NICE National Institute for Health and Care Excellence

NICE guidance

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

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

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 and retreatment with taxanes (for example, cabazitaxel). Some people may be eligible for radium-223 dichloride, but no evidence was submitted comparing lutetium-177 vipivotide tetraxetan with radium-223 dichloride, so this comparison could not be considered.

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 a trial directly comparing lutetium-177 vipivotide tetraxetan with cabazitaxel, but this has limitations. Indirect comparisons suggest that lutetium-177 vipivotide tetraxetan may work better than cabazitaxel. But these also have limitations. So, the evidence for lutetium-177 vipivotide tetraxetan compared with cabazitaxel is uncertain.

When compared with best supportive care, lutetium-177 vipivotide tetraxetan meets NICE's criteria for a life-extending treatment at the end of life. It is unclear whether this is the case when it is compared with cabazitaxel because of the uncertainty in the clinical evidence. The most likely cost-effectiveness estimates for lutetium-177 vipivotide

tetraxetan compared with best supportive care and cabazitaxel are higher than what NICE normally considers an acceptable use of NHS resources, even when taking the end of life criteria into consideration. So, it is not recommended for routine use.

Because of the high cost-effectiveness estimates and a lack of new data comparing lutetium-177 vipivotide tetraxetan with relevant medicines, it 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 it 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 cancer is likely to be smaller. 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.

Access to PSMA imaging is limited, but is needed to determine eligibility for treatment with lutetium-177

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 most people with prostate cancer, clinicians rely on conventional CT and bone scans. 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 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 is 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. Technetium-99m-labelled PSMA is used for single-photon emission computerised tomography (SPECT). It is an option that may become more widely available, 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 is a relevant comparator for people with symptomatic bone metastases only, but no comparative evidence is presented

3.5 With hormone-relapsed metastatic prostate cancer, metastases can occur in multiple locations, and 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 only bone metastases 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 only have bone metastases, but only 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 only bone metastases is not straightforward. This is because metastases in lymph nodes may not be included when counting 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 plus best supportive care. This found both a survival benefit and symptomatic benefit with radium-223 dichloride. It also 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. Advanced Accelerator Applications also argued that there was not enough evidence for the population that 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 their bones. 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 indication, but there is no evidence for when taxanes are 'medically unsuitable'

3.6 There are 3 situations in which 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 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.

  In response to the second consultation, the company submitted 2 new scenario analyses based on findings from a study by Ahmadzadehfar et al. (2021). This investigated the prognostic impact of previous treatments in people having lutetium-177. It showed that people who had had previous

chemotherapy had poorer survival outcomes than people who had not. This was supported by several other published studies identified. The company suggested that failure of previous taxane treatment was an important prognostic factor and that people for whom taxanes are 'medically unsuitable' may have a better prognosis with lutetium-177 treatment than the wider population. In its new scenario analyses, lower hazard ratios were applied to radiographic progression-free survival and overall survival to explore the assumption of a better prognosis in the 'medically unsuitable' population. The company acknowledged limitations in using evidence from a population that had not had previous taxane-based chemotherapy as a proxy for a population in which taxanes were unsuitable, and so maintained the more conservative assumption of no difference in efficacy in its base-case analysis. The ERG and the clinical lead for the Cancer Drugs Fund also urged the committee to be cautious when considering the Ahmadzadehfar et al. (2021) study because:

- the study was retrospective, with potential for lag-time bias (that is, it was unclear whether people who have not had previous chemotherapy were in an earlier timepoint in their disease progression, compared with people who have had previous treatment)
- it was not clear why people did not have previous chemotherapy; only 19 out of the 102 people who had not had chemotherapy had contraindications
- there was considerable uncertainty about the generalisability of the results to people for whom taxanes were 'medically unsuitable' because of the lack of clinical-effectiveness data for this group.

The committee was concerned that the company's scenario analyses (which assumed that people for whom taxanes are 'medically unsuitable' have a better prognosis than the wider population) contradicted clinical expert opinion that their prognosis was likely to be worse. It also understood that the evidence informing the better prognosis assumption may not reflect the population for which taxanes are 'medically unsuitable'. It recalled it had not seen scenario analyses that explored a worse prognosis in this population, and acknowledged the population's high unmet need. It concluded that it was appropriate to consider the whole population included in lutetium-177's marketing authorisation indication, including people for whom taxanes are

'medically unsuitable'. But it was aware that it had insufficient evidence with which to assess the potential value of lutetium-177 in the population for whom taxanes are 'medically unsuitable'. It agreed that any conclusions made for this population would be substantially uncertain.

