NICE National Institute for Health and Care Excellence

NICE guidance

Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel

Technology appraisal guidance
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Your responsibility

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

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

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

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

Contents

This guidance replaces TA255.

1 Recommendations

1.1 Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy, only if:

- the person has an eastern cooperative oncology group (ECOG) performance status of 0 or 1
- the person has had 225 mg/m^2 or more of docetaxel
- treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first)
- the company provides cabazitaxel according to the commercial arrangement.

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

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

2 The technology

2.1 Cabazitaxel (Jevtana, Sanofi) is an antineoplastic drug in a class of drugs known as taxanes, which includes paclitaxel and docetaxel. Taxanes disrupt the microtubular network essential for mitotic and interphase cellular functions, therefore inhibiting cell division and causing cell death. Cabazitaxel has a UK marketing authorisation for use 'in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen'. It is administered by intravenous infusion.

2.2 The summary of product characteristics lists the following adverse reactions for cabazitaxel as being very common (that is, occurring in 1 in 10 or more people): anaemia, leukopenia, neutropenia, thrombocytopenia, anorexia, dysgeusia, dyspnoea, cough, diarrhoea, nausea, vomiting, constipation, abdominal pain, alopecia, back pain, arthralgia, haematuria, fatigue, asthenia and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price of cabazitaxel is £3,696 per 60-mg vial (excluding VAT; British national formulary [BNF] edition 70). The company originally agreed a patient access scheme with the Department of Health and a commercial access arrangement with NHS England. Under the terms of this agreement, Sanofi facilitated the supply of cabazitaxel in pre-prepared (compounded) intravenous infusion bags containing the number of milligrams needed for each individual patient or in vials, at a reduced price with a discount reflecting the average cost of waste per patient from part-used vials (this discount in addition to the patient access scheme). Sections 3.36, 4.19, 4.21 and 4.32 in the committee discussion of this guidance reflect original committee discussions around commercial ways to mitigate concerns about wastage.

In October 2020 the company agreed an updated commercial arrangement with NHS England and NHS Improvement which replaces the original commercial access arrangement. This makes cabazitaxel available to the NHS with a discount. The size of the discount is

commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

2.4 NICE published technology appraisal guidance on cabazitaxel in 2012; it did not recommend cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Since then, additional evidence has been published and the company has agreed a new patient access scheme. Accordingly, NICE decided to update its guidance on cabazitaxel.

3 Evidence

The appraisal committee considered evidence submitted by Sanofi and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical effectiveness

Overview of the clinical trial

3.1 TROPIC is a phase III randomised open-label multicentre trial that compared cabazitaxel with mitoxantrone in men with metastatic hormone-relapsed prostate cancer. The trial recruited people whose disease had progressed on or after treatment with docetaxel. Patients aged 18 years or older were randomised 1:1 to have either:

- 25 mg/m^2 of cabazitaxel intravenously every 3 weeks in combination with 10 mg prednisone (or prednisolone) orally or
- 12 mg/m^2 of mitoxantrone intravenously every 3 weeks with 10 mg prednisone (or prednisolone) orally.

The investigators capped the treatment for both drugs at a maximum of 10 cycles to minimise the risk of mitoxantrone-induced cardiac toxicity. All patients within the trial had previously had chemotherapy. None of the patients who entered the trial had previously had enzalutamide or abiraterone.

3.2 The company stated that mitoxantrone was equivalent to best supportive care. To support this statement, it referred to an analysis that used data from 2 separate trials to compare mitoxantrone plus prednisone with prednisone alone (Green et al. 2015). There was no significant difference in overall survival between mitoxantrone and prednisolone, so the company concluded that mitoxantrone was a reasonable proxy for best supportive care.

Outcomes

3.3 The primary outcome measure in TROPIC was overall survival, defined as the time from the date of randomisation to death from any cause. If it was unknown whether the patient was still alive, the survival time was censored at the last date the patient was known to be alive, or at the data cut-off date. Secondary outcomes included progression-free survival defined as the time from randomisation to any one of: tumour progression, prostate-specific antigen (PSA) progression, pain progression, or death from any cause.

Statistical analysis

3.4 The company presented an analysis of TROPIC that was published after a median follow-up of 20.5 months (study cut-off date: 10 March 2010), at which point 585 deaths had occurred. The trial included 2 analyses: intention to treat and per protocol. The intention-to-treat analysis included all randomised patients (n=755); the results are shown in table 1. The per-protocol analysis for adverse events included only those patients who had at least 1 dose of the study treatment (n=742).

Subgroup of patients with an ECOG performance status of 0 to 1 who had had 225 mg/m^2 or more of docetaxel

3.5 The company presented a subgroup analysis that was post hoc (not specified up front in the design of the trial) for patients in TROPIC with an eastern cooperative oncology group (ECOG) performance status of 0 to 1 (lower scores reflect better function) who had had 225 mg/m^2 or more of docetaxel. The company highlighted that in NICE's 2012 technology appraisal guidance on cabazitaxel the committee had considered that this subgroup represented clinical practice in England. The subgroup comprised 632 (83.7%) patients out of a total of 755 randomised patients (table 1).

3.6 In the subgroup analysis (table 1) median overall survival was 15.6 months (95% confidence interval [CI] 13.96 to 17.28) in the cabazitaxel group and 13.4 months (95% CI 11.99 to 14.52) in the mitoxantrone group. The difference was 2.2 months. The risk of death

was statistically significantly lower in the cabazitaxel group than in the mitoxantrone group (hazard ratio [HR] 0.69; 95% CI 0.57 to 0.82; p<0.001).

Table 1 Results of TROPIC

Outcome	Intention-to-treat analysis for mitoxantrone (n=377)	Intention-to-treat analysis for cabazitaxel (n=378)	Subgroup (ECOG 0 to 1 and ≥225 mg/m^2 docetaxel) for mitoxantrone (n=313)	Subgroup (ECOG 0 to 1 and ≥225 mg/m^2 docetaxel) for cabazitaxel (n=319)
Median progression-free survival (months)	1.41	2.76	1.41	2.76
Difference in progression-free survival (months)	1.35	1.35	1.35	1.35
Hazard ratio (95% CI)	0.75 (0.65 to 0.87); p<0.001	0.75 (0.65 to 0.87); p<0.001	0.76 (0.65 to 0.89); p=0.001	0.76 (0.65 to 0.89); p=0.001
Median overall survival (months)	12.78	15.08	13.37	15.61
Difference in overall survival (months)	2.30	2.30	2.24	2.24
Hazard ratio (95% CI)	0.72 (0.61 to 0.84); p<0.001	0.72 (0.61 to 0.84); p<0.001	0.69 (0.57 to 0.82); p<0.001	0.69 (0.57 to 0.82); p<0.001

Abbreviations: n, number; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Network meta-analysis

3.7 No trials have directly compared the effectiveness of cabazitaxel with abiraterone or enzalutamide. The company did a network meta-analysis to compare the effectiveness of these 3 drugs indirectly using a fixed-effects model. It identified the COU-AA-301 and AFFIRM trials from its systematic literature review. AFFIRM compared enzalutamide (with or without oral prednisone) with placebo (with or without oral prednisone). COU-AA-301 compared abiraterone plus prednisone with placebo plus prednisone.

3.8 The company noted that the definition of progression in TROPIC was different to the definition in COU-AA-301 and AFFIRM because TROPIC used a multiple-component endpoint. Therefore, the company chose radiographic progression-free survival to inform its network meta-analysis, which it defined as the time from randomisation to the first occurrence of tumour progression (based on the Response Evaluation Criteria in Solid Tumors [RECIST] criteria) or death from any cause.

3.9 The network meta-analysis showed that enzalutamide improved radiographic progression-free survival, but not overall survival, compared with cabazitaxel. There was no difference between cabazitaxel and abiraterone in either overall survival or radiographic progression-free survival.

3.10 The company advised that its network meta-analysis assumed that the trial populations, and control-group treatments, were similar across all 3 of the included trials. The company noted that these assumptions may not be met, and so the results of the network meta-analysis should be treated with caution.

