NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more treatments

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lutetium-177 vipivotide tetraxetan 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, clinical experts 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 recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see 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 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, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: February 2023

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 document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using lutetium-177 vipivotide tetraxetan in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 14 March 2023

Third appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 4

1 Recommendations

1.1 Lutetium-177 vipivotide tetraxetan is not recommended, within its marketing authorisation, for treating prostate-specific membrane antigen (PSMA) positive hormone-relapsed metastatic prostate cancer in adults:

- after taxane-based chemotherapy and an anti-androgen or
- when taxanes are 'medically unsuitable'.

1.2 This recommendation is not intended to affect treatment with lutetium-177 vipivotide tetraxetan that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatments for hormone-relapsed metastatic prostate cancer that has progressed after taxane-based chemotherapy and an anti-androgen include best supportive care, radium-223 dichloride and retreatment with taxanes (for example, cabazitaxel).

Evidence from a clinical trial shows that lutetium-177 vipivotide tetraxetan increases the time before the cancer gets worse and how long people live compared with best supportive care. There is also evidence from an early trial directly comparing lutetium-177 vipivotide tetraxetan with cabazitaxel but this has limitations. Indirect comparisons suggest that lutetium-177 vipivotide tetraxetan may be more effective than cabazitaxel. But these also have limitations. So, the evidence for lutetium-177 vipivotide tetraxetan compared with cabazitaxel is uncertain. Radium-223 dichloride may be a comparator for a subgroup of people. But no evidence was submitted for this comparison, so it could not be considered.

Lutetium-177 vipivotide tetraxetan meets NICE's criteria for a life-extending treatment at the end of life compared with best supportive care. It is unclear whether this is the case when it is compared with cabazitaxel or radium-223 dichloride

because of the uncertainty in the clinical evidence. But, for the comparison with best supportive care and cabazitaxel, the most likely cost-effectiveness estimates for lutetium-177 vipivotide tetraxetan are much higher than what NICE normally considers an acceptable use of NHS resources. So, it is not recommended for routine use.

Also, because of the high cost-effectiveness estimates and a lack of new comparative data with relevant medicines, lutetium-177 vipivotide tetraxetan cannot be recommended for use in the Cancer Drugs Fund.

2 Information about lutetium-177 vipivotide tetraxetan

Marketing authorisation indication

2.1 Lutetium-177 vipivotide tetraxetan (Pluvicto, Advanced Accelerator Applications) is indicated for 'the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for lutetium-177 vipivotide tetraxetan.

Price

2.3 The list price of lutetium-177 vipivotide tetraxetan is £20,000 per 7,400 MBq single dose vial per treatment cycle (excluding VAT; company submission). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Advanced Accelerator Applications, a review of this submission by the evidence review group (ERG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

There is an unmet need for new treatments for PSMA-positive hormone-relapsed metastatic prostate cancer

3.1 There are limited treatment options for prostate-specific membrane antigen (PSMA) positive hormone-relapsed metastatic prostate cancer after an anti-androgen and taxane-based chemotherapy, or when taxanes are 'medically unsuitable' (see section 3.6). Also, people with advanced or metastatic prostate cancer have a poor prognosis. The patient experts explained that the condition affects all aspects of the lives of people who have it and can affect the lives of their families and friends. They noted that there is no curative treatment, and that there is a need for new treatments that improve quality and length of life. The clinical experts noted that the only available active treatment for most people is taxane-based chemotherapy, which can have debilitating side effects. In contrast, a patient expert described leading an active and high-quality life with few side effects while having lutetium-177 vipivotide tetraxetan (from now referred to as lutetium-177). The clinical experts highlighted the importance of treatment sequencing and that lutetium-177 may be more effective earlier in the treatment pathway, when the volume of cancer is likely to be lower. The committee was aware that it can only evaluate a treatment within its marketing authorisation, but understood the importance of patient choice in shared decision making with their clinicians. Also, lutetium-177 can target bone and visceral metastases. It concluded that there is an unmet need for effective treatment options for

PSMA-positive hormone-relapsed metastatic prostate cancer that improve quality of life and survival, and have few side effects.

Treatment pathway

Lutetium-177 is positioned appropriately in the treatment pathway

3.2 The treatment options for people with hormone-relapsed metastatic prostate cancer for which chemotherapy is not yet indicated, include:

- abiraterone or enzalutamide if neither has been used before (see NICE's technology appraisal guidance on enzalutamide and on abiraterone for treating hormone-relapsed metastatic prostate cancer before chemotherapy is indicated) or
- 'watchful waiting', then
- docetaxel (see NICE's technology appraisal guidance on docetaxel for the treatment of hormone-refractory metastatic prostate cancer).

After docetaxel, abiraterone or enzalutamide can be used if neither has been used before, but a taxane can be used again (that is, cabazitaxel or docetaxel retreatment). The company highlighted that docetaxel retreatment is infrequent, which was confirmed by the clinical experts. Radium-223 dichloride is an option for people who have symptomatic bone metastases and no known visceral metastases (see NICE's technology appraisal guidance on radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases). The clinical experts agreed with the positioning of lutetium-177 in the treatment pathway, that is, for people who have had an anti-androgen and docetaxel, when docetaxel was suitable. The committee concluded that lutetium-177 was positioned appropriately in the treatment pathway.

