NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA376.

1 Recommendations

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

- they have already had docetaxel **or**
- docetaxel is contraindicated or is not suitable for them.

The drug is only recommended if the company provides radium-223 dichloride with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with radium-223 dichloride was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of 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.

Marketing authorisation

2.2 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'.

Adverse reactions

2.3 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.

Recommended dose and schedule

2.4 Radium-223 dichloride is administered by intravenous injection at a recommended dose of 55 kBq/kg body weight every 4 weeks for 6 injections.

Price

2.5 The company's submission states that radium-223 is available at a radioactivity of 6.6 MBq in a 6-ml vial at a list price of £4,040 (excluding VAT). The company estimates the cost of a full course of treatment to be £24,240. The company (Bayer's) that holds the marketing authorisation for radium-223 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. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The appraisal committee considered evidence submitted by Bayer and a review of this submission by the evidence review group (ERG). This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases. It focused on updated cost-effectiveness analyses for the subgroup who have not had docetaxel and for whom docetaxel is not suitable.

3.1 In brief, the key clinical evidence in the company's submission came from ALSYMPCA, a randomised double-blind placebo-controlled trial comparing radium-223 with placebo in people with hormone-refractory prostate cancer with painful bone metastases. It included people who had previously had docetaxel and people who had not, and the primary endpoint was overall survival. The trial collected quality-of-life data, which was assessed using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) and EuroQoL-5 dimensions (EQ-5D) questionnaires. See the committee papers for full details of the evidence, and the history for full details of the evidence used for NICE's original technology appraisal guidance on radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases.

4 Committee discussion during the original appraisal

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 docetaxel therapy on the basis that radium-223 is not proposed to be offered to 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 also noted that radium-223 was available through the Cancer Drugs Fund at the time of this appraisal 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 it concluded that 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. The committee 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 because of 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

depended on whether the bone metastases were symptomatic and whether the alkaline phosphatase (ALP) level was increasing because 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 docetaxel therapy, and concluded that abiraterone is the relevant comparator for radium-223 in this group of people.

Clinical effectiveness during the original appraisal

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 people 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 about 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 for all patients in the study, 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, for all patients in the study, 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 ALP 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 using 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 docetaxel therapy, the committee did not consider it relevant to discuss the indirect comparison for people who had not had 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 during the original appraisal

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 ALP 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 people 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 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's guide to the methods of technology appraisal 2013

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 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 log-normal 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. 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 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. It noted that the impact of the choice of parametric distribution resulted in an incremental cost-effectiveness ratio (ICER) in a range of £40,700 per quality-adjusted life year (QALY) gained using the log-normal distribution and up to £67,500 per QALY gained using the Weibull distribution. 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 no-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. The committee further concluded that, in general, there was uncertainty in the company's approach of modelling overall survival, including the choice of parametric distribution used.

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 in the radium-223 arm. 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 was a range of issues involved, such as how the survival curves were modelled (see section 4.13), and not just the uncertainty relating to the cohort flow calculation. 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's 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 EuroQoL-5 dimensions (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 because 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, when 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 increased the ICER 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 increased the ICER 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. 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 that 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 in 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 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. It noted the consultation comment from the company that treatment waste is very rare and has happened less than 5 times in the past year, suggesting that this does not warrant a formal agreement. The committee also noted the comments from a consultee that some centres seemed unaware of arrangements to refund the cost of wasted doses and that the number of doses not used was far higher than 2 in the period since radium-223 was made available in the UK. The committee considered that a transparent formal arrangement would be needed to eliminate any uncertainty and to ensure that all centres would have access to the company's proposed approach. 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 would worsen the cost-effectiveness estimates for that comparison, although the magnitude of the impact is unknown.

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 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 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 noted a further consultation comment that, in addition to alpha emissions, radium-223 and its daughter products emit a range of gamma and beta emissions, and that the risk of hospitalisation for reasons other than administration cannot be discounted. Another consultee commented that the implementation period for radium-223 should be extended if there is no existing radium-223 service. However, the committee heard from the company that, because radium-223 has been available through the Cancer Drugs Fund for some time, most centres are already established, and this would allow access to the technology for most patients in England. The committee noted that it had not received any data or information that would help quantify any additional costs and so it concluded that the potential additional cost to the NHS of providing treatment with radium-223 was uncertain. The committee also concluded that it had not seen any evidence to suggest that the implementation period for radium-223 should be extended.

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 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 section 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 that a diminishing benefit, which 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 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 to £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 several scenarios explored by the ERG, and noted that radium-223 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 the 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 had 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 1,807 people to be eligible for treatment in 2014, and had estimated that this would rise to 1,972 people by 2018. The committee, noting that these figures were considerably less than 7,000, 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.

4.26 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 about several 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 was likely to be 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.