Cost effectiveness

Overview of the model

3.11 The company produced a partitioned survival model to assess the cost

effectiveness of cabazitaxel compared with mitoxantrone. In its base case the company modelled the subgroup of patients in TROPIC (see section 3.5) who had an ECOG performance status of 0 to 1 and previously had at least 225 mg/m^2 of docetaxel.

3.12 The company considered it standard NHS practice to treat hormone-relapsed prostate cancer with either abiraterone or enzalutamide in the pre-chemotherapy setting, that is, before docetaxel. Thus, in its main analyses, the company compared cabazitaxel with best supportive care, which it stated was the same as mitoxantrone (see section 3.2). However, in an alternative pathway (without abiraterone or enzalutamide before docetaxel) the company compared cabazitaxel with abiraterone and cabazitaxel with enzalutamide.

3.13 The company's Markov model had 3 states representing disease progression from stable disease through to progressive disease and death. It included a 10-year time horizon, 3-week cycle lengths and discounting of costs and health benefits at 3.5%. The company included the costs incurred by the NHS and personal and social services. The base-case model compared 2 treatments:

- Mitoxantrone, 12 mg/m^2 every 3 weeks in combination with 10 mg/day of oral prednisolone.
- Cabazitaxel, 25 mg/m^2 every 3 weeks in combination with 10 mg/day of oral prednisolone.

Clinical parameters

3.14 To model time to disease progression and time to death for the subgroup (patients in TROPIC with an ECOG performance status of 0 to 1 who previously had at least 225 mg/m^2 of docetaxel), the company's original base case used a log-normal curve for time to progression and a Weibull curve for time to death. In its response to the appraisal consultation document, the company submitted analyses using a piecewise curve to predict overall survival with cabazitaxel (see section 3.29 and section 3.36).

Health-related quality of life

3.15 The company did not collect data on health-related quality of life in TROPIC, so it took utility values from the UK early access programme (EAP) that allowed the company to provide cabazitaxel to patients before its official launch. The programme measured the health-related quality of life (using the EQ-5D) of men who had been treated with cabazitaxel after docetaxel. In the stable disease state of the model, utility increased with successive cycles of cabazitaxel treatment. The utility value was 0.70 during the first cycle and 0.82 during the tenth cycle. In the progressive disease state, the utility was 0.63 until the last 3 months of life in which the company set utility at 0.

3.16 Disutility values for adverse events were not collected in either the UK EAP or in TROPIC. The company derived disutility values associated with experiencing each adverse event from a literature review that was done for NICE's 2012 technology appraisal guidance on cabazitaxel. These studies included breast and lung cancer, but not prostate cancer.

Treatment-related adverse events

3.17 The company modelled 15 adverse events using the proportions of adverse events in TROPIC, and included all at grade 3 and above that occurred in 2% or more of patients in any TROPIC treatment group. In addition, the company included deep vein thrombosis and peripheral sensory neuropathy as they were classified as important based on clinical expert opinion.

Resource use

3.18 The company estimated resource use (such as the frequency of hospital admissions and adverse events) using data from: TROPIC; a UK clinical audit; and opinion from experts. It estimated costs using the British national formulary (BNF), NHS reference costs and data from the personal social services research unit.

3.19 In the stable disease state, the company included costs of acquiring drugs (for active treatment, pre-medications and concomitant

medications), costs of administering chemotherapy, costs of managing disease including hospitalisation and testing, and costs of adverse events. Costs for active treatment, pre-medications and administering chemotherapy were applied for up to 10 cycles for cabazitaxel and mitoxantrone (the maximum number allowed in TROPIC). Mitoxantrone comes in vials and the dose depends on body surface area. The company assumed that the mean body surface area was 1.9 m^2 (based on clinical opinion; the mean body surface area observed in TROPIC was 2.01 m^2). It also assumed that some mitoxantrone would be wasted when a vial was opened but not fully used.

3.20 The dose of cabazitaxel depends on body surface area. Prior to this appraisal, cabazitaxel was only purchased in vials. Because an individual dose may not require a whole vial, and the summary of product characteristics does not permit vial sharing, this meant that some cabazitaxel was wasted. In response to the appraisal consultation document, the company explained that it has set up a new compounding scheme. The company provided the following details of the scheme:

- Sanofi will sell the licensed formulation of cabazitaxel (60-mg vials) to a number of companies already used by the NHS for compounding products.
- No compounding fee will be payable by the NHS.
- The compounding company will prepare intravenous-infusion bags of cabazitaxel in accordance with the summary of product characteristics.
- The bags will be sold to NHS trusts at a price not to exceed the per-milligram patient access scheme price.
- Sanofi will cover the costs of: drug wastage, transport to NHS hospitals, and bags that are returned unused because a patient could not have a scheduled dose.

  Because of this compounding scheme, the company's model assumed there was no wastage of cabazitaxel. After the guidance was published, the commercial access agreement was changed so that NHS trusts also have the option of purchasing cabazitaxel in vials; see section 2.3.

3.21 In the progressed disease state, the company included: acquisition costs

for chemotherapy and best supportive care given after disease progression; costs of administering chemotherapy; and costs of managing disease including hospitalisation, imaging and testing.

3.22 In response to the appraisal consultation document, the company increased the level of discount in its patient access scheme. The updated base-case results using the increased discount are given in section 3.37.

Company's scenario analyses

3.23 The company's scenario analyses compared cabazitaxel (including patient access scheme discount) with enzalutamide (at list price) and, separately, abiraterone (at list price). Although both enzalutamide and abiraterone are offered by their respective companies to the NHS with discounts, the enzalutamide discount is confidential and not known to Sanofi. The scenario analyses used the intention-to-treat results from TROPIC. The company assumed that patients take enzalutamide and abiraterone until disease progression or death, whereas patients use cabazitaxel for up to 10 cycles.

3.24 The company took the hazard ratios reflecting the effectiveness of abiraterone and enzalutamide compared with cabazitaxel from its network meta-analysis, and applied these to the parametric distributions modelling overall survival and progression-free survival with cabazitaxel. The company used a Weibull curve to model progression-free survival. The company did not report a fully incremental analysis.

3.25 Because of the confidential discounts the ERG recalculated the company's scenario analyses using the patient access scheme discounts for cabazitaxel, enzalutamide and abiraterone.

Key issues raised by the Evidence Review Group

Network meta-analysis

3.26 The ERG agreed with the company's concerns about the assumptions

made in the company's network meta-analysis (see section 3.10). The ERG noted that in the presence of between-study heterogeneity, a fixed-effects model is not appropriate; it advised that instead the company should have used a random-effects model. The ERG did an analysis using a random-effects model and a weakly informative prior for the between-study standard deviation. The results showed no statistically significant difference between any of the treatments in either overall survival or radiographic progression-free survival.

3.27 The ERG also noted that the company used hazard ratios for the network meta-analysis which may not have been appropriate. In the COU-AA-301 study for abiraterone compared with placebo, the placebo overall survival curve crosses the abiraterone curve at 24 months; this means that the proportional hazards assumption may not hold. Accordingly, the ERG advised that the results of the network meta-analysis should be treated with caution.

3.28 The ERG noted that 18% of patients in the cabazitaxel group of TROPIC withdrew from treatment because of adverse events, compared with 8% in the enzalutamide group of AFFIRM and 13% in the abiraterone group of COU-AA-301. The company, in response to a clarification question before the first committee meeting, presented a fixed-effects network meta-analysis of adverse events. The results showed an increase in anaemia and nausea with cabazitaxel compared with best supportive care, abiraterone and enzalutamide. In addition there was an increased incidence of diarrhoea with cabazitaxel compared with best supportive care and abiraterone.