Eligibility is determined by PSMA imaging, but access to this is limited and not standard practice across the NHS

3.3 PSMA is a transmembrane protein found on prostate cancer cells. Its expression is usually increased in poorly differentiated, metastatic and

hormone-relapsed prostate cancer. To have lutetium-177, a person needs to have their PSMA-positivity status confirmed. This can be done using PSMA positron-emission tomography CT (PET-CT) scans. This type of scan uses low-dose radiation to check the activity of cells in different parts of the body. PSMA-specific tests use radiolabelled PSMA to image the prostate cancer cells, and to determine lymph node involvement and whether there are distant metastases. The clinical experts explained that PET-CT scans are used in salvage therapy options after radical therapy. They explained that, for prostate cancer, clinicians rely on conventional CT and bone scans for most people. They noted that evidence suggests about 80% to 85% of people with hormone-relapsed metastatic prostate cancer have a PSMA-positive status. This is because PSMA expression increases along the treatment pathway. The committee acknowledged that the summary of product characteristics for lutetium-177 notes that eligibility for the treatment should be assessed using PSMA imaging. It noted that it had not seen any evidence on how well lutetium-177 works in people in whom PSMA expression has not been confirmed. It also reiterated that it can only appraise a technology within its marketing authorisation. The clinical experts explained that there is a lack of consensus about using PSMA PET-CT scans in the treatment pathway. This is because of varied access and the limited treatment options available that need this specific test. They noted that, in some centres, people have a scan at diagnosis, about 5% to 10% of which are a PSMA PET-CT scan. They also noted that about 50% to 75% of people may have a PSMA PET-CT scan at some stage in the treatment pathway. The clinical experts agreed that a scan is more likely the more advanced the prostate cancer is, and with additional lines of treatment. They explained that repeat scans may be needed even if the PSMA status had been determined earlier in the treatment pathway because changes in status are possible. The committee agreed that, although some people already have PSMA PET-CT scans in the NHS, clinical practice varies and they are not standard for everyone. The clinical experts explained that choline

is typically used for PET-CT scans, but that fluorine and gallium are alternatives. Technetium-99m-labelled PSMA is used for single-photon emission computerised tomography (SPECT). It is an option that may become more widely available, with upscale particularly possible, because research has shown it to be an accurate but cheaper alternative to PET-CT scans. The clinical and patient experts agreed that access to PSMA imaging varies across the UK. But they expected its use to increase. The clinical lead for the Cancer Drugs Fund agreed that geographical access to PSMA imaging varies. They added that investment would be needed to ensure access is timely and equitable. The committee concluded that PSMA imaging is needed to determine eligibility for treatment with lutetium-177.

Comparators

Cabazitaxel and best supportive care are relevant comparators for hormone-relapsed metastatic prostate cancer with metastases

3.4 The NICE scope for this appraisal lists docetaxel, cabazitaxel and radium-223 dichloride as comparators for lutetium-177. But the company submission only included cabazitaxel and best supportive care as comparators. The company and ERG agreed that, for the whole population, retreatment with docetaxel is infrequent, so it was excluded as a comparator. The committee concluded that cabazitaxel and best supportive care were relevant comparators for hormone-relapsed metastatic prostate cancer with metastases.

Radium-223 dichloride may be a relevant comparator for people with symptomatic bone metastases only, but more evidence is needed

3.5 The committee was aware that, with hormone-relapsed metastatic prostate cancer, metastases can occur in multiple locations, and that available treatment options can depend on these locations. Radium-223 dichloride was excluded as a comparator from the company's decision problem. This was because the company considered that radium-223

dichloride is recommended only when there are symptomatic bone metastases, and no visceral metastases. The clinical experts estimated that about 80% to 90% of people may have bone metastases alone when having first-line treatment. But they explained that the proportion of visceral metastases increases with progression and further lines of treatment. One expert estimated that about 30% of people who could have lutetium-177 may have bone metastases alone, but 10% to 15% would have isolated symptomatic bone metastases (as needed for treatment with radium-223). The clinical experts also explained that estimating what proportion of the eligible population has bone metastases alone is not straightforward. This is because the presence of metastases in lymph nodes may not be included in the proportion of people with visceral metastases. The clinical experts explained that radium-223 dichloride is not an option if there are metastases in the lymph nodes or peritoneal disease. The company noted that radium-223 dichloride has a different mechanism of action from lutetium-177 and it is used to alleviate bone pain, whereas lutetium-177 would be used to improve survival. During consultation, the company that makes radium-223 dichloride argued that the indication for its use was wider than simply bone pain secondary to symptomatic bone metastases. The clinical experts highlighted ALSYMPCA, a trial that compared radium-223 dichloride plus best supportive care with placebo and best supportive care. This found both a survival benefit and symptomatic benefit with radium-223 dichloride. Also, it looked at symptomatic bone metastases as a secondary outcome. The clinical experts explained that, in clinical practice, radium-223 dichloride is often used to treat symptomatic bone pain. The company also argued that there was not enough evidence for a population who had previously had an anti-androgen and taxane chemotherapy to compare radium-223 dichloride with lutetium-177. In response to consultation, the company that makes radium-223 dichloride argued that around 30% of people with hormone-relapsed metastatic prostate cancer would be eligible for radium-223. A clinical expert