4.27 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 is novel and specifically targets areas of increased bone turnover, and so offers 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. It 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 the recommendations had an impact on NICE's duties under the equalities 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 could be addressed by a technology appraisal. The committee also noted the consultation comment that patients for whom docetaxel was unsuitable because of a comorbidity or disability would not have the opportunity to have radium-223. The committee emphasised that its recommendation for radium-223 for people who have not had docetaxel, and for whom docetaxel is contraindicated or unsuitable was made because radium-223 was not cost effective in this population. Given the high ICER and uncertainties (see sections 4.22 and 4.26), the committee agreed that the recommendation could be justified and was in line with the committee's role in applying the cost-effectiveness criteria, and was a proportionate means of achieving a legitimate aim. The committee could not identify any special factors that would justify making a positive recommendation for this population even with the high ICER. It concluded that there was no need to alter or add to its recommendations.

Cancer Drugs Fund reconsideration

4.30 This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases. Specifically, because the original appraisal recommended radium-223 only for the people who had previously had docetaxel, the Cancer Drugs Fund subsequently offered radium-223 to people who had not had docetaxel. The committee considered the company's updated cost-utility analysis for people who have not had docetaxel, and for whom docetaxel is contraindicated or unsuitable. In its revised analysis, the company:

- re-analysed data on time to progression defined by serum ALP and data on time to an SRE from ALSYMPCA to address the issue related to the flow of the cohort through the model
- used a longer time horizon of 10 years
- used subgroup-specific utilities for the group who had not had prior docetaxel from ALSYMPCA

- used data on medical resource use from ALSYMPCA
- used Ford et al. (2013) to derive the costs of treating SREs
- updated all other unit costs data to 2015 values
- presented scenario analyses to address areas of uncertainty.

In addition, the company provided new evidence defining the group of people for whom docetaxel is not suitable.

Definition of the population

4.31 The committee discussed the company's criteria for defining the people for whom docetaxel is not suitable. It noted that these criteria were based on a consensus agreement by 6 oncologists, 1 of whom attended the committee meeting, and included:

- contraindications to docetaxel such as hypersensitivity to the active substance, a neutrophil count of less than 1.5×10^9/litre, or severe liver impairment
- a platelet count of less than 100×10^9/litre
- ongoing treatment with an immunosuppressant for any condition
- an ECOG performance status of 3 or greater
- comorbidities and an ECOG performance status of 2 or greater
- comorbidities, including:
  - a Charleston comorbidity score of 5 or above
  - severe chronic obstructive pulmonary disease
  - symptomatic heart failure
  - history of bowel disease

  - peripheral neuropathy
  - ongoing treatment for tuberculosis
  - recurrent pancreatitis
  - poor liver function
  - poorly controlled diabetes
  - poor peripheral circulation
  - splenectomy plus prophylactic antibiotics
  - recurrent sepsis
- poor cognition or social support, which results in inability to understand treatment and provide consent.

4.32 The committee recognised that many of the criteria listed were also exclusion criteria for ALSYMPCA, suggesting the possibility that there is no evidence of efficacy of radium-223 in these people. It heard from the clinical expert that there was no clinical or biological reason why the efficacy of radium-223 would differ based on suitability for docetaxel. The committee also questioned whether it was reasonable to offer radium-223 to people who cannot take docetaxel given the special warnings and adverse events included in the summary of products characteristics for radium-223. While the committee recognised that some people, for example, those with absolute neutropenia, would not be offered either treatment, the clinical experts confirmed that there are people who cannot take docetaxel but who can take radium-223, such as people with renal impairment, people taking immunosuppressants and those with poor performance status. The clinical expert also pointed out that radium-223 might be more suitable for people with cognitive impairment. The committee accepted the comments from the clinical experts, and concluded that there is a clinically recognised group for whom radium-223 would be suitable because docetaxel is contraindicated or unsuitable.

Definition of the comparator

4.33 The committee recognised that the population for whom docetaxel was not suitable differed from the population for whom chemotherapy is not yet clinically indicated. The committee discussed the appropriate comparator. It noted that, in the original appraisal, it deemed this to be best supportive care. The committee also heard from the clinical expert that docetaxel is a very effective treatment for people for whom it is suitable; the committee was not presented with evidence comparing radium-223 with docetaxel in this group of people. The committee concluded that best supportive care remained the appropriate comparator for people for whom docetaxel is not suitable.

Revised analysis

4.34 The committee considered whether the company's revised analysis sufficiently addressed the committee's concerns in the original technology appraisal of radium-223. It noted that the company re-analysed data on progression and SREs from ALSYMPCA and, in the analyses, people who died were considered to have had an event and were no longer censored. It heard from the ERG that this corrected the issues related to the flow of the cohort through the model. The committee agreed that using a longer time horizon of 10 years was preferable because it captured all the necessary differences in costs and benefits associated with treatment. It also agreed that applying subgroup-specific utilities and updating the costs of treating SREs was in line with its conclusions in the original appraisal. The committee heard from the ERG that the company's revisions resulted in fixing a bug in the model that played a major role in reducing the company's base-case ICER from £40,700 per QALY gained in the original appraisal to £26,000 in the revised analysis. The committee concluded that these revisions were appropriate.