Economic model

3.29 The ERG noted that in NICE's 2012 technology appraisal guidance on cabazitaxel the committee preferred the piecewise approach for extrapolating TROPIC data rather than the methods presented by the company. This was because some patients in the cabazitaxel group died from neutropenia early in the trial, which may have biased the predicted survival times from a single extrapolation curve. The ERG asked why the company had not used piecewise curves to model overall survival. Piecewise methods use independent distributions to calculate transition

probabilities during different time periods; for example, using a Kaplan–Meier curve at the start of the model, then after a cut-off point using a parametric distribution. In response to a clarification question from NICE before the committee meeting, the company presented results using a piecewise curve for the cabazitaxel arm (specifically, using a Kaplan–Meier curve for the first 2.1 months and a Weibull curve thereafter) and a Weibull curve for the mitoxantrone arm, as unchanged from the base case. The ERG advised that the piecewise curve for overall survival with cabazitaxel is likely to be more appropriate than the single Weibull curve the company used in its base case. The company's new analyses submitted in response to the appraisal consultation document used the piecewise curve for overall survival with cabazitaxel.

3.30 The ERG raised concerns about how the company had modelled patients who stop treatment with cabazitaxel or mitoxantrone. It noted that patients in the stable disease state continued treatment until:

- the disease progressed and the patient moved to the progressed disease health state or
- the patient died or
- the patient had the maximum 10 cycles of treatment, in which case they remained in the stable disease state or
- treatment was stopped for other reasons (such as adverse events), in which case they remained in the stable disease state.

The ERG advised that the company's approach incorrectly estimated both drug costs and utility values for patients who stop treatment for 'other reasons'. The ERG did an analysis that did not allow treatment stopping for 'other reasons'; this increased the company's incremental cost-effectiveness ratio (ICER) slightly. The company's new analyses submitted in response to the appraisal consultation document did not allow treatment stopping for 'other reasons'.

3.31 The company included a disutility in the quality-adjusted life year (QALY) calculations to account for the assumed reduced quality of life experienced by people with progressive disease in their last 3 months of life. The ERG noted that this disutility was applied to all deaths in the model rather than only people with progressive disease. The company's

new analyses submitted in response to the appraisal consultation document removed this disutility. Removing the disutility slightly increased the ICER for cabazitaxel compared with mitoxantrone.

3.32 The ERG advised that for generic drugs it is more appropriate to use prices from the electronic market information tool (eMIT) than the BNF because eMIT is based on the price paid by English hospitals. Using eMIT prices slightly increased the ICER comparing cabazitaxel with mitoxantrone. The company's new analyses submitted in response to the appraisal consultation document used the eMIT price for mitoxantrone.

3.33 The ERG highlighted that 3 different estimates were available for the costs of treatment in the progressed-disease health state. The most expensive estimate (£1,767.02) was based on the mitoxantrone group in the TROPIC trial. The least expensive estimate (£1,192.81) was based on the cabazitaxel group in TROPIC. The third estimate was from a UK clinical audit (£1,364.07). The company's base case used the estimate from the cabazitaxel group in TROPIC for the costs of treatment after cabazitaxel, and the estimate from the mitoxantrone group in TROPIC for the costs of treatment after mitoxantrone, abiraterone or enzalutamide. In the ERG's opinion, the company should have used the same post-progression treatment costs for cabazitaxel and each of the comparators. Accordingly, the ERG used the UK clinical audit to estimate the post-progression treatment costs for cabazitaxel and the comparators. This slightly reduced the ICER for cabazitaxel compared with mitoxantrone. The company's new analyses submitted in response to the appraisal consultation document used the UK clinical audit to estimate post-progression treatment costs.

3.34 The ERG noted that the company assumed no wasted cabazitaxel. During NICE's 2012 technology appraisal of cabazitaxel, clinical experts advised that because cabazitaxel is supplied in vials, there is likely to be some wastage of cabazitaxel in NHS clinical practice, but there was uncertainty about how much waste would occur. For the committee to consider at its first meeting, the ERG did an analysis, which assumed that a cycle of treatment with cabazitaxel would incur the cost of 1 vial of cabazitaxel and that the NHS would bear the cost of drug wastage from partly used vials. This increased the ICER for cabazitaxel compared with

mitoxantrone (the results are confidential and cannot be reported here).

3.35 The ERG's exploratory base case included the following assumptions:

- Do not model stopping treatment for reasons other than disease progression, death or reaching the maximum number of treatment cycles.
- Do not model a reduced utility value for the last 3 months of progressive disease.
- Use eMIT prices for generic drugs.
- Use UK clinical audit data for the costs of post-progression treatment and the proportion of patients who have best supportive care.

Company's response to consultation

Cabazitaxel compared with best supportive care

3.36 In response to consultation the company submitted an updated base case, using the committee's preferred assumptions (see sections 4.12 to 4.17) to compare cabazitaxel with best supportive care. The updated base case included the following assumptions:

- Increase the patient access scheme discount for cabazitaxel.
- Do not model stopping treatment for reasons other than disease progression, death or reaching the maximum number of treatment cycles.
- Do not model a reduced utility value for the last 3 months of progressive disease.
- Use eMIT price for mitoxantrone.
- Use UK clinical audit data for the costs of post-progression treatment and the proportion of patients who have best supportive care.
- Use a piecewise curve to predict overall survival with cabazitaxel.

- Use the per-milligram pricing of cabazitaxel (that is, assume that it is purchased in pre-prepared intravenous-infusion bags so there is no waste). After the guidance was published, the commercial access agreement was changed so that NHS trusts also have the option of purchasing cabazitaxel in vials (see section 2.3).

3.37 The company's deterministic base case estimated that cabazitaxel (with updated patient access scheme discount) compared with mitoxantrone resulted in an ICER of £45,159 per QALY gained (incremental costs £10,682, incremental QALYs 0.237). The probabilistic ICER was £45,982 per QALY gained.

ERG critique of company's updated base case

3.38 The ERG reviewed the company's updated base-case analysis and confirmed that the inputs were appropriate. The ERG could replicate the company's results.

Cabazitaxel compared with enzalutamide, abiraterone and best supportive care

3.39 After consultation, the ERG did a fully incremental analysis comparing cabazitaxel (with updated patient access scheme discount) with enzalutamide, abiraterone and best supportive care (represented by mitoxantrone). Over the course of this appraisal, the patient access scheme for abiraterone changed from a simple discount to a complex scheme (dose capping). The ERG's analyses used the new complex patient access scheme for abiraterone. The ERG used its random-effects network meta-analysis (see section 3.26) to estimate the effectiveness of cabazitaxel compared with each treatment. The ERG's incremental analysis showed that cabazitaxel was extendedly dominated by best supportive care and enzalutamide. An intervention is 'extendedly dominated' when it is more costly and less effective than a combination of 2 comparators (in this case, best supportive care and enzalutamide). Abiraterone was also extendedly dominated by best supportive care and enzalutamide.

3.40 The ICERs for cabazitaxel compared with best supportive care were

substantially higher in the ERG's fully incremental analysis than the ERG's pairwise comparison of cabazitaxel with mitoxantrone in its base case. The incremental analysis used the network meta-analysis results to estimate the effectiveness of each treatment, whereas the pairwise comparison used data from TROPIC only. The ERG advised that the network meta-analysis assumes proportional hazards, but the data may not meet this assumption. Both the ERG and the company stated that the results of the network meta-analysis should be treated with caution.

3.41 The ERG noted that the company did not compare cabazitaxel with radium-223 dichloride, as specified in NICE's scope. In response to a clarification question from NICE before the committee's first meeting, the company provided results from ALSYMPCA: a randomised trial that compared radium-223 dichloride with placebo. In ALSYMPCA, the subgroup of patients treated with radium-223 dichloride and who had previously had docetaxel had a median overall survival of 14.4 months (95% CI 12.5 to 15.5). For comparison, patients in the cabazitaxel group of TROPIC (intention-to-treat analysis) had median overall survival of 15.1 months (95% CI 14.0 to 16.5). The ERG noted that both overall survival and progression-free survival with radium-223 dichloride appeared to be similar to that with cabazitaxel and that if the cost effectiveness of these 2 drugs were compared, drug costs would likely be a key driver. The ERG presented an analysis comparing the costs of cabazitaxel and radium-223 dichloride (including the confidential patient access scheme discounts for both drugs); the results are confidential and cannot be reported here.