explained that, in practice, fewer people have radium-223 (which is supported by real-world evidence). The clinical lead for the Cancer Drugs Fund confirmed that, in England, around 700 people start radium-223 each year compared with around 1,000 people starting cabazitaxel. Also, people having lutetium-177 often have cancer recurrence in bones. So, both radium-223 dichloride and lutetium-177 have a place in the treatment pathway because they can be used in a complementary way. The committee concluded that radium-223 dichloride is a relevant comparator for some people, but noted that it had not seen comparative evidence for this group. So, it concluded that it could not make any decision on the comparison of lutetium-177 with radium-223 dichloride for people with symptomatic bone metastases and no known visceral metastases.

Subgroups

It is appropriate to include the whole marketing authorisation, but there is no evidence for when taxanes are 'medically unsuitable'

3.6 There are 3 populations for whom lutetium-177's marketing authorisation applies:

- when further taxane treatment is possible
- when further taxane treatment after docetaxel is not possible
- when taxane treatment is 'medically unsuitable'.

This matches the NICE scope for this appraisal, but the company did not provide any clinical-effectiveness evidence for when taxanes are 'medically unsuitable'. A clinical expert commented that, based on retrospective studies, the prognosis for this group is likely to be worse. The clinical experts noted that lutetium-177 appeared to be well tolerated in trials. They also noted that it is a targeted treatment with relatively few side effects compared with taxane chemotherapy. So, they thought it is likely to be suitable for more people, including when taxane chemotherapy

is unsuitable. The clinical experts explained that taxanes may be 'medically unsuitable' because of:

- medical reasons such as a low red blood count or comorbidities
- social reasons such as living far away from a chemotherapy centre, which could affect access to treatment for potential sepsis associated with chemotherapy
- patient choice.

They added that it would be reasonable for people to decline further taxane treatment, given its side effect profile. The patient experts agreed that lutetium-177 would be preferred to taxane-based treatment when considering its favourable side effect profile. For example, they said it allowed them to lead an active lifestyle. The clinical experts estimated that lutetium-177 could be an option for about 30% of people for whom taxanes are 'medically unsuitable'. The committee noted that no clinical evidence had been provided for this subgroup. It concluded that it was appropriate to consider the whole population included in lutetium-177's marketing authorisation, including when taxanes are 'medically unsuitable'. This is because a proportion of people for whom taxanes are 'medically unsuitable' would be able to have lutetium-177. But it acknowledged a likely worse prognosis in this subgroup. It agreed that scenario analyses using the same relative treatment effect as for the wider population, but with a higher baseline risk and so a worse overall survival, would be useful.

Clinical evidence

The VISION trial is generalisable to clinical practice in the NHS

3.7 The clinical-effectiveness evidence for lutetium-177 compared with standard care was from the VISION trial. This was a phase 3, global, multicentre, prospective, open-label, randomised, controlled trial that compared lutetium-177 plus standard care with standard care alone. There were 831 adults enrolled in the full analysis set (intention to treat).

The inclusion criteria involved at least 1 anti-androgen and 1 or 2 taxane treatment regimens. The trial stratified people according to:

- baseline lactate dehydrogenase level
- Eastern Cooperative Oncology Group (ECOG) performance score
- whether there were liver metastases
- whether anti-androgen treatment was part of standard care at baseline.

The clinical experts agreed that the baseline characteristics were generalisable to NHS clinical practice. The committee noted that only 1 anti-androgen is used in NHS practice but more than 2 could be used in VISION. In the full analysis set, about 54% of people having lutetium-177 had 1 anti-androgen and about 46% had best supportive care. In the trial, most people had an ECOG performance score of 0 or 1. The clinical experts commented that people with an ECOG performance score of more than 1 may still have treatment if the score is because of symptoms related to the cancer rather than comorbidities. The committee concluded that, overall, VISION is generalisable to NHS clinical practice.

Lutetium-177 is clinically effective compared with standard care but a high withdrawal rate from VISION means the effect size is uncertain

3.8 The primary outcomes in VISION were overall survival and radiographic progression-free survival. These were presented in 2 analysis sets, the full analysis set and a progression-free survival full analysis set. In the progression-free survival set, randomisation was after a US Food and Drug Administration approved education measure implemented to reduce withdrawals from the trial. Before this measure was implemented, 56% of people in the control arm withdrew from the trial before having the randomly assigned treatment compared with 16% after the education measure. In comparison, before it was implemented, 1% of people in the lutetium-177 arm withdrew compared with 4% after the education measure. The results for the full analysis set showed an increase in overall survival for lutetium-177 compared with standard care (hazard ratio