Clinical evidence

The VISION trial is generalisable to clinical practice in the NHS

3.7 The clinical-effectiveness evidence for lutetium-177 compared with best supportive care was from the VISION trial. This was a phase 3, global, multicentre, prospective, open-label, randomised controlled trial that compared lutetium-177 plus 'best supportive/standard of care' with 'best supportive/standard of 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 they had 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 previously had 1 anti-androgen and about 46% of people having 'standard of care' alone previously had 1 anti-androgen. 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 was generalisable to NHS clinical practice.

Lutetium-177 is clinically effective compared with best supportive care alone, 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 was 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 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 an 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, and the adjusted hazard ratios were greater than the unadjusted data. The committee agreed that accounting for any bias introduced in VISION and by the withdrawal rates was appropriate. It concluded that lutetium-177 appeared to be more clinically effective than standard care. But it agreed that high levels of withdrawals from VISION from the control 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 compared with best supportive care.

Lutetium-177 may be better tolerated than chemotherapy and its adverse events in the trial reflect people's experiences 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 with standard care. Higher rates of the treatment-emergent adverse events of fatigue and myelosuppression, and more grade 1 and 2 levels of dry mouth, nausea, vomiting and hypersensitivity, were seen with lutetium-177 than with 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 and 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 (EORTC) 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

It is not appropriate to include studies with people who had not had an anti-androgen in the network

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 to VISION in methods, the diagnostic process, intervention production and dose, and the stratification of people
- was not powered to assess 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).

In its network meta-analysis, the ERG included TheraP because it was direct evidence. The ERG also excluded the comparisons of anti-androgen treatment with placebo, and of cabazitaxel with best supportive care. So, its indirect comparison included only 3 studies: CARD, TheraP and 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 did not think it should be included because the trial population did not reflect UK clinical practice. They also pointed out that the trial had been used to show that 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 previous 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 explained that, although it had included TheraP in its network meta-analysis

because it is important to include direct evidence for an unbiased treatment effect estimate, the trial had limitations:

- differences in the population compared with VISION, such as different doses of the intervention used
- the bioequivalence of the study drug with lutetium-177 was not established
- it was not powered to detect 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 also did not reflect 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. (2016) should 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. (2016) affected the estimation of the treatment effect of cabazitaxel compared with that of standard care, and so the comparison of lutetium-177 and cabazitaxel. At the second meeting, the ERG noted a real-world evidence study on the use of cabazitaxel (Watson et al. 2022) that included 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 did not think that studies should be in the network if they included people who had not had an anti-androgen. The committee preferred TheraP to be included 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 it was not appropriate to include studies with people who have not had an anti-androgen in the network. This was because previous anti-androgen treatment is likely to be a treatment effect modifier.

Random-effects network meta-analyses may be preferable

3.11 In response to consultation, the company submitted a 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 fixed-effect network meta-analysis 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 have explored using a baseline risk-adjusted network meta-analysis including all the studies. It also concluded that, if an adequately fitting model could be derived, this should be used in all subsequent analyses. This was 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.

All approaches to estimate the relative treatment effect between lutetium-177 and cabazitaxel are associated with high uncertainty

3.12 At the third committee meeting, the company provided:

- a Bucher indirect treatment comparison between the CARD trial and a subgroup of people from VISION who met the eligibility criteria for CARD (that is, had cancer that had progressed within 12 months of having a previous anti-androgen) and who had had an anti-androgen as part of standard care
- an unanchored matching adjusted indirect comparison (MAIC) based on the cabazitaxel arm from the CARD trial, and a subgroup of people from the lutetium-177 arm of the VISION trial who had an anti-androgen as part of standard care.

The ERG was concerned by the company's new Bucher indirect treatment comparison and unanchored MAIC analyses because:

- unadjusted VISION data was used
- TheraP was excluded
- the Bucher indirect treatment comparison was equivalent to a fixed-effect

network meta-analysis assuming no heterogeneity between the CARD trial and the subgroup from VISION who had had an anti-androgen and whose cancer progressed within 12 months of having a previous anti-androgen

- multiple important covariates were not adjusted for in the unanchored MAIC.