4 Committee discussion

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

4.1 The committee considered current treatments available in the NHS in England for people with metastatic hormone-relapsed prostate cancer. It was aware that initial treatment options include enzalutamide, abiraterone and best supportive care. It heard from the clinical experts that people whose disease has progressed are offered docetaxel only if their Karnofsky performance-status score is 60% or more. The committee heard from the clinical experts that people whose disease progressed after docetaxel may be offered:

- radium-223 dichloride (if they have symptomatic bone metastases and no known visceral metastases) or
- cabazitaxel (currently available through the Cancer Drugs Fund) or
- abiraterone or enzalutamide (if they have not had abiraterone or enzalutamide before) or
- best supportive care.

4.2 The committee discussed the relevant comparators for cabazitaxel (that is, treatments that would be offered to NHS patients if cabazitaxel were not available). The committee noted that radium-223 dichloride was included in the scope, had been widely used through the Cancer Drugs Fund, and was now recommended by NICE for treating hormone-relapsed prostate cancer with bone metastases in people with no known visceral metastases who have had docetaxel previously (NICE's technology appraisal guidance on hormone-relapsed prostate cancer with bone metastases). The committee heard from the clinical experts that radium-223 dichloride is not a relevant comparator because it targets bone metastases only (rather than other metastases) and is

limited to people who have symptomatic bone metastases and no known visceral metastases. It heard from the company that radium-223 dichloride is not a relevant comparator because the population in the main trial of radium-223 dichloride differed from the population in the main trial of cabazitaxel, indicating that these drugs would be used for different patient populations in clinical practice. However, the committee noted that median overall survival was similar in the placebo arms of the 2 trials, which suggests that the people in the trials were at a similar stage of disease progression. Whilst the committee acknowledged that radium-223 dichloride was not a suitable treatment for the entire population relevant to this appraisal, it noted that radium-223 dichloride was recommended by NICE for a subgroup of that population. The committee concluded that radium-223 dichloride was a relevant comparator for the subgroup of people with symptomatic bone metastases and no known visceral metastases.

4.3 The committee discussed additional comparators for cabazitaxel, noting that abiraterone or enzalutamide were options only for people who had not taken either of these drugs previously. The committee was aware of the company's response to consultation, in which the company stated that some people who have not had abiraterone or enzalutamide before docetaxel have disease that is not suitable for abiraterone or enzalutamide after docetaxel (such as people with poorly differentiated tumours and whose disease had progressed rapidly after previous treatments). The committee concluded that:

- For people who had abiraterone or enzalutamide before docetaxel, or whose disease is not suitable for treatment with abiraterone or enzalutamide, the relevant comparators are best supportive care and radium-223 dichloride.
- For people who have not had abiraterone or enzalutamide the relevant comparators are abiraterone, enzalutamide, radium-223 dichloride and best supportive care.
- Regardless of treatment history, radium-223 dichloride is a comparator only for people with symptomatic bone metastases and no known visceral metastases.

4.4 The committee heard from patient experts about their experience of metastatic hormone-relapsed prostate cancer. The patient experts

stated that, at this stage of disease, patients and their families value treatments which extend life, even if for a short period, and the hope that this offers. The committee also heard that patients want treatments that improve quality of life. The committee heard from the patient experts that cabazitaxel is usually well tolerated and is therefore an important option for treating people with metastatic hormone-relapsed prostate cancer. The committee was aware that it is important to patients to have a choice of effective treatments. The committee concluded that patients wanted to have the option of treatment with cabazitaxel.

Clinical effectiveness

4.5 The committee considered the clinical-effectiveness evidence submitted by the company (see section 3.1). TROPIC was a large, open-label, multinational, phase III, randomised trial comparing cabazitaxel plus prednisone or prednisolone (subsequently referred to as cabazitaxel) with mitoxantrone plus prednisone or prednisolone (subsequently referred to as mitoxantrone). The committee discussed whether the treatments that patients had before they entered the TROPIC trial were relevant to clinical practice in England, because the trial was conducted before abiraterone and enzalutamide were available. It was aware that in clinical practice in England, abiraterone and enzalutamide are sometimes offered before docetaxel (see section 4.1). The committee heard from the clinical experts that patients in TROPIC were on their second or third line of treatment, which means that the patients in the trial are similar to people who would have cabazitaxel in the NHS. The committee concluded that TROPIC provided estimates of efficacy that were generalisable to the NHS in England, although it was somewhat uncertain whether the magnitude of benefit observed in TROPIC would be observed in the NHS because of differences in treatment history between these 2 populations.

4.6 The committee noted that, in the company's opinion, the population relevant to the appraisal was represented by the subgroup of patients in TROPIC with an eastern cooperative oncology group (ECOG) performance score of 0 or 1 who had had 225 mg/m^2 or more of docetaxel. The company considered this subgroup relevant to clinical practice in England because people with an ECOG score above 1 are not

suitable for treatment with chemotherapy, and 225 mg/m^2 or more of docetaxel is the minimum dose used in clinical practice. The committee agreed that this subgroup is closest in characteristics to the patients who would be offered cabazitaxel through the NHS in England.

4.7 The committee considered whether mitoxantrone is equivalent to best supportive care as proposed by the company. The committee questioned why the company had included mitoxantrone, which does not have a marketing authorisation in the UK for treating metastatic hormone-relapsed prostate cancer, as the comparator in the pivotal trial. The clinical experts stated that, when the trial was designed, mitoxantrone was frequently used in clinical practice because there were few treatment options available. The committee considered the evidence submitted by the company to support equivalence of mitoxantrone and best supportive care. It noted that the Green et al. (2015) study showed no statistically significant difference in overall survival between mitoxantrone and prednisone (see section 3.2). The committee noted that although the evidence suggests no statistically significant difference between mitoxantrone and prednisone, this does not demonstrate equivalence. The committee concluded that, in the absence of evidence of equivalence, mitoxantrone could be considered similar to best supportive care.

4.8 The committee considered the results of TROPIC, focusing on the subgroup of people with an ECOG performance score of 0 or 1 who had had 225 mg/m^2 or more of docetaxel. The committee was aware that the TROPIC data were analysed in 2010 and that these results had been available to the committee for NICE's 2012 technology appraisal of cabazitaxel. The results showed that cabazitaxel prolonged survival and progression-free survival compared with mitoxantrone (see table 1). The committee heard from the evidence review group (ERG) that a lack of blinding in the open-label trial design could bias the results. The committee agreed that estimates of treatment effect for subjective outcomes such as pain and symptom deterioration (both of which were included in the definition of progression-free survival) may be biased by the lack of blinding. The committee concluded that, in people with an ECOG performance score of 0 or 1 who had had 225 mg/m^2 or more of docetaxel, cabazitaxel compared with mitoxantrone improves overall

survival and progression-free survival. It further concluded that the estimated treatment effect for disease progression may be affected by bias within the trial design.

4.9 The committee considered the company's fixed-effects network meta-analysis comparing cabazitaxel with best supportive care, abiraterone and enzalutamide. The results showed that there was no significant difference in overall survival between cabazitaxel, abiraterone and enzalutamide (see section 3.9). It also showed that radiographic progression-free survival was shorter with cabazitaxel than with enzalutamide. The committee noted that the incidence of anaemia and nausea was higher with cabazitaxel than with abiraterone and enzalutamide (see section 3.28). The committee was aware of a number of concerns about the network meta-analysis:

- The company advised that radiographic progression-free survival was longer for patients in the control group of TROPIC than for patients in the control groups of the abiraterone and enzalutamide trials, suggesting that the trials differed in their populations and/or efficacy of the control treatments. The committee noted that the control treatments differed between trials: the cabazitaxel trial used mitoxantrone and prednisone or prednisolone; the abiraterone trial used placebo and prednisone or prednisolone; and the enzalutamide trial used placebo alone. The committee had previously noted that mitoxantrone and prednisolone appear to have similar effects on overall survival, but equivalence has not been demonstrated and their relative effect on progression-free survival is unknown. The committee concluded that the network meta-analysis may be biased because of potential differences between trials in populations and control treatments, but it was not clear whether the potential bias would be an advantage or a disadvantage for cabazitaxel.
- The company used a fixed-effects model. The ERG advised, and the committee agreed, that this was not appropriate because of the heterogeneity between the 3 trials.