[HR] 0.62, 95% confidence interval [CI] 0.52 to 0.74). Results for radiographic progression-free survival were only available for the analysis set after education measures were implemented, meaning there was missing data for people who withdrew from the trial earlier. The results showed an increase in radiographic progression-free survival for lutetium-177 compared with standard care (HR 0.40, 99.2% CI 0.29 to 0.57). The committee had concerns about the large proportion of withdrawals from the trial in the control group. The ERG explained that this was because people who withdrew from the trial were unlikely to have been a random selection. This would have introduced bias into the clinical estimates through informative censoring. The company confirmed that people were censored (removed from the analysis) but that it had adjusted for this in exploratory survival analyses, which showed a small difference in the results. The committee agreed that the difference was small but potentially important. The company adjustment included an inverse probability of censoring weighting analysis. Also, the adjusted hazard ratios were greater than the unadjusted data. The committee agreed that accounting for any bias introduced in VISION and withdrawal rates was appropriate. It concluded that lutetium-177 appeared to be clinically effective compared with standard care. But it agreed that high levels of withdrawals from VISION from the standard-care arm meant the clinical outcomes were uncertain. It concluded that results from analyses adjusting for this were needed to estimate the relative treatment effect of lutetium-177.

Lutetium-177's adverse events in the trial reflect the experiences of people having it in clinical practice

3.9 Feedback from the clinical and patient experts described lutetium-177 as well tolerated with relatively few side effects compared with taxane-based chemotherapy. The results from VISION showed that adverse events were more frequent with lutetium-177 than standard care. Higher rates of the treatment-emergent adverse events of fatigue and myelosuppression, and more grade 1 or 2 levels of dry mouth, nausea, vomiting and

hypersensitivity, were seen with lutetium-177 than standard care. A patient expert explained that, although they experienced fatigue while having lutetium-177, it was only for 1 week, rather than the entire treatment cycle. They noted that this did not affect their ability to do normal daily activities, in contrast to the 12 to 18 months it took for them to fully recover from having docetaxel. The clinical experts explained that there are usually more side effects with chemotherapy, including neutropenia, fatigue and nausea. Also, evidence from the TheraP trial directly comparing lutetium-177 with cabazitaxel showed fewer grade 3 or 4 adverse events. It also showed a better quality of life with lutetium-177 in some domains of the European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire. TheraP was a phase 2, multicentre, open-label, randomised, controlled trial in people with hormone-relapsed metastatic prostate cancer who had had docetaxel and an anti-androgen. Overall, the clinical experts agreed that they would expect a better quality of life with lutetium-177 than with cabazitaxel. The committee concluded that lutetium-177 may be better tolerated than chemotherapy, and that the adverse events seen in the trials reflected people's experience in clinical practice.

Indirect treatment comparison

The network meta-analysis is associated with high uncertainty, all included trials have limitations and there is heterogeneity between trials

3.10 The company's network meta-analysis indirectly compared lutetium-177 with cabazitaxel even though there was direct evidence from TheraP. The company argued that TheraP was not suitable to use because it:

- was a phase 2 trial
- had differences compared with VISION in methods, the diagnostic process, intervention production and dose, and the stratification of people
- was not powered for overall survival.

Instead, the company used TheraP as supportive evidence. The company's network meta-analysis included 6 randomised controlled trials, and produced a network of:

- cabazitaxel compared with best supportive care, with no previous anti-androgen treatment (TROPIC)
- an anti-androgen compared with placebo, with no previous anti-androgen treatment (COU-AA-301; AFFIRM; Sun et al. 2016)
- cabazitaxel compared with an anti-androgen (CARD)
- lutetium-177 compared with standard care (VISION).

The ERG preferred to include the direct evidence from TheraP. Also, it excluded the comparisons of anti-androgen treatment with placebo, and of cabazitaxel with best supportive care from the network. So, it limited its indirect comparison to 3 studies (CARD, TheraP, VISION). For the company's and ERG's analyses, the study populations all had hormone-relapsed metastatic prostate cancer but there was heterogeneity between the populations. The company, ERG and clinical experts agreed that all the trials were associated with limitations. Both the ERG's and company's network meta-analyses included CARD (an open-label randomised trial), but the clinical experts disagreed with its inclusion. This was because the trial population did not reflect UK clinical practice. They added that the trial had been used to show that using anti-androgen treatment was not effective if used more than once in the treatment pathway. People included in the trial had relapsed on an anti-androgen within the last 12 months, which likely affected treatment outcomes. The committee recalled that an anti-androgen would only be used once in the treatment pathway in the NHS. The ERG also explained that it included TheraP in its network meta-analysis because it is important to include direct evidence for an unbiased treatment effect estimate. But the ERG did recognise that TheraP had limitations, including:

- differences in the population compared with VISION, such as different doses of the intervention used

- that the bioequivalence of the study drug with lutetium-177 was not established
- that it was not powered for detecting survival differences between lutetium-177 and cabazitaxel.