  At the third meeting, the company explained that the covariate selection in the unanchored MAIC was based on a systematic literature review of prognostic variables and this was confirmed with clinical expert opinion. The systematic literature review found 20 variables that had a strong association with overall survival. But the ERG was concerned that several of the top 5 variables had not been adjusted for in the unanchored MAIC. The committee was concerned that the unanchored MAIC had not accounted for all treatment effect modifiers and disease prognostic factors. The assumption that all effect modifiers and prognostic factors are accounted for in an unanchored MAIC is reported in Technical Support Document 18. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate. The committee concluded that all approaches that had been presented to estimate the relative treatment effect between lutetium-177 and cabazitaxel were associated with high uncertainty. This was because all the trials had limitations and because of the heterogeneity between trial populations.

Cost effectiveness

The company's model structure is appropriate for decision making

3.13 In its submission, the company presented a 3-state partitioned survival model to estimate the cost effectiveness of lutetium-177 compared with cabazitaxel and best supportive 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 corrections by the ERG. It concluded the model structure was suitable for decision making.

Using a naive comparison between lutetium-177 and cabazitaxel increases uncertainty and potential bias in the estimates

3.14 The company acknowledged that its network meta-analysis had limitations in estimating the relative treatment effect for lutetium-177 compared with cabazitaxel. So, it 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 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 and potential bias in 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 requested an analysis that:

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

In response to the second appraisal consultation document, the company provided the scenario analysis requested by the committee. This used the real-world evidence as the reference overall survival estimate for cabazitaxel, then applied the hazard ratios from the network meta-analysis. The committee concluded that using the real-world evidence study was appropriate for estimating survival for people having cabazitaxel.

The survival gain for lutetium-177 compared with cabazitaxel is uncertain

3.15 The company's initial approach had relied on using non-randomised data when randomised data was better suited, and vice versa. The committee thought that using randomised data to estimate absolute event rates ran the risk of results that would not reflect NHS practice. It also thought that using observational data to estimate relative effects ran the risk of biased 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. In response to the second appraisal consultation document, the company revised its economic model to use overall survival data from the real-world evidence to inform the absolute efficacy of cabazitaxel. The hazard ratio derived from the unanchored MAIC (see section 3.12) was then applied to the cabazitaxel overall survival curve to estimate the overall survival for lutetium-177. The hazard ratio from the ERG's preferred network meta-analysis informed relative efficacy for lutetium-177 compared with cabazitaxel for radiographic progression-free survival. The hazard ratio for radiographic progression-free survival from the unanchored MAIC was explored in scenario analysis. The committee appreciated the company's use of the real-world evidence in its revised model and noted it was useful to consider. But it had concerns over the company's unanchored MAIC (see section 3.12). The committee recalled its conclusion that all the approaches it had seen to estimate the relative treatment effect between lutetium-177 and cabazitaxel were associated with high uncertainty (see section 3.12). It noted that the scenarios gave highly variable results for survival gain, particularly when the hazard ratio estimates from the ERGs network meta-analysis were used.

Health-related quality of life

The utility estimates are uncertain

3.16 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 using treatment-dependent utilities lacked face validity
- 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 company's utility values 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 the standard care 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.

Treatment-independent utilities with adverse event decrements including grade 2 adverse events are preferred

3.17 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 continued to use 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 a person's 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 and 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. At the third committee meeting, the company maintained its preference for treatment-dependent utility values. It explained that treatment-independent utilities were unlikely to fully account for peoples' experience of treatment, particularly with cabazitaxel. The company provided 3 scenario analyses using treatment-independent utility values and adverse event utility decrements with revised assumptions about adverse events for fatigue and neuropathy. It used all-grade adverse event incidence for neuropathy and fatigue instead of grade 2 and above. This was because of a lack of separately reported adverse event incidence for grade 2 adverse events in the CARD and VISION trials, and for disutility estimates for grades 1 and 2. The ERG was concerned that including all-grade incidence for neuropathy and fatigue did

not adequately reflect the committee's preferences and was likely to overestimate the impact on cabazitaxel. The committee recalled the high psychological burden that can be associated with best supportive care and cabazitaxel treatment, as described by the clinical and patient experts. The committee preferred to have treatment-independent utilities with adverse event decrements including grade 2 adverse events. It found it helpful to consider the company's scenario analyses exploring treatment-independent utilities and adverse event utility decrements with revised assumptions about adverse events for fatigue and neuropathy. It also accepted that using treatment-dependent utility values for decision making may be appropriate. But it was uncertain because it had not seen any further evidence on the extent and duration of the additional burden associated with treatment with cabazitaxel. It considered that the scenarios exploring both treatment-dependent and treatment-independent utility values were helpful to consider.