- The network meta-analysis assumed proportional hazards in each trial (that is, the ratio of the risk of death between treatment groups stays constant over time). The ERG advised that the data from the abiraterone trial violated this assumption (see section 3.27).

  The committee considered the results of the ERG's revised network meta-analysis using a random-effects model (see section 3.26). This showed no significant difference between cabazitaxel, abiraterone and enzalutamide in overall survival or radiographic progression-free survival. The committee noted that there were no data to inform the between-study standard deviation in the ERG's random-effects analysis, meaning that the results could overestimate uncertainty in the effects of treatments. The committee accepted that the random-effects network meta-analysis results were uncertain but, in the absence of more robust evidence, it concluded that cabazitaxel, abiraterone and enzalutamide all had a similar effect on overall survival and radiographic progression-free survival.

4.10 The committee discussed the effectiveness of cabazitaxel compared with radium-223 dichloride, noting that the company did not present any evidence for this comparison. The committee was aware of the ERG's crude comparison which suggested that median overall survival and progression-free survival were similar for both cabazitaxel and radium-223 dichloride (see section 3.41). The committee acknowledged that this basic comparison was at high risk of bias. It concluded that there was no evidence that cabazitaxel and radium-223 dichloride have different effects on survival.

Cost effectiveness

4.11 The committee considered the company's economic model, noting that it was a partitioned-survival model (that is, the transitions between health states were derived from curves of progression-free survival and overall survival). The model compared cabazitaxel with mitoxantrone, which was a proxy for best supportive care. The committee noted that the modelled population was the subgroup of people in TROPIC with an ECOG performance score of 0 or 1 who had had 225 mg/m^2 or more of docetaxel. It was aware that, in scenario analyses, the company compared cabazitaxel with abiraterone and, separately, with

enzalutamide. When comparing cabazitaxel with abiraterone or enzalutamide, the modelled population was not the subgroup, but rather all randomised patients in TROPIC because the network meta-analysis used this population. The committee concluded that the company's model was acceptable, but it should have included radium-223 dichloride as a comparator.

4.12 The committee considered the estimates of overall survival in the company's model (see section 3.14), noting that in its original base case the company used a Weibull curve to extrapolate overall survival. The committee heard from the ERG that, in the early stages of the trial, some patients treated with cabazitaxel died from febrile neutropenia and that this may have affected the predicted survival times if using a single extrapolation curve. The committee was aware that, in response to a clarification question before the first committee meeting, the company presented a scenario analysis that used a piecewise extrapolation for cabazitaxel (see section 3.29). The piecewise extrapolation used the observed Kaplan–Meier curve from TROPIC for the first 2.1 months and a Weibull curve thereafter. The committee heard from the company that 2.1 months was chosen because the trial protocol was altered at this point to allow prophylaxis with granulocyte-colony stimulating factor, which reduced the number of deaths from neutropenia. The committee heard that the ERG preferred the piecewise approach rather than a single Weibull curve. The committee accepted that the choice of 2.1 months as the time point for changing distribution was rational and clinically plausible. The committee concluded that a piecewise curve was the most appropriate method for modelling overall survival with cabazitaxel, and it noted that the company had adopted this approach in its response to consultation.

4.13 The committee discussed the source of efficacy estimates in the model. It heard during consultation that, when comparing cabazitaxel with best supportive care, the company preferred to use data from TROPIC instead of the results of the network meta-analysis. The company reiterated its concerns about the network meta-analysis and stated that it did not consider it appropriate to use indirect data to compare cabazitaxel with best supportive care. The committee agreed that it was appropriate to use TROPIC data when comparing cabazitaxel with best supportive care

only. When comparing cabazitaxel with additional comparators (best supportive care, abiraterone and enzalutamide) the committee preferred a fully incremental analysis. The committee was aware that the only fully incremental analysis presented to the committee came from the ERG and used efficacy estimates from the random-effects network meta-analysis. The committee acknowledged that the network meta-analysis had many limitations, but it did include the TROPIC data and it permitted a fully incremental analysis. The committee concluded that the appropriate efficacy estimates came from:

- TROPIC (see table 1), for the base-case comparison of cabazitaxel with best supportive care
- the ERG's random-effects network analysis, for the scenario comparing cabazitaxel with best supportive care, abiraterone and enzalutamide.

4.14 The committee considered the utility values in the company's economic model. It was aware that the company had not collected quality-of-life data in TROPIC, so it had used EQ-5D utility values from an open-label single-arm study of 112 patients treated with cabazitaxel (the UK early access programme; see section 3.15). The committee heard from the ERG that people in the early access programme were less likely to have had multiple rounds of chemotherapy than patients in TROPIC (11% of patients in the UK early access programme had had at least 2 previous chemotherapy regimens compared with 31% in TROPIC). This meant that patients in TROPIC were likely to be more unwell than those in the early access programme. The committee was aware that the company had modelled a utility value of 0 for the final 3 months of life. It heard from the ERG that this reflected the assumed reduced quality of life towards the end of life for people with progressive disease. It heard from the ERG that the company applied this disutility to all people who died and not just to people who died with progressive disease. The committee was aware that the ERG preferred to remove the zero utility, and it noted that the company had done this in its analyses submitted in response to the appraisal consultation document. The committee acknowledged the limitations of using data from the UK early access programme but, in the absence of more robust evidence on health-related quality of life, it concluded that the company had used the best available data to estimate utility values.

4.15 The committee considered the cost of drugs in the model, noting that the company used the price for mitoxantrone from the British national formulary (BNF) in its original base case. The committee considered that prices from the electronic marketing information tool (eMIT) are more appropriate for generic drugs because they reflect the average price paid by NHS hospitals. The committee concluded that it preferred to consider the eMIT price for mitoxantrone, and noted that the company had done this in its analyses submitted in response to the appraisal consultation document.

4.16 The committee considered the method used by the company to model stopping treatment with cabazitaxel or mitoxantrone. It heard from the ERG that the company's original base case had incorrectly calculated drug costs and utility values for people who stopped treatment for reasons other than disease progression. The committee was aware that, to correct for this, the ERG's exploratory analysis did not permit stopping treatment for reasons other than disease progression, death, or reaching the maximum 10 cycles of treatment. The committee concluded that it preferred the ERG's approach to modelling stopping treatment and it noted that the company had adopted this approach in its response to the appraisal consultation document.

4.17 The committee considered the company's choice of costs for patients in the post-progression health state. It heard from the ERG that the company's original base case had used different estimates of cost for post-progression treatments, depending on whether patients had cabazitaxel or one of the comparator treatments at the start of the model. The ERG preferred to use the same post-progression treatment costs for cabazitaxel and each of the comparators. The committee was aware that the ERG used a UK clinical audit to estimate the costs of treatments after disease progression for cabazitaxel and all of the comparators. The committee noted that this reduced the incremental cost-effectiveness ratio (ICER) when comparing cabazitaxel with mitoxantrone. The committee concluded that the model should use UK clinical audit data to inform post-progression costs for all patients in the model and it noted that the company had done this in its response to the appraisal consultation document.

4.18 The committee considered the duration of treatment with cabazitaxel in the company's economic model, noting that the marketing authorisation does not specify a maximum number of cycles of treatment. The committee noted that the company had modelled a maximum of 10 cycles of treatment with cabazitaxel to reflect the maximum cycles permitted in TROPIC. The committee heard from the clinical experts that in clinical practice patients routinely have no more than 10 cycles. The clinical experts also advised that, if the committee were to recommend cabazitaxel, it would be appropriate to limit treatment to 10 cycles. The committee concluded that it was appropriate to limit cabazitaxel treatment to 10 cycles in the model.