Including TheraP in the ERG's network meta-analysis for radiographic progression-free survival gave a smaller hazard ratio for lutetium-177 compared with cabazitaxel. So, the comparison was slightly more favourable to lutetium-177. The clinical experts agreed that TROPIC was also not reflective of clinical practice because only 1% or fewer people would have cabazitaxel without a previous anti-androgen. The committee noted that COU-AA-301, AFFIRM and Sun et al. would only be included in the network meta-analysis if TROPIC was included. The populations in these 4 studies had not had an anti-androgen. The committee recalled that treatments used earlier in the pathway were likely to be more effective (see section 3.1) and, in clinical practice, anti-androgens are used before chemotherapy. The ERG suggested that treatment sequencing and anti-androgen sensitivity could be confounding factors. It commented that including TROPIC, COU-AA-301, AFFIRM and Sun et al. affected the estimation of treatment effect of cabazitaxel compared with standard care, and so the comparison of lutetium-177 and cabazitaxel. At the second meeting, the ERG noted a study on the real-world evidence use of cabazitaxel (Watson et al. 2022) and outcomes in hormone-relapsed metastatic prostate cancer. This showed an interaction between anti-androgen response and the effectiveness of cabazitaxel. Specifically, cabazitaxel was associated with increased overall survival when the cancer progressed after an anti-androgen within 12 months, compared with when it progressed after 12 months. So, the ERG disagreed with including studies in the network that included people who had not had an anti-androgen. In response to consultation, the company submitted a new fixed-effect network meta-analysis with inverse probability of censoring weighting-adjusted VISION data for overall survival. For radiographic progression-free survival, it used interval imputed VISION data, and

included the TheraP trial. The committee concluded that both network meta-analyses were associated with high uncertainty. This was because all the trials had limitations and because of the heterogeneity between trial populations. It preferred inclusion of TheraP in the network meta-analysis as a source of direct evidence for lutetium-177 compared with cabazitaxel. It noted the limitations associated with the generalisability of TROPIC (because people had not had an anti-androgen, which was not aligned with the population of interest). So, it concluded that expanding the network to include studies with people who have not had an anti-androgen was not appropriate because previous anti-androgen treatment is likely to be a treatment effect modifier.

Both fixed-effect and random-effects network meta-analyses are associated with uncertainty

3.11 In its submission, the company used a fixed-effect network meta-analysis, which assumed no heterogeneity between studies. But the ERG preferred to use a random-effects model, with an informative prior, to account for the heterogeneity between studies. TheraP included 200 people and CARD included 250 people, which the committee considered to be relatively small compared with VISION. Using a random-effects model for the network meta-analysis would give approximately equal weighting to all 3 studies (see section 3.10) compared with a fixed-effect model, in which VISION would have more weight. The committee considered other approaches such as using additional trials to generate an informative prior or a multilevel network meta-regression using individual patient data from VISION. It acknowledged that an analysis of the size of effect of included studies would be possible with scenario analyses. The committee also noted that the adjusted estimates from VISION using the inverse probability of censoring weighting analysis (see section 3.8) should have been used in the network meta-analysis. It concluded that the company should explore using a baseline risk-adjusted network meta-analysis including all the studies. It also concluded that, if an adequately fitting model can be derived, this should be used in all subsequent analyses.

This is because it may give the most robust estimate of treatment effect, given the data. After consultation, the company explored baseline risk-adjusted network meta-analyses at 6, 12 and 18 months for overall survival and radiographic progression-free survival to account for heterogeneity. But it said that this did not improve the model fit. The ERG noted that there were not enough details on the methodology for adjustment for it to critique the methodology. In response to consultation, the company also presented an updated fixed-effect network meta-analysis and scenario analyses using a random-effects and a random-effects with non-informative DuMouchel priors model. At the second meeting, the company explained that it did not consider a random-effects model and informative priors selected by the ERG to be sufficient to address heterogeneity issues because of the sparse network. It added that any informative prior should be validated through expert elicitation. The ERG agreed with the limitations of its informative prior. But it added that it did address some aspects of heterogeneity, unlike the company's approach using a fixed-effect model that assumed no heterogeneity. The committee acknowledged the difficulties with using an appropriate prior. It also noted advice from the ERG that it had a minimal effect on the mean estimated hazard ratios for overall survival and radiographic progression-free survival. The committee concluded that the studies included in the network meta-analysis had more of an effect on the results than the informative priors (see section 3.10). It also maintained that a random-effects model may be more appropriate because it would account for heterogeneity.

Cost effectiveness

The company's model is appropriate for decision making

3.12 In its submission, the company presented a 3-state partitioned survival model to estimate the cost effectiveness of lutetium-177 compared with cabazitaxel and standard care. The 3 health states were progression-free, after progression and death. The model cycle was weekly, with no half-

cycle correction, and had a 10-year time horizon. The ERG explained that the company had presented 1 cost-effectiveness analysis for the entire indicated population for lutetium-177. Only the comparator was different across subgroups (see section 3.6). The committee also noted that the quality-adjusted life years (QALYs) were accrued from people living longer, with a better quality of life while having lutetium-177. The committee acknowledged the uncertainties in the model, which included some model corrections by the ERG. It concluded the model was suitable for decision making.

Real-world evidence to estimate survival with cabazitaxel is appropriate but a network meta-analysis should inform relative treatment effect

3.13 The company acknowledged that its network meta-analysis had limitations in estimating the relative treatment effect for lutetium-177 compared with cabazitaxel. So, the company did a retrospective real-world evidence study. This combined data from 5 UK databases and aligned the population with a population with hormone-relapsed metastatic prostate cancer after an anti-androgen and a taxane. In its submission, the company estimated overall survival with cabazitaxel from its real-world evidence study. Radiographic progression-free survival data was not analysed in the real-world evidence study because of:

- inconsistency challenges when relying on a proxy to identify treatment progression in hormone-relapsed metastatic prostate cancer
- high levels of censored data if people do not have a further treatment.