4.35 The committee noted that, in the company's revised base case, the company did not take into account the committee's preferred assumptions identified in the original appraisal about modelling of survival and duration of utility benefit. Looking at the company's scenario analyses, the committee noted that doubling the weekly rate of mortality after 104 weeks, as preferred by the committee in the original appraisal, increased the company's base-case ICER from £26,000 to

£33,700 per QALY gained. The committee was aware that the company also explored the effect of capping the utility benefits associated with radium-223 using different time points, rather than assuming that the benefit lasted indefinitely. For the worst case scenario, in which the company assumed the benefit would last only up to 24 weeks, the ICER increased to £32,200 per QALY gained. The committee concluded that the company's base case did not include all the committee's preferred assumptions and chose to consider the scenario analyses.

4.36 The committee recalled that it did not accept the data on medical resource use included in the company's revised base case in its original appraisal. It was aware that the ERG excluded these data, and made other corrections, when revising the company's base case. The committee noted that the ERG's revisions increased the ICER from the company's new base-case estimate of £26,000 per QALY gained to £31,200 per QALY gained. It heard from the ERG that the abstract used to estimate the costs contained very little information, and including these costs could lead to double counting of costs already included in the model. The committee heard from the company that it had fixed some of the issues related to double counting, but the company and clinical expert accepted that some residual double counting may remain and also that the model may have excluded additional cost savings associated with radium-223 in reducing hospital admissions. Having noted that the data on resource use came from an unpublished abstract (albeit data from ALSYMPCA), the committee considered that the evidence was not transparent, and so could not assess the analyses behind the data. The committee accepted that there may have been residual double counting of costs and concluded that the medical resource-use data should be excluded from the analysis.

4.37 The committee understood that there were concerns about treatment waste in the original appraisal. It noted the company's comment that it refunded the hospitals on the 12 occasions when the treatment was not used in 2016, resulting in refunds for less than 0.5% of doses supplied in 2016. The company and the clinical expert explained to the committee that treatment waste was rare, and that the hospitals are aware of the arrangements by the company to refund wasted doses. The committee recognised that this is not a formal arrangement with the NHS, and that treatment waste could have cost implications for the NHS. The company stated that the arrangement has been communicated to hospitals

and will continue to be communicated. The committee also heard from the company that incorporating waste into the economic analysis would probably increase the total cost of radium-223 by approximately 0.5% based on experience in clinical practice. Having heard from the company and the clinical expert, the committee concluded that the potential for waste was not common and is not a key driver of the cost-effectiveness result. It also concluded that the company's arrangement to refund waste should be communicated appropriately to the relevant treatment centres.

4.38 The committee considered the most plausible ICER for radium-223. It had previously concluded that the medical resource-use data should be excluded; therefore, the ERG's estimate of £31,200 per QALY gained was more appropriate than the company's estimate of £26,000 per QALY gained. When the rate of mortality was doubled after 104 weeks, the ERG's estimate increased to £39,300 per QALY gained. The committee noted that the company and the ERG both provided a scenario that combined capping utility benefit at 52 weeks and doubling mortality after 104 weeks. This increased the ERG's estimate further from £39,300 to £47,900 per QALY gained. The committee noted that, if the benefit lasted for longer than 52 weeks but did not extend over a life time, the ICER would be lower than £47,900 per QALY gained. The committee noted that using the Weibull distribution rather than log-normal to extrapolate survival increased the ICER further to £56,200 per QALY gained. The committee recalled its discussions on the appropriate distribution for extrapolating survival in the original appraisal (see section 4.13). It was aware that the company's approach of doubling the rate of mortality was an attempt to minimise the uncertainty from using the log-normal distribution. The committee had previously concluded that the company's approach of modelling overall survival was uncertain, including the choice of parametric distribution. The committee noted that its concerns in the original appraisal also applied to the revised analysis. Therefore, it decided that it would consider both Weibull and log-normal distributions. On the balance of the evidence, the committee concluded that the most plausible ICER for radium-223 plus best supportive care compared with best supportive care alone for people who are not suitable for docetaxel would be below £50,000 per QALY gained, even when accounting for waste.

4.39 The committee was aware that it had previously concluded that radium-223 was considered a life-extending end-of-life treatment for people who have not had

docetaxel, and for whom docetaxel is contraindicated or unsuitable. Therefore, the committee concluded that radium-223 was a cost-effective use of NHS resources and should be recommended for this group of people. The committee also concluded that clinicians and patients would need to take into account several factors including comorbidities (see sections 4.31, 4.32 and 4.33) to identify people for whom docetaxel is not suitable, but for whom radium-223 is suitable.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.4 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 healthcare professional responsible for their care thinks that radium-223 is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund.

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.

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.

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