4.19 The committee considered the company's rationale for not including wastage of cabazitaxel in its economic model. The committee was aware that the company had assumed wastage for mitoxantrone. It heard from the company that cabazitaxel is currently supplied in vials but, in the future, will be supplied to NHS trusts per milligram (see section 3.20). Under the new system, the NHS orders the number of milligrams of cabazitaxel needed per patient and the company facilitates the supply of cabazitaxel to the NHS hospital in a compounded intravenous-infusion bag for each patient. The company advised that in the new arrangement the NHS only pays for the milligrams used. The company provided confirmation from NHS England that it is appropriate to supply and purchase cabazitaxel in this way. The committee was aware of the ERG's analyses, showing that using per-milligram pricing of cabazitaxel decreased the ICER for cabazitaxel compared with mitoxantrone (see section 3.34). The committee was satisfied with the information provided by the company and concluded that the economic model should include per-milligram pricing of cabazitaxel, that is, the model should not include wastage. (After the guidance was published, the commercial access agreement was changed so that NHS trusts also have the option of purchasing cabazitaxel in vials; see section 2.3.)

4.20 The committee discussed the cost effectiveness of cabazitaxel, noting that the appropriate comparators depend on which treatments patients had had before (see section 4.3). It also noted that all analyses were limited because they did not include radium-223 dichloride, which it agreed was a relevant comparator for people with symptomatic bone

disease and no known visceral metastases.

4.21 For people who previously had abiraterone or enzalutamide, and for people whose disease is unsuitable for treatment with abiraterone or enzalutamide, the committee discussed the cost effectiveness of cabazitaxel compared with mitoxantrone (a proxy for best supportive care). The committee noted that the company's updated base-case ICER (assuming no wastage of cabazitaxel and including the updated confidential patient access scheme discount) was £45,159 per quality-adjusted life year (QALY) gained (incremental costs £10,682; incremental QALYs 0.237). The committee agreed that it preferred to use probabilistic rather than deterministic ICERs, because probabilistic analyses reflect some of the uncertainty around the mean health and cost inputs in the model. The probabilistic ICER was £45,982 per QALY gained. The committee noted that, in line with its preferences, the company's updated analysis included the following assumptions:

- used piecewise curve fitting for overall survival with cabazitaxel (see section 4.12)
- did not use a utility value of 0 for the final 3 months of life (see section 4.14)
- used the eMIT price for mitoxantrone (see section 4.15)
- did not model stopping treatment for reasons other than disease progression, death or reaching the maximum number of treatment cycles (see section 4.16)
- used a UK audit to inform post-progression resource use and treatment choice, for all patients in the model (see section 4.17)
- per-milligram pricing for cabazitaxel (that is, assume that it is purchased in pre-prepared intravenous infusion bags so there is no waste; see section 4.19). After the guidance was published, the commercial access agreement was changed so that NHS trusts also have the option of purchasing cabazitaxel in vials (see section 2.3).

The committee concluded that the most plausible ICER for cabazitaxel compared with best supportive care was £45,982 per QALY gained.

4.22 For people who have not previously had abiraterone or enzalutamide, the

committee discussed the cost effectiveness of cabazitaxel compared with abiraterone, enzalutamide and best supportive care. Enzalutamide has a confidential patient access scheme so NICE asked the ERG to perform a fully incremental analysis using the confidential discount. To avoid disclosing the confidential discount for enzalutamide, the detailed results of the analyses cannot be reported here. The analyses used the committee's preferred assumptions listed in section 4.21, except that overall survival with cabazitaxel was extrapolated with a Weibull curve because the ERG did not have full details of the committee's preferred piecewise curve. The committee considered the results of the ERG's incremental analysis which showed that cabazitaxel was extendedly dominated in both the deterministic and probabilistic analyses. An intervention is 'extendedly dominated' when it is more costly and less effective than a combination of 2 comparators. In this analysis, cabazitaxel was extendedly dominated by enzalutamide and best supportive care. The committee noted that abiraterone was also extendedly dominated by enzalutamide and best supportive care. The committee was aware that the results of the network meta-analysis, which informed the incremental analysis, were highly uncertain (see sections 4.9 and 4.10) and showed no statistically significant difference in overall survival or progression-free survival between the 3 treatments. It further noted that the ERG's analysis showed the total costs for cabazitaxel were lower than the total costs for abiraterone and enzalutamide. Although cabazitaxel also generated fewer total QALYs than abiraterone and enzalutamide the difference was small, especially compared with abiraterone. The committee noted that the analysis showed cabazitaxel is extendedly dominated by enzalutamide and best supportive care, but that this result was very uncertain because of the limitations of the network meta-analysis. The committee agreed that the relative cost effectiveness of the treatments was uncertain, but concluded that the analyses indicated cabazitaxel was likely to be less costly than enzalutamide and abiraterone.

4.23 The committee discussed the place of cabazitaxel in the treatment pathway, noting that it could potentially be used for people who previously had docetaxel followed by abiraterone, enzalutamide or radium-223 dichloride. The committee appreciated that it had not seen evidence that cabazitaxel was clinically effective at this point in the

pathway, and that the ERG's report noted there was 'no high-quality evidence from prospective controlled trials to guide optimum sequencing of these agents after docetaxel treatment'. It was also aware that the economic modelling assumed that cabazitaxel was used instead of abiraterone or enzalutamide, rather than after these drugs. Accordingly, the committee was unable to make a recommendation on the use of cabazitaxel for people who had docetaxel followed by abiraterone, enzalutamide or radium-223 dichloride.

End-of-life considerations

4.24 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

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

4.25 The committee considered the end-of-life criteria separately for 2 groups:

- people who had had abiraterone or enzalutamide before docetaxel (this group also includes people who had not had abiraterone or enzalutamide before, but for whom abiraterone and enzalutamide were not clinically suitable)

- people who had not previously had abiraterone or enzalutamide.

  The committee took this approach because the appropriate comparators depend on which treatments patients had had before (see section 4.1). The committee had concluded that radium-223 dichloride was a comparator (see section 4.2); accordingly, it would have preferred to assess whether cabazitaxel met the extension-to-life criterion relative to radium-223 dichloride. However, the committee was unable to do this because it had not been presented with analyses that compared the clinical effectiveness of cabazitaxel and radium-223 dichloride.

4.26 For people who had abiraterone or enzalutamide before docetaxel, and for people unsuitable for treatment with abiraterone or enzalutamide, the committee considered the short life-expectancy criterion. The committee noted a literature review by West et al. (2014) of life expectancy in people with hormone-relapsed prostate cancer that was presented by the company; it showed that for people treated with docetaxel the median overall survival was 19 months. The committee concluded that the short life-expectancy criterion was met. The committee noted the results of TROPIC, which showed that cabazitaxel extended survival compared with mitoxantrone by a mean of 4.1 months in the subgroup of people with an ECOG performance score of 0 or 1 who had had 225 mg/m^2 ormore of docetaxel. The committee was aware of the uncertainty surrounding this estimate because the company based it on extrapolated data and because the people in the trial had not been treated with abiraterone or enzalutamide before docetaxel (because the trial was done before these treatments were available). Nonetheless, the committee concluded that the extension-to-life criterion was met. The committee discussed the population size, noting the company's estimate that 1,690 people in England would be eligible for treatment with cabazitaxel. The committee concluded that all of the end-of-life criteria were met for people treated with enzalutamide or abiraterone before docetaxel and for people unsuitable for treatment with abiraterone or enzalutamide.

4.27 The committee considered each end-of-life criterion in turn for people who had not had enzalutamide or abiraterone. For the criterion of short life expectancy, the committee agreed that the relevant estimates of life expectancy came from people who had docetaxel and then abiraterone,

enzalutamide or – for selected patients – radium-223 dichloride because these treatments were part of established care in the NHS. It noted the ERG's evidence showing that median overall survival in the intervention group of the trials of abiraterone and enzalutamide after docetaxel was 15.8 and 18.4 months respectively. The committee concluded that, even though the mean life expectancy would exceed the median life expectancy, the short life-expectancy criterion was met. For the criterion of extension to life the committee noted that the network meta-analysis showed no statistically significant difference in overall survival between cabazitaxel, abiraterone and enzalutamide. It also heard from the company that there was no robust evidence that cabazitaxel offered an extension to life of at least 3 months compared with abiraterone and enzalutamide. Therefore the committee concluded that this criterion was not met. The committee further concluded that the small population size criterion was met based on its considerations in section 4.26. Overall, the committee concluded that cabazitaxel did not meet the criteria for end-of-life consideration, in the group of people not previously treated with abiraterone or enzalutamide.

4.28 The committee considered whether cabazitaxel is an innovative technology. It heard from the company that cabazitaxel has been specifically developed to address docetaxel resistance. However, the committee was not presented with a case, substantiated by data, showing that cabazitaxel treatment adds demonstrable and distinctive benefits of a substantial nature that have not already been adequately captured in the QALY measure.

4.29 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Committee conclusions

4.30 The committee considered the use of cabazitaxel in people with metastatic hormone-relapsed prostate cancer previously treated with docetaxel. The committee acknowledged that cabazitaxel was a clinically effective treatment that prolonged life and was valued by patients.

- For people who previously had abiraterone or enzalutamide, or whose disease was unsuitable for these treatments, the committee noted that the most plausible ICER for cabazitaxel compared with mitoxantrone (a proxy for best supportive care) was £45,982 per QALY gained. It further noted that, for this group of people, cabazitaxel met the criteria to consider it an 'end-of-life' treatment. The committee concluded that, given the greater weight for QALYs at the end of life, cabazitaxel could be considered a cost-effective use of NHS resources.

- For people who had not had abiraterone or enzalutamide, the committee noted that the cost-effectiveness results showed cabazitaxel was extendedly dominated by enzalutamide and best supportive care. It further noted that, for this group of people, cabazitaxel did not meet the criteria for consideration as an end-of-life treatment. However, the committee acknowledged that the incremental analysis was informed by the network meta-analysis, which was highly uncertain. It noted that the ERG's fully incremental analysis showed that cabazitaxel had lower total costs, and lower total QALYs, than abiraterone and enzalutamide. The committee expected that, given the choice between cabazitaxel, abiraterone and enzalutamide, many patients and clinicians would choose abiraterone or enzalutamide because they are associated with fewer adverse events than cabazitaxel and are taken orally. The committee was aware of responses to consultation, highlighting that prostate cancer is a heterogeneous disease and it is important to have a choice of treatments so that the most suitable one can be selected for each individual. Having considered all of the evidence carefully, the committee agreed that it was a good use of NHS resources to offer cabazitaxel as a treatment option for the group of patients with metastatic hormone-relapsed prostate cancer not previously treated with abiraterone or enzalutamide.

4.31 The committee agreed that it would have preferred to see analyses comparing cabazitaxel with radium-223 dichloride for the subgroup of people with symptomatic bone metastases and no known visceral

metastases after treatment with docetaxel. The committee heard from the company that only a small number of patients in TROPIC belonged to this subgroup, and it was not possible to extract data for these patients. The committee accepted that there was no evidence to inform a comparison of cabazitaxel with radium-223 dichloride, and radium-223 dichloride was a comparator for only a small subgroup. The committee was aware of advice from clinical and patient experts, and responses to consultation, stating that cabazitaxel and radium-223 dichloride work in different ways and the choice of treatment is informed by the characteristics of the individual's disease, clinical experience and patient preference. The committee considered the ERG's analysis comparing the costs of cabazitaxel and radium-223 dichloride (including the confidential patient access scheme discounts) and concluded that the costs of these drugs were not substantially different. Having considered all of the evidence carefully, the committee agreed that it was a good use of NHS resources to offer cabazitaxel as a treatment option.

4.32 The committee discussed the details of its recommendation. It agreed to recommend cabazitaxel only for people with an ECOG performance status of 0 or 1 who had previously had 225 mg/m^2 or more of docetaxel, because this reflects the subgroup from TROPIC that formed the basis of the evidence for clinical and cost effectiveness. The committee recommended cabazitaxel only if patients stop treatment when the disease progresses or after a maximum of 10 cycles (whichever happens first) because this reflects the use in the main trial and the assumptions in the economic model. The committee also recommended cabazitaxel only if trusts purchase compounded bags of cabazitaxel, because cabazitaxel would not be cost effective if the NHS were to purchase vials (because some cabazitaxel would be wasted, which increases the overall cost of treatment). (After the guidance was published, the commercial access agreement was changed so that NHS trusts also have the option of purchasing cabazitaxel in vials without incurring wastage costs; see section 2.3.) The committee concluded that cabazitaxel was both clinically and cost effective and could be recommended as a treatment option in the NHS, subject to the conditions in section 1.1.

4.33 The committee considered whether its recommendations were

associated with any potential issues related to equality. The committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

Summary of appraisal committee's key conclusions

Key conclusion

Cabazitaxel in combination with prednisone or prednisolone is recommended for treating hormone-relapsed metastatic prostate cancer previously treated with docetaxel, subject to the conditions in section 1.1.

In the relevant subgroup for the appraisal (that is, people with an ECOG performance score of 0 or 1 who had had 225 mg/m^2 or more of docetaxel), the committee concluded that cabazitaxel compared with mitoxantrone improves overall survival.

Despite concerns about the network meta-analysis, the committee concluded that cabazitaxel, abiraterone and enzalutamide all had a similar effect on overall survival.

The appropriate comparators depend on which treatments people have had before. For people who have previously had abiraterone or enzalutamide, or whose disease was unsuitable for these treatments, the most plausible incremental cost-effectiveness ratio (ICER) for cabazitaxel compared with mitoxantrone (a proxy for best supportive care) was £45,982 per quality-adjusted life year (QALY) gained. For this group of people, cabazitaxel met the criteria to consider it an 'end-of-life' treatment. The committee concluded that, given the greater weight for QALYs at the end of life, cabazitaxel could be considered a cost-effective use of NHS resources.

For people who had not had abiraterone or enzalutamide before, cabazitaxel was extendedly dominated by enzalutamide and best supportive care. However, this incremental analysis was informed by the network meta-analysis which was highly uncertain. Cabazitaxel had lower total costs, and lower total QALYs, than abiraterone and enzalutamide. The committee expected that, given the choice between cabazitaxel, abiraterone and enzalutamide, many patients and clinicians would choose abiraterone or enzalutamide because they are associated with fewer adverse events than cabazitaxel

and are taken orally. The committee was mindful of responses to consultation, advising that it is important to have a choice of treatments. Having considered all of the evidence carefully, the committee agreed that it was a good use of NHS resources to offer cabazitaxel as a treatment option for people with metastatic hormone-relapsed prostate cancer not previously treated with abiraterone or enzalutamide.

See sections 1.1, 4.8, 4.9, 4.3 and 4.30.

Current practice

Clinical need of patients, including the availability of alternative treatments

For people with metastatic hormone-relapsed prostate cancer treated with docetaxel, treatment options include: radium-223 dichloride (if they have symptomatic bone metastases and no known visceral metastases), cabazitaxel (currently available through the Cancer Drugs Fund), abiraterone, enzalutamide or best supportive care. Abiraterone or enzalutamide would be offered only to people who have not previously had abiraterone or enzalutamide.

See section 4.1.

The technology

Proposed benefits of the technology: how innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

The company stated that cabazitaxel has been developed to address docetaxel resistance. However, the committee was not presented with a case, substantiated by data, showing that the treatment adds demonstrable and distinctive benefits of a substantial nature that have not been adequately captured in the QALY measure.

See section 4.28.

What is the position of the treatment in the pathway of care for the condition?