The clinical experts thought that, because the data from the real-world evidence study reflected clinical practice, it was likely to better represent overall survival and be the best source of data. But results from this study gave a median overall survival with cabazitaxel that was less than that in the standard-care arm in VISION. The ERG thought that this lacked face validity (that is, the results were unexpected). It added that treatment sequencing and previous response to anti-androgen treatment may be

associated with the treatment effect of cabazitaxel. The committee agreed that the real-world evidence study was a useful data source, and provided a measure of survival representative of NHS clinical practice. The company's propensity score weighting analysis (that adjusted for some baseline characteristics between VISION and the real-world evidence study) showed similar results to the unadjusted analysis. But the ERG had concerns that the prognostic covariates had not been selected appropriately, and highlighted the importance of the effects of differences in patient populations. It suggested that a better use of the real-world evidence study would be to use it as a reference group. This would mean the company could apply relative effect measures (hazard ratios) based on network meta-analyses to estimate overall survival for lutetium-177. Also, the ERG suggested using the real-world evidence study to find out the lines of treatment of cabazitaxel used in clinical practice, and time to progression with an anti-androgen. The committee agreed that using a naive comparison between lutetium-177 and cabazitaxel increased uncertainty in and potential bias into the estimates. It also agreed that there were uncertainties. One was about whether the company's adjusted analysis effectively accounted for all possible confounding variables. Another was about whether these were adjusted for appropriately because the weighting did not achieve balance in any of the adjusted prognostic covariates. So, it preferred:

- using data from the real-world evidence study to estimate the absolute event estimates for cabazitaxel
- applying a hazard ratio from the network meta-analysis to estimate the relative effect for survival for lutetium-177.

The committee concluded that using the real-world evidence study was appropriate for estimating survival for people having cabazitaxel. But it thought that the relative treatment effect compared with lutetium-177 should come from the proposed re-analysed network meta-analysis, if appropriate (see section 3.11). At consultation, the company responded to

the committee's concerns about whether its propensity score weighting analysis adjusted for appropriate prognostic factors. It did a targeted literature review to identify characteristics that can represent clinically important prognostic variables that affect survival in this disease area. The company identified 13 clinically important prognostic factors, but only 4 were adjusted for using propensity score weighting in the real-world evidence analysis. The ERG had concerns with the methods used for the targeted literature review. The committee agreed with the ERG's view of the substantial risk associated with unaccounted confounding variables. The company did not provide the scenario analysis requested by the committee (using the real-world evidence as the reference overall survival estimate for cabazitaxel, then applying the hazard ratios from the network meta-analysis). This was because of inconsistency concerns between the overall and radiographic progression-free survival data sources. The company also highlighted the limitations of the network meta-analysis for estimating the relative effectiveness of lutetium-177 and cabazitaxel, particularly whether CARD gives an accurate estimate of the expected benefit of cabazitaxel (see section 3.10). So, it preferred to use VISION to estimate absolute survival. Also, it considered both the propensity score weighting analysis and its network meta-analysis (that included anti-androgen-naive populations) for the relative overall survival estimate. But the committee's view was that the randomised and non-randomised data were being used when each was less suited. That is, the company's approach relied on using non-randomised data when randomised data was better suited, and vice versa. Specifically, the committee thought that using randomised data to estimate absolute event rates runs the risk of results that do not reflect NHS practice. It also thought that using observational data to estimate relative effects runs the risk of biased treatment effects because of unadjusted confounding variables. The committee noted that NICE's technical support document 13 makes this distinction, advocating registry data to estimate absolute baseline event rates and randomised evidence to quantify relative differences. The

committee concluded that it still preferred using the real-world evidence to estimate survival for people having cabazitaxel and the network meta-analysis to estimate the relative treatment effect of cabazitaxel compared with lutetium-177.

Health-related quality of life

The utility estimates are uncertain

3.14 In its model, the company preferred to use treatment-dependent utility values before and after progression. This was to capture the tolerability and side effects of chemotherapy, and the psychological effects of having cabazitaxel. The company estimated values for lutetium-177 and standard care using a generalised linear mixed model fitted to EQ-5D-3L estimates mapped from EQ-5D-5L data collected in VISION. The model included terms for treatment assignment, progression status and the interaction between them. Because the interaction term was statistically significant, the company concluded it was appropriate to stratify quality of life according to treatment as well as progression status. For cabazitaxel, the company used the utility value from NICE's technology appraisal guidance on cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel for the postprogression state. But the company did not use the value from this technology appraisal for the preprogression health state with cabazitaxel, which was higher than it had estimated for lutetium-177. Instead, it assumed that utility with cabazitaxel would be the same as with standard care until progression. The ERG preferred treatment-independent utility values, before and after progression. This was:

- because of a lack of face validity using treatment-dependent utilities
- for consistency across treatments
- to avoid introducing bias because of the high proportion of withdrawal rates in the VISION standard-care arm in which people had higher baseline health-related quality of life.

The ERG explained that the utility values used by the company suggested a lower health-related quality of life after progression when having cabazitaxel compared with best supportive care and lutetium-177. Also, the health-related quality of life with lutetium-177 after progression was greater than that with cabazitaxel before progression. Because this did not have face validity, the ERG provided an additional exploratory analysis. This used treatment-dependent utilities and assumed the utility value for cabazitaxel was the average between the lutetium-177 and cabazitaxel utilities. The ERG added that information from the UK Early Access Programme suggested that utilities may be stable for cabazitaxel after previously progressing on docetaxel, before and after progression. Also, the ERG suggested that, after considering adverse effects, it was unlikely for cabazitaxel utility to be less than that for standard care. The clinical and patient experts explained that best supportive care and cabazitaxel can be associated with a high psychological burden. This is because of previous progression on a taxane or not having active treatment. The committee agreed that within-state differences were possible. It also agreed that lutetium-177 utility may be higher than that for cabazitaxel and standard care, even for people at the same stage of cancer progression. The ERG highlighted the potential for informative censoring when analysing the EQ-5D-5L data (see section 3.8). This was because people who withdrew from the control arm of VISION had greater baseline quality of life than people who continued. This meant that the quality-of-life estimates for standard care were likely underestimated. The committee considered whether it was possible to adjust for withdrawal in the health-related quality-of-life results. It considered that it may have been possible to apply inverse probability censoring weighting analyses to account for withdrawals. If there was still a meaningful difference in results between treatments, the uncertainty of using treatment-dependent utility values would be reduced. In response to consultation, the company determined that the analysis described by the committee was not possible. This was because people who withdrew from the control arm of VISION had a

higher baseline quality of life. Also, the company did not know a suitable method for addressing the missing EQ-5D data in VISION. The company maintained using treatment-dependent utility values, but assumed an average utility between lutetium-177 and best supportive care for the cabazitaxel utility. The clinical experts added that the utility would be expected to be lower at baseline with cabazitaxel. This is because the condition can deteriorate if chemotherapy is delayed because of patient preferences, or because utility can be affected by the anxiety of having a similar chemotherapy again. The ERG clarified that the utility decrements were applied to the treatment-independent utility values for grade 3 or 4 adverse events. A clinical expert added that persistent grade 2 side effects, such as fatigue or neuropathy, can have a debilitating effect on people. The committee acknowledged that it preferred to have treatment-independent utilities with adverse event decrements including grade 2 adverse events. The committee usually prefers treatment-independent utility values. But it accepted that using treatment-dependent utility values for decision making may be appropriate in this appraisal because grade 2 adverse events had not been included. But it thought that scenarios including treatment-dependent and treatment-independent utility values would be helpful.

Costs in the model

The costs of PSMA testing for the whole population need to be included in the cost-effectiveness estimates

3.15 At the first committee meeting, the cost-effectiveness estimates did not include the costs of PSMA testing (see section 3.3). The committee noted that the costs should have accounted for PET-CT or SPECT scans, and radiotracers. It recalled that the summary of product characteristics for lutetium-177 notes that eligibility for treatment should be assessed using PSMA imaging. So, it concluded that the costs of PSMA testing should have been included in the base-case estimates for the entire population, as per the NICE scope for this appraisal. At the first meeting, the number

of people needing PSMA imaging was thought to be between 100% (if everyone needs a new scan to determine eligibility) and 25% (if 75% of people have a scan as part of standard care and no additional imaging is needed). Also, it was agreed that the costs should reflect the proportion of PSMA-positive cancer in the relevant population, to account for PSMA-negative cancer. At consultation, the company included costs for 25% of the population needing a SPECT scan, and a scenario for 100% of the population needing a SPECT scan. The ERG preferred a scenario for 100% of the population needing a SPECT or PET-CT scan, with a scenario for 25% of the population needing a scan. At the second meeting, the clinical experts agreed that 50% to 60% of trusts may have access to PSMA testing. This testing is used in other settings as well as the hormone-relapsed metastatic prostate cancer setting. The clinical lead for the Cancer Drugs Fund noted that routine access to PSMA testing can depend on geographical location. They also noted that accounting for the costs of PSMA testing in 50% to 75% of the patient population is appropriate. A clinical expert added that there is more access in the south than the north of England. The company agreed that geographical location is a factor in accessing PSMA PET scans, and that use of the scans will increase in the future. The committee agreed that, although PSMA testing is available in some trusts and regions, access differs. So, it agreed that it was reasonable to account for PSMA testing costs for 50% to 75% of the population with hormone-relapsed metastatic prostate cancer. Also, the committee noted that there are additional costs associated with accounting for and disposal of lutetium-177 that should be taken into consideration.

Cost-effectiveness estimate

Lutetium-177 is not a cost-effective option for hormone-relapsed metastatic prostate cancer at the price chosen by the company

3.16 NICE's guide to the methods of technology appraisal notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per

QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of the confidential commercial arrangements for lutetium-177, cabazitaxel and other postprogression treatments, the cost-effectiveness estimates cannot be reported here. To address the committee's preferred assumptions, the company did several new analyses. These were:

- including the costs of PSMA testing, as per the NICE scope for this appraisal, for 75% of people having treatment with lutetium-177, and scenarios of up to 100% of people having a SPECT scan (see section 3.3 and section 3.15)
- inverse probability of censoring weighting-adjusted estimates from VISION used in the network meta-analyses (see section 3.8 and section 3.11)
- exploring the use of all studies in the network meta-analysis in a baseline risk-adjusted model (see section 3.10 and section 3.11)
- using the ERG's costs in the model because they are more representative of NHS practice (see section 3.16 and section 3.17).

The committee noted that the company did not provide cost-effectiveness results for its preferred analyses, which included:

- scenarios when taxanes are 'medically unsuitable' in which a higher baseline risk, so a worse overall survival, is modelled but with the same relative treatment effect as for the wider population (see section 3.6)
- a subgroup analysis comparing lutetium-177 with radium-223 dichloride when there is symptomatic bone metastases only and no known visceral metastases (see section 3.5)
- using real-world evidence on survival with cabazitaxel as a reference group for the absolute event estimates, and applying a hazard ratio

from the re-analysed network meta-analysis to estimate survival for lutetium-177 for the relative estimates (see section 3.13)

- including scenario analyses for treatment-dependent and treatment-independent utility values to account for uncertainty (see section 3.14).

End of life

Lutetium-177 meets the end of life criteria compared with standard care but comparison with cabazitaxel is uncertain

3.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company proposed that lutetium-177 does meet the end of life criteria compared with best supportive care based on:

- it being indicated for people with a short life expectancy (that is, less than 24 months)
- there being sufficient evidence that it can offer an extension to life (that is, a mean value of at least 3 months).

In VISION, the median overall survival was 15.3 months for lutetium-177 compared with 11.3 months for best supportive care. The mean undiscounted life years gained for lutetium-177 in VISION compared with best supportive care and cabazitaxel in the company's model showed an increase in survival. But the results are confidential and cannot be reported here. The ERG agreed that the short life expectancy criterion was met for people with hormone-relapsed metastatic prostate cancer after an anti-androgen and taxane-based chemotherapy. But it thought that the extension to life criterion was only met for the comparison of lutetium-177 with best supportive care. The committee agreed that the end of life criteria were likely met for the comparison with best supportive care. But it did not see the preferred estimates of lutetium-177 compared with cabazitaxel. It also did not see any evidence on the comparison of lutetium-177 with radium-223 dichloride. So, the committee could not

assess whether the end of life criteria were met for these. It concluded that, in the absence of analysis with the committee's preferred assumptions of lutetium-177 with cabazitaxel, it was not clear whether lutetium-177 would extend life by 3 months or more. So, an updated model and survival estimates are needed for it to be able to assess whether lutetium-177 meets end of life criteria compared with all comparators. It also concluded that, if the comparison with cabazitaxel does not meet end of life criteria, then its cost-effectiveness threshold should be well below £30,000 per QALY. This is to account for uncertainties with this comparison (see section 3.13).

The cost-effectiveness estimates for lutetium-177 are uncertain but suggest that it is not cost effective

3.18 The committee recalled high uncertainty in the results from the company's cost-effectiveness modelling and estimates using the end of life criteria. It noted modelling for cabazitaxel was particularly uncertain because there was no direct treatment comparison. It concluded that the most likely cost effectiveness of lutetium-177 compared with standard care and cabazitaxel were considerably above the level that NICE normally considers an acceptable use of NHS resources. This was even if the end of life criteria were applicable.

Cancer Drugs Fund

Lutetium-177 is not suitable for use in the Cancer Drugs Fund

3.19 The committee considered whether lutetium-177 could be recommended for use within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The company indicated that it may explore a managed access route for the subgroup for whom taxanes are not 'medically suitable'. But there was a lack of new comparative data with the relevant comparators. The cost-effectiveness estimates for lutetium-177 were above that considered an

effective use of NHS resources. So, the committee concluded that it could not be considered for use in the Cancer Drugs Fund.

Other factors

There are no equality issues to address in this technology appraisal

3.20 The marketing authorisation for lutetium-177 includes people for whom taxanes are 'medically unsuitable'. The committee noted that, on average, this group may be older than people who can have a taxane. It recalled that it would look at all relevant subgroups within the marketing authorisation (see section 3.6), so its recommendation for lutetium-177 was not affected by this. It concluded that its recommendation for lutetium-177 would not have a different effect on people protected by the equality legislation than on the wider population.

Lutetium-177 is not innovative beyond what is captured in the cost-effectiveness estimates

3.21 The company described lutetium-177 as innovative because it:

- offers a targeted approach to treating hormone-relapsed metastatic prostate cancer
- has a different mechanism of action (as a radioligand) than other treatments for prostate cancer
- addresses an unmet need.

The committee acknowledged the innovative aspects of lutetium-177. But it concluded that there were no additional benefits associated with it that had not been captured in the cost-effectiveness estimates.

Conclusion

Lutetium-177 is not recommended

3.22 The committee did not see cost-effectiveness estimates using its preferred modelling assumptions or within the range considered an

acceptable use of NHS resources. So, it concluded that it could not recommend lutetium-177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.

4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

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.

Chair

Baljit Singh

Chair, appraisal committee

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.

Summaya Mohammad

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