Costs in the model

Including costs for having a PET-CT or SPECT scan as part of PSMA testing for 62.5% of people having lutetium-177 is appropriate

3.18 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. 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 isneeded). It was also 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 in which 100% of the population needed a SPECT scan. The ERG

preferred to use 100% of the population needing a SPECT or PET-CT scan, with a scenario in which 25% of the population needed a scan. At the second meeting, the clinical experts agreed that 50% to 60% of trusts 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. The company revised its base case to include costs related to having either a PET-CT or SPECT scan as part of PSMA testing for 62.5% of people having lutetium-177, which was the midpoint between the committee's preferred lower and upper estimates (50% and 75%, respectively). The ERG agreed with this approach. The committee concluded that this approach was appropriate for decision making. But it noted that there was still uncertainty in the additional costs associated with accounting for and disposal of lutetium-177.

Cost-effectiveness estimate

Cost-effectiveness results are available for some but not all of the committee's preferred analyses

3.19 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 explored several analyses over the course of this appraisal. These included:

- including the costs of PSMA testing, as per the NICE scope, for 62.5% of people having lutetium-177 (see section 3.3 and section 3.18)
- inverse probability of censoring weighting-adjusted estimates from VISION used in the network meta-analyses (see section 3.8, section 3.10 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)
- applying the hazard ratio for overall survival from the unanchored MAIC (after weighting) to the cabazitaxel real-world evidence to estimate the overall survival for lutetium-177 (see section 3.12 and section 3.15)
- using the ERG's costs in the model because they better represent NHS practice
- including scenario analyses for treatment-dependent and treatment-independent utility values to account for uncertainty (see section 3.17).

  The company did not provide cost-effectiveness results for some of the committee's preferred analyses, which included:

- scenarios in which taxanes are 'medically unsuitable' and 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 are symptomatic bone metastases only and no known visceral metastases (see section 3.5)

End of life

Lutetium-177 meets the end of life criteria when compared with

standard care, but when compared with cabazitaxel this is uncertain

3.20 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 met 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 the committee was uncertain about whether lutetium-177 would extend life by 3 months or more compared with cabazitaxel. It concluded that, if lutetium-177 did not meet the end of life criteria when compared with cabazitaxel, the maximum acceptable ICER would be well below £30,000 per QALY gained because of the uncertainties (see section 3.12, section 3.14 and section 3.15). The committee 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 the comparison with radium-223 dichloride.

The cost-effectiveness estimates for lutetium-177 are uncertain but none give ICERs within the range normally considered to be cost effective

3.21 The committee recalled high uncertainty in the results from the company's cost-effectiveness modelling and in the relative treatment effect estimates used to assess the end of life criteria. It noted modelling for cabazitaxel was particularly uncertain because there was no direct treatment comparison. It also considered that, once confidential discounts on comparators and postprogression treatments were included, all the cost-effectiveness estimates for lutetium-177 compared with standard care and cabazitaxel from the company and the ERG were considerably above what NICE normally considers an acceptable use of NHS resources. This was even if the end of life criteria were applicable. So, the committee concluded that it was confident that lutetium-177 did not represent an effective use of NHS resources when compared with standard care and cabazitaxel.

Cancer Drugs Fund

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

3.22 The committee considered whether lutetium-177 could be recommended for use in 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 of people for whom taxanes are not 'medically suitable'. But there was a lack of new comparative data for 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

3.23 The marketing authorisation for lutetium-177 includes people for whom taxanes are 'medically unsuitable'. The committee noted that, on average, these people may be older than people who can have a taxane. It recalled that it would look at all relevant subgroups within the marketing authorisation indication (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 equality legislation than on the wider population.

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

3.24 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

3.25 The committee did not see cost-effectiveness estimates 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
Vice 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.

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