For people who had abiraterone or enzalutamide before docetaxel, or whose disease is not

suitable for treatment with abiraterone or enzalutamide, the relevant comparators are best supportive care and radium-223 dichloride.

For people who have not had abiraterone or enzalutamide the relevant comparators are abiraterone, enzalutamide, radium-223 dichloride and best supportive care.

Regardless of treatment history, radium-223 dichloride is a comparator only for people with symptomatic bone metastases and no known visceral metastases.

See section 4.3.

Adverse reactions

The summary of product characteristics lists anaemia, leukopenia and neutropenia as the 3 most common adverse reactions.

See section 2.2.

Evidence for clinical effectiveness

Availability, nature and quality of evidence

TROPIC was a large, open-label, multinational, phase III, randomised trial comparing cabazitaxel plus prednisone or prednisolone with mitoxantrone plus prednisone or prednisolone.

See section 4.5.

Relevance to general clinical practice in the NHS

In the company's opinion, the population relevant to the appraisal was represented by the subgroup of patients in TROPIC with an eastern cooperative oncology group (ECOG) performance score of 0 or 1 who had had 225 mg/m^2 or more of docetaxel. The committee agreed that this subgroup is closest in characteristics to patients in England who would be offered cabazitaxel.

See section 4.6.

Uncertainties generated by the evidence

The committee noted that TROPIC was conducted before abiraterone and enzalutamide were available, and it questioned whether the trial results would generalise to NHS patients who had these treatments before docetaxel. The committee heard from clinical experts that, because patients in TROPIC were on their second or third line of treatment, they are similar to NHS patients who previously had abiraterone or enzalutamide. The Committee accepted this, but noted the uncertainty in generalising the magnitude of benefit observed in TROPIC to the population in England.

See section 4.5.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

The committee agreed that the relevant population for the appraisal is represented by the subgroup of people in TROPIC with an ECOG performance score of 0 or 1 who had had 225 mg/m^2 or more of docetaxel. Within this population, no subgroups were identified.

See section 4.6.

Estimate of the size of the clinical effectiveness including strength of supporting evidence

Median overall survival was 15.6 months in the cabazitaxel group and 13.4 months in the mitoxantrone group. The difference was 2.2 months (hazard ratio 0.69; 95% confidence interval 0.57 to 0.82; p<0.001).

The evidence review group's (ERG's) revised network meta-analysis (using a random-effects model) showed no significant difference between cabazitaxel, abiraterone and enzalutamide in overall survival or radiographic progression-free survival.

See sections 3.6 and 4.9.

How has the new clinical evidence that has emerged since NICE's 2012 technology appraisal guidance on cabazitaxel influenced the current recommendations?

For the present appraisal, the company's submission used an analysis of the TROPIC trial that was done in 2010. These results had been available for NICE's 2012 technology appraisal on cabazitaxel. The submission for the present appraisal included more mature data on health-related quality of life from the UK Early Access Programme; these data were not available for NICE's 2012 technology appraisal on cabazitaxel.

See sections 2.4, 3.4 and 4.14.

Evidence for cost effectiveness

Availability and nature of evidence

The company submitted a partitioned-survival model based on the subgroup of people in TROPIC with an ECOG performance score of 0 or 1 who had had 225 mg/m^2 or moreof docetaxel. The base-case model compared cabazitaxel with mitoxantrone (a proxy for best supportive care). In scenario analyses, the company compared cabazitaxel with abiraterone and, separately, with enzalutamide; these scenarios included the intention-to-treat analysis from TROPIC.

See section 4.11.

Uncertainties around and plausibility of assumptions and inputs in the economic model

The company's model excluded radium-223 dichloride, which was a relevant comparator.

The company did not include cabazitaxel wastage in its economic model. The committee heard from the company that cabazitaxel is currently supplied in vials but, in the future it will be supplied to NHS trusts per milligram (see section 3.20). Under the new system, the NHS orders the number of milligrams of cabazitaxel needed per patient and the company facilitates the supply of cabazitaxel in a compounded intravenous-infusion bag for each patient. The company advised that in the new arrangement the NHS only pays for the milligrams used. The company provided confirmation from NHS England that this supply process is appropriate. (After the guidance was published, the commercial access

agreement was changed so that NHS trusts also have the option of purchasing cabazitaxel in vials.)

There were additional uncertainties in the modelling which had a smaller impact on the ICER.

See sections 4.2, 4.11 to 4.19 and 2.3.

Incorporation of health-related quality-of-life benefits and utility values: have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

The company had not collected quality-of-life data in TROPIC, so it used EQ-5D utility values from an open-label single-arm study of cabazitaxel. The committee acknowledged the limitations to this 'UK early access programme' but, in the absence of more robust evidence on health-related quality of life, it concluded that the company had used the best available data to estimate utility values.

See section 4.14.

Are there specific groups of people for whom the technology is particularly cost effective?

No.

What are the key drivers of cost effectiveness?

Of all the scenario analyses presented by the ERG, including cabazitaxel wastage had the biggest impact on the ICER.

See section 3.34.

Most likely cost-effectiveness estimate (given as an ICER)

For people who previously had abiraterone or enzalutamide, and for people whose disease is unsuitable for treatment with abiraterone or enzalutamide, the company's updated base-case ICER (assuming no wastage of cabazitaxel and including the updated

confidential patient access scheme discount) was £45,159 per QALY gained (incremental costs £10,682; incremental QALYs 0.237). The probabilistic ICER was £45,982 per QALY gained.

For people who have not previously had abiraterone or enzalutamide, the ERG's incremental analysis showed that cabazitaxel was extendedly dominated by enzalutamide and best supportive care. This result was very uncertain because of the limitations of the network meta-analysis. The committee agreed that the relative cost effectiveness of the treatments was uncertain, but concluded that the analyses indicated cabazitaxel was likely to be less costly than enzalutamide and abiraterone.

See sections 4.21 and 4.22.

How has the new cost-effectiveness evidence that has emerged since the 2012 technology appraisal guidance influenced the current recommendations?

In NICE's 2012 technology appraisal of cabazitaxel the committee's most plausible ICER was above £87,500 per QALY gained. Since then, additional evidence has been published. The company has agreed a new patient access scheme and a new arrangement for supplying compounded intravenous-infusion bags of cabazitaxel to reduce wastage costs.

After the guidance was published, the commercial access agreement was changed so that NHS trusts also have the option of purchasing cabazitaxel in vials.

See sections 2.4, 4.19 and 2.3.

Additional factors taken into account

Patient access schemes (PPRS)

The PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

The company has agreed a simple discount patient access scheme with the Department of Health. In addition, the company has agreed a commercial access agreement with NHS England. Under the terms of this agreement, Sanofi facilitates the supply of cabazitaxel in 2 ways:

- In a pre-prepared (compounded) intravenous infusion bag containing the number of milligrams needed for each individual patient. This aspect of the arrangement was agreed before the guidance was published.
- In vials, at a reduced price with a discount reflecting the average cost of waste per patient from part-used vials (this discount is in addition to the patient access scheme). The company will provide a rebate to NHS England equivalent to the cost of compounding per patient. The arrangement for supplying cabazitaxel in vials was agreed in August 2016, after guidance publication.

See sections 4.29, 2.3, 3.20 and 5.4.

End of life considerations

For people who had abiraterone or enzalutamide before docetaxel, and for people unsuitable for treatment with abiraterone or enzalutamide, the committee concluded that the end-of-life criteria were met.

The committee considered the end-of-life criteria for people who had not had enzalutamide or abiraterone. For the criterion of extension to life the committee noted that the network meta-analysis showed no statistically significant difference in overall survival between cabazitaxel, abiraterone and enzalutamide. It also heard from the company that there was no robust evidence that cabazitaxel offered an extension to life of at least 3 months compared with abiraterone and enzalutamide. The committee concluded that cabazitaxel did not meet the end-of-life criteria in the group of people not previously treated with abiraterone or enzalutamide.

See sections 4.26 and 4.27.

Equalities considerations and social value judgements

The committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

See section 4.33.

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

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

5.3 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has metastatic hