noted that assuming a utility benefit lasting 104 weeks and applying utility values specific
to the no-prior-docetaxel group, the ICER increases from £40,700 to £52,400 per QALY gained using a 5-year time horizon. It also noted that using the same time horizon, applying utility values specific to the no-prior-docetaxel group and assuming a utility benefit lasting 26 weeks the ICER increased from £40,700 to £62,000 per QALY gained. The Committee concluded that although the quality-of-life benefits with radium-223 compared with best supportive care could extend beyond 24 weeks, the duration of this benefit is uncertain, but would likely diminish over time and could not be assumed to extend over a person’s lifetime.

4.17 The Committee considered the costs used in the model. It considered the concerns highlighted by the ERG on the possible double counting of SREs and adverse event costs, the costing of first SREs only and the cost of pathological fractures in the model (see sections 3.37 and 3.38). However it noted from the ERG’s exploratory analyses in the original model, that changes to these parameters had minimal impact on the base-case ICER. The Committee noted that the total cost of radium-223 was based on the average number of injections used in ALSYMPCA rather than the recommended dose of 6 injections, but it accepted the company’s rationale that this reflected the number of doses on which the efficacy data were based.

4.18 The Committee considered the company’s additional evidence relating to medical resource use from the ALSYMPCA study. It noted that the additional data were based on an abstract and that it suggested that, for the no-prior-docetaxel group there were 4.58 fewer hospital days for radium-223 compared with best supportive care. The Committee considered that the abstract contained very little information about the numbers of patients and the duration of the outcome measures. It noted that NICE and the
ERG had previously requested the company provide the ALSYMPCA resource use data and that the company had stated that it would not be helpful for the purposes of economic modelling because the data collected were protocol-driven rather than representing clinical practice. The Committee noted the very limited amount of information provided in the abstract and given the company statement that the information on resource use would not be helpful for the purposes of economic analysis the Committee concluded that it could not consider these data further.

4.19 The Committee also discussed whether treatment waste was incorporated into the cost estimates. It heard from the company that there would be no radium-223 waste because the treatment for each patient would be ordered, based on their weight, and prepared in advance. However, the Committee was concerned that injections would be wasted if a patient did not attend for treatment, particularly given patient comorbidities and potential difficulties getting to specialist centres. It heard from a clinical expert that in her clinical practice, a patient is seen at an additional appointment 1 week before ordering the treatment in order to ensure that person is well enough to travel, which was a method of preventing waste. The Committee was uncertain how many clinics used this approach; it noted that it would mean an additional cost for the appointment that would offset potential savings from reduced waste. The Committee noted that the company had also assumed no waste for abiraterone. It noted the company's comments in response to consultation, which stated that the potential for waste was small and that the company refunds wasted doses if a patient is unable to attend the hospital because of illness or death. The Committee considered that it could not take this into account because this was not a formal arrangement between the company and the NHS. The Committee concluded that there was added
uncertainty in the assumptions about waste, but it agreed that the true costs of treatment waste were difficult to estimate. It also concluded that incorporating waste into the comparison of radium-223 with best supportive care will worsen the cost-effectiveness estimates for that comparison.

4.20 The Committee discussed the costs associated with administering radium-223. The Committee noted that for radium-223, the company had used the administration costs for chemotherapy (see section 3.19) and in its response to consultation, the company highlighted the ease of administering radium-223 with the cost of administration being no greater than intravenous chemotherapy. It was concerned whether this was appropriate given that radium-223 is a radiopharmaceutical. It heard from the clinical experts who stated that the costs of preparing and administering radium-223 were similar to those of a chemotherapy even though it is a radiopharmaceutical; the exception to this is the need for nuclear medicine resources, which the clinical experts stated were available in most oncology centres. The Committee noted comments from consultation that suggested that a significant number of people could be expected to be suitable for this treatment and that there were costs associated with a radiopharmaceutical product such as radium-223 that had not been taken into account, for example: resourcing for radiopharmacy, radiation protection and training. The Committee heard from the company that although a nuclear medicines physician is needed to give radium-223, radium-223 is an alpha emitter and it is less toxic and harmful compared with other radiopharmaceuticals. In addition, the company stated that radium-223 is given on an outpatient basis, unlike other radiopharmaceuticals, and therefore would not need additional resources beyond what is available for other radiopharmaceuticals. The Committee had not received any data or
information that would help quantify such costs and it therefore concluded that the potential additional cost to the NHS of providing treatment with radium-223 was uncertain.

4.21 The Committee noted that the company had assumed, in addition to routine follow-up visits, an additional £161 monthly administration cost for abiraterone. It did not consider it appropriate to include an additional administration cost for abiraterone because the clinical experts stated that this would have been captured in the costs estimated for routine monitoring and follow-up visits. The Committee noted the ERG’s exploratory analysis that estimated the monthly cost of abiraterone based on 4 weeks rather than 4.33 weeks used by the company. It heard from the clinical experts that the monthly dose for chemotherapy is typically calculated in weekly increments and should be based on 4 weeks rather than a calendar month. The Committee concluded that the company’s estimated costs for abiraterone may have been overestimated.

4.22 The Committee considered whether radium-223 could be considered a cost-effective use of NHS resources compared with best supportive care for those people who have not had prior docetaxel, and for whom docetaxel is contraindicated or unsuitable. It noted that the company’s base-case ICER for radium-223 compared with best supportive care in this group using ALP-defined progression was £38,200 per QALY gained. It further noted that the ERG’s adjustments to the model (see section 3.39) increased the base-case ICER to £40,700 per QALY gained. The Committee considered that there was uncertainty about the utility values (see section 4.15 and 4.16), and noted that the company should have applied the values derived from the no-prior-docetaxel population rather than from all patients in the ALSYMPCA study. This increased the base-case ICER further from £40,700 per QALY
gained to £49,600 per QALY gained. The Committee was aware that this estimate incorporated a sustained lifelong quality-of-life benefit for radium-223 compared with best supportive care. The Committee considered a diminishing benefit that would not extend over a lifetime was a more likely scenario and noted this increased the ICER from £49,600 per QALY gained to £52,400 per QALY gained and up to £62,000 per QALY gained (see section 4.16). The Committee considered that doubling the weekly probability of mortality at a time earlier than 3 years, making an adjustment to the calculation of the cohort flow in line with the company’s formula and accounting for radium-223 waste (see sections 4.13, 4.14 and 4.19) would increase the ICER further. The Committee noted that none of the analyses presented explored the impact of all these uncertainties simultaneously; however it considered that the effects would be additive. Therefore, it concluded that the most plausible ICER for radium-223 compared with best supportive care for those people who have not had prior docetaxel, and for whom docetaxel is contraindicated or unsuitable was likely to be above £50,000 per QALY gained; this is above the range normally considered cost effective: £20,000–£30,000 per QALY gained.

4.23 The Committee considered whether radium-223 could be considered a cost-effective use of NHS resources compared with abiraterone for the prior-docetaxel subgroup. It was aware that abiraterone was available with a confidential patient access scheme discount and noted that the company and the ERG presented analyses using several assumed discounts for abiraterone. The Committee noted that the analysis that most closely matched the actual patient access scheme discount for abiraterone showed that radium-223 dominated abiraterone using the ERG’s preferred assumptions, which included removing the administration cost for abiraterone. The Committee considered the
effect of a number of scenarios explored by the ERG, and noted that radium-233 dominated abiraterone in most of these scenarios. The Committee acknowledged that there was uncertainty in these analyses. It noted that there were marginal differences in QALYs, which meant small differences in costs had a dramatic effect on the results. It considered that exploratory analyses around most of the assumptions had minimal impact on the ICER. It was also aware that data on ALP were not reported for the abiraterone trial, which meant that the PSA progression was used. It was aware from the discussions with the clinical experts that PSA does not correlate well with the presence or extent of bone metastases; therefore it considered that the use of PSA progression may have biased any analysis against radium-223 as shown in the various comparisons with best supportive care. The Committee considered that if radium-223 were to be recommended in the group of people who had previously had treatment with docetaxel, it would be an additional treatment option to abiraterone. The Committee decided to take a pragmatic approach of judging the uncertainty based on all the above factors in addition to actual results of the ERG’s exploratory analyses. On that basis, it concluded that the most plausible ICER will fall within the acceptable range and that radium-223 could be considered a cost-effective treatment option compared with abiraterone for the prior-docetaxel subgroup. Therefore radium-223 should be recommended as an option for people with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases who have previously had docetaxel.

4.24 The Committee discussed whether radium-223 for hormone-relapsed prostate cancer with bone metastases fulfilled the criteria for a life-extending, end-of-life treatment for people in whom docetaxel is contraindicated or unsuitable, which are that:
• the treatment is indicated for patients with a short life expectancy, normally less than 24 months
• there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment
• the treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.25 The Committee noted that the median survival of people who had had placebo in ALSYMPCA was 11.5 months, which is less than 24 months. The Committee noted from ALSYMPCA trial data that there was a median gain of 4.6 months compared with best supportive care for people who have not had prior docetaxel. The mean estimates from the model using the log-normal distribution also showed that the overall survival gain for radium-223 compared with best supportive care was more than 3 months, but the actual figures were designated academic in confidence by the company. The Committee noted that the company had estimated 1807 people to be eligible for treatment in 2014, and had estimated that this would rise to 1972 people by 2018. The Committee, noting that these figures were considerably less than 7000, considered that the population size criterion had been met. The Committee concluded that for people who have not had prior docetaxel and for whom docetaxel is contraindicated or unsuitable the first 3 criteria for end-of-life had been met.
Having concluded that the end of life criteria were met for people who have not had prior docetaxel, and for whom docetaxel is contraindicated or unsuitable, the Committee discussed whether radium-223 could be considered a cost-effective use of NHS resources for this population. The Committee acknowledged the uncertainties regarding a number of assumptions in the model; the calculation of the cohort flow, the modelling of overall survival, utilities and treatment waste. Given the Committee considered that the most plausible ICER is above £50,000 per QALY gained (section 4.22), it concluded that the magnitude of additional weight that would need to be assigned to the QALY benefits in this patient group would be too great for radium 223 to be considered a cost-effective use of NHS resources. Therefore, the Committee concluded that radium 223 could not be recommended for those people who have not had prior docetaxel, and for whom docetaxel is contraindicated or unsuitable. The Committee was unable to make any recommendations for radium-223 for people who can have docetaxel because no evidence was submitted by the company.

The Committee discussed how innovative radium-223 is in its potential to make a significant and substantial impact on health-related benefits. It agreed that radium-223 was novel and specifically targets areas of increased bone turnover, and so offered a step change in treating hormone-relapsed prostate cancer with bone metastases. However, it considered that this was already captured in the QALY calculation. The Committee noted the company’s comment that the reduction in fatigue associated with radium-223 treatment as shown in the Functional Assessment of Cancer Therapy – Prostate (FACT-P) may not have been captured in the EQ-5D based QALY calculation. However, it noted that the QALY calculation was based on both EQ-5D and time trade-off
estimates, and considered that fatigue was already captured in the QALY calculation through the other dimensions of the EQ-5D, and that there were no additional gains in health-related quality of life over those already included in the QALY calculations. The Committee concluded that the innovative aspects of radium-223 were already incorporated in the economic analyses.

4.28 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising radium-223. The Committee noted NICE’s position statement in this regard, and accepted the conclusion ‘that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of radium-223. It therefore concluded that the PPRS Payment Mechanism was not relevant for its consideration of the cost effectiveness of radium-223.

4.29 The Committee examined whether there were any potential issues affecting groups protected by equality legislation. The Committee noted the comments from some consultees that prostate cancer was more common in men aged 60 years and older and in men of African–Caribbean origin. It also noted the comments from clinical experts that the complexities associated with the delivery of radioactive isotopes could potentially limit access to radium-223 treatment for people who live in areas where there are no specialist cancer centres able to administer the treatment. The Committee discussed whether these issues had an impact on NICE’s duties under the equalities legislation. It considered that these were not
issues that can be addressed by a technology appraisal. It concluded that its preliminary recommendations do not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations.

**Summary of Appraisal Committee’s key conclusions**

<table>
<thead>
<tr>
<th>TAXXX</th>
<th>Appraisal title: Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases</th>
<th>Section</th>
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<tbody>
<tr>
<td>Key conclusion</td>
<td>Radium-223 dichloride is recommended as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases, only if they have had treatment with docetaxel and the company provides radium-223 dichloride with the discount agreed in the patient access scheme.</td>
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<td>The Committee concluded that radium–223 plus best supportive care was more effective in treating hormone-relapsed prostate cancer with bone metastases compared with best supportive care alone, and that it would be reasonable to assume that radium-223 and abiraterone had similar effectiveness in delaying disease progression and prolonging survival.</td>
<td>4.6, 4.9</td>
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<td>The Committee concluded that the most plausible ICER for radium-223 compared with best supportive care for those people who have not had prior docetaxel, and for whom docetaxel is contraindicated or unsuitable was likely to be above £50,000 per quality adjusted life year (QALY) gained. Based on the uncertainties in the model and trial data, the Committee concluded that the magnitude of additional weight that would need to be assigned to the QALY benefits in this patient group would be too great for radium-223 to be considered a cost-effective use of NHS resources. Therefore it could not recommend radium-223 for this group of people.</td>
<td>4.22, 4.26</td>
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<td>For the comparison with abiraterone in the subgroup who have previously had docetaxel, the Committee decided to take a pragmatic approach of judging the uncertainty based on multiple factors and concluded that the most plausible incremental cost-effectiveness ratio (ICER) will fall within the acceptable range and that radium–223 could be considered cost effective.</td>
<td>4.23</td>
</tr>
</tbody>
</table>
### Current practice

<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The Committee heard from the patient experts that bone metastases are very distressing for patients and their families, particularly as a result of bone pain and fatigue, which have a profound impact on patients’ quality of life. It also noted the comments from consultees that bone metastases affect mobility and that full-time care would often be needed for people to carry out daily activities. The Committee recognised the need for alternative treatment options with the potential to improve quality of life in people with bone metastases associated with hormone-relapsed prostate cancer, and concluded that radium-223 could potentially be a treatment option.</th>
</tr>
</thead>
</table>

### The technology

<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>The Committee agreed that radium-223 was novel and specifically targets areas of increased bone turnover, and so offered a step change in treating hormone-relapsed prostate cancer with bone metastases. However, it considered that this was already captured in the QALY calculation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>The Committee heard from clinical experts that people who have not had previous docetaxel therapy, and for whom docetaxel is suitable would not be offered treatment with radium-223 because docetaxel would always be the preferred treatment option. However, in response to consultation it was highlighted that this was not the case because in the ALSYMPCA trial, patients could be offered radium-223 if they declined to take docetaxel. The Committee accepted the views of the clinical experts that there is a clinically recognised group who have not had previous docetaxel and for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable. Radium-223 is also an option alongside abiraterone in the second-line setting in people who have had docetaxel. The clinical experts stated that the choice to use radium-223 rather than abiraterone in this setting depended on whether the bone metastases were symptomatic and whether the alkaline phosphatase (ALP) level was increasing, given that radium-223 specifically targets areas of bone metastases.</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>The Committee concluded that the current evidence indicates that radium-223 has an acceptable adverse event profile.</td>
</tr>
<tr>
<td><strong>Evidence for clinical effectiveness</strong></td>
<td></td>
</tr>
<tr>
<td>Availability, nature and quality of evidence</td>
<td>The Committee noted that the key clinical evidence in the company’s submission came from the ALSYMPCA trial, which compared radium-223 plus best supportive care with placebo plus best supportive care. The Committee noted that the network of evidence in the second-line setting, that is in the prior-docetaxel group, was limited to 2 trials, the abiraterone trial COU-AA-301 and the subgroup of people who had had docetaxel in ALSYMPCA; each provided direct comparisons with best supportive care. On the balance of the available evidence, the Committee concluded that it was appropriate to compare radium-223 with abiraterone in people who have previously had docetaxel using the indirect comparison.</td>
</tr>
<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>The Committee concluded that ALSYMPCA was relevant to UK clinical practice for patients without visceral metastases.</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Uncertainties generated by the evidence | The Committee noted that in ALSYMPCA, the group who had not had docetaxel included people who had refused docetaxel or who had not had access to it, in addition to patients for whom docetaxel was unsuitable.  
The Committee noted that for people who have had prior docetaxel therapy there were some differences between the trials included in the indirect comparison, particularly in the definitions of progression, median prostate-specific antigen (PSA) scores and the statistical handling of censored data. The Committee noted that the differences in the hazard ratios for overall survival and progression-free survival were not statistically significant. | 4.5  
4.8  
4.9 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | None | |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee noted that radium-223 was associated with a statistically significant median overall survival benefit of 3.6 months across all patients, and that the median overall survival benefit in the subgroups who had and who had not had prior docetaxel were 3.1 months and 4.6 months respectively. However, noting that that not all patients in ALSYMPCA who had not had prior docetaxel were genuinely unable to have it, the Committee questioned whether the 4.6-months overall survival gain in the trial could be generalised to the population in UK clinical practice for whom docetaxel is contraindicated or unsuitable. The Committee also noted that across all patients radium-223 was associated with statistically significant reductions in median time to first skeletal-related event (SRE), median time to PSA, and total alkaline phosphatase progression. It also noted that radium-223 was associated with health-related quality of life benefits compared with placebo. The Committee, while recognising the uncertainties generated by the indirect comparison, concluded that it would be reasonable to assume that radium-223 and abiraterone had similar effectiveness in delaying disease progression and prolonging survival. | 4.6 |

| For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations? | Not applicable | – |
### Evidence for cost effectiveness

| Availability and nature of evidence | Given that the company did not submit evidence comparing radium-223 with docetaxel, the Committee could only consider the cost-effectiveness of radium-223 compared with best supportive care for people in whom docetaxel is contraindicated or unsuitable, and for radium-223 compared with abiraterone in people who have previously had docetaxel. | 4.10 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee concluded that the company’s choice of a 5-year time horizon was not in line with the NICE reference case and that a lifetime time horizon would have been more appropriate to capture all relevant costs and benefits. The Committee accepted PSA progression for the comparison with abiraterone in the absence of any other alternative measure of progression, but for the comparison with best supportive care, it considered that ALP progression was the most appropriate measure of progression to base its decision on. The Committee noted that only 1 person was at risk of death after 3 years and it considered that doubling the weekly probability of mortality at a time-point when more people were at risk would be more informative. The Committee agreed that the calculation of the cohort flow was an important issue and there was uncertainty relating to the most appropriate approach. The Committee concluded that although the quality-of-life benefits with radium 223 compared with best supportive care could extend beyond 24 weeks, the duration of this benefit is uncertain, but would likely diminish over time and could not be assumed to extend over a person’s lifetime. The Committee noted that there was added uncertainty in the assumptions about waste, which had not been accounted for either radium-223 or abiraterone. It agreed that the true costs of treatment waste were difficult to estimate but concluded that incorporating waste into the comparison of radium-223 with best supportive care will worsen the cost-effectiveness estimates. | 4.12 |

|  |  |  |
| Incorporation of health-related quality-of-life benefits and utility values | The Committee considered that fatigue was already captured in the QALY calculation through the other dimensions of the EQ-5D, and that there were no additional gains in health-related quality of life over those already included in the QALY calculations. Therefore, the Committee concluded that the innovative aspects of radium-223 were already incorporated in the economic analyses. | 4.27 |
| Are there specific groups of people for whom the technology is particularly cost effective? | None | |
| What are the key drivers of cost effectiveness? | For the comparison with abiraterone, there were marginal differences in QALYs, which meant small differences in costs had a large effect on the results. For the comparison of radium-223 with best supportive care, the cost effectiveness of radium-223 was significantly worsened by equalising the quality-of-life values between the arms after week 24 and by using PSA-progression. | 4.23 3.43 |

The Committee had not received any data or information that would help quantify such costs and it therefore concluded that the potential additional cost to the NHS of providing treatment with radium-223 was uncertain.

The Committee noted that the company had assumed, in addition to routine follow-up visits, an additional £161 monthly administration cost for abiraterone, and that it had calculated the cost of abiraterone based on calendar months rather than 4 weeks. It concluded that the company’s estimated costs for abiraterone may have been overestimated.
| Most likely cost-effectiveness estimate (given as an ICER) | The Committee concluded that the most plausible ICER for radium-223 compared with best supportive care for those people who have not had prior docetaxel, and for whom docetaxel is contraindicated or unsuitable was likely to be above £50,000 per QALY gained. The Committee was unable to make any recommendations for radium-223 for people who can have docetaxel because no evidence was submitted by the company. The Committee took a pragmatic approach of judging uncertainties based on multiple factors and concluded that the most plausible ICER for radium-223 compared with abiraterone will fall within the acceptable range. | 4.22 |

| Additional factors taken into account | The company that holds the marketing authorisation for radium-223 (Bayer) has agreed a patient access scheme with the Department of Health which makes radium-223 available with a discount applied to all invoices. The level of the discount is commercial in confidence. Abiraterone, a comparator in this appraisal, is available to the NHS through a simple discount patient access scheme, for which the level of the discount is confidential and cannot be disclosed. The Committee considered whether it should take into account the consequences of the PPRS 2104, and in particular the PPRS Payment Mechanism. It concluded that the PPRS Payment Mechanism was not relevant for its consideration of the cost effectiveness of radium-223. | 2.3 |

| | | 3.23 |

| | | 4.28 |
End-of-life considerations | The Committee concluded that for people who had not had prior docetaxel and in whom docetaxel is contraindicated or unsuitable, the end-of-life criteria of short life expectancy, extension to life, and small population size, had all been met.

The Committee acknowledged the uncertainties regarding a number of assumptions in the model; the calculation of the cohort flow, the modelling of overall survival, utilities and treatment waste. Given the Committee considered that the most plausible ICER is above £50,000 per QALY gained (section 4.22), it concluded that the magnitude of additional weight that would need to be assigned to the QALY benefits in this patient group would be too great for radium-223 to be considered a cost-effective use of NHS resources. Therefore, the Committee concluded that radium-223 could not be recommended for those people who have not had prior docetaxel, and for whom docetaxel is contraindicated or unsuitable. The Committee was unable to make any recommendations for people who can have docetaxel because no evidence was presented by the company. | 4.25 4.26

Equalities considerations and social value judgements | The Committee noted the potential equality issues from some consultees and clinical experts, but considered that these were not issues that can be addressed by a technology appraisal. It concluded that its preliminary recommendations do not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations. | 4.29

## 5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013](https://www.gov.uk/government/publications/national-institute-for-health-and-care-excellence-constitution-and-functions-and-health-and-social-care-information-centre-functions-regulations-2013) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hormone-relapsed prostate cancer, symptomatic bone metastases, no known visceral metastases and only if they have had treatment with docetaxel and the doctor responsible for their care thinks that radium-223 is the right treatment, it should be available for use, in line with NICE’s recommendations.

5.4 The Department of Health and Bayer have agreed that radium-223 will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5.5 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation. Further information is available on the NICE website.

Published

- **Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen.** NICE technology appraisal guidance 316 (2014).
- **Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen.** NICE technology appraisal guidance 259 (2012).
- **Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.** NICE technology appraisal guidance 255 (2012).
- **Prostate cancer: diagnosis and treatment.** NICE guideline 58 (2008).
- **Cryotherapy as a primary treatment for prostate cancer.** NICE interventional procedure guidance 145 (2005).
- **Cryotherapy for recurrent prostate cancer.** NICE interventional procedure guidance 119 (2005).
- **High-intensity focused ultrasound for prostate cancer.** NICE interventional procedure guidance 118 (2005).
- **Improving outcomes in urological cancers.** NICE cancer service guidance CSGUC (2002).
7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, Appraisal Committee
May 2015
8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3 year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queen’s University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
GP, West Coker Surgery, Somerset

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black
GP, Mortimer Medical Practice, Herefordshire
Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

John Dervan
Lay Member

Dr Martin Duerden
Assistant Medical Director, Betsi Cadwaladr University Health Board, North Wales

Susan Dutton
Senior Medical Statistician, Oxford Clinical Trials Research Unit

Christopher Earl
Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Gillian Ells
Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh
Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York
Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Dr Paul Hepple
General Practitioner, Muirhouse Medical Group

Professor John Hutton
Professor of Health Economics, University of York

Professor Peter Jones
Emeritus Professor of Statistics, Keele University

Professor Steven Julious
Professor in Medical Statistics, University of Sheffield

Dr Tim Kinnaird
Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Warren Linley
Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Dr Malcolm Oswald
Lay Member

Professor Femi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust and Metropolitan Borough Council

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford
Dr Murray Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie
Lay Member

Dr Alison Talbot-Smith
Consultant in Public Health, Herefordshire Clinical Commissioning Group

Guideline representatives
The following individuals, representing the Guideline Development Group responsible for developing NICE’s clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

Dr John Graham
Director, National Collaborating Centre for Cancer

NICE project team
Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Nwamaka Umeweni, Chris Chesters and Christian Griffiths
Technical Leads

Zoe Charles and Nwamaka Umeweni
Technical Adviser

Kate Moore
Project Manager
9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen HTA Group:


B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Bayer

II. Professional/expert and patient/carer groups:

- Prostate Cancer UK
- South Asian Health Foundation
- Tackle Prostate Cancer
- British Association of Urological Nurses
- British Nuclear Medicine Society
- British Uro-Oncology Group
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- MRC Clinical Trials Unit
- Aberdeen HTA Group
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on radium-223 dichloride by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr David Bottomley, Consultant Clinical Oncologist, nominated by the British Uro-oncology Group – clinical expert
- Dr Isabel Syndikus, Consultant Clinical Oncologist, nominated by the Royal College of Physicians – clinical expert
- Nigel Lewis-Baker, nominated by Prostate Cancer UK – patient expert
- David Smith, nominated by the Prostate Cancer Support Federation – patient expert
E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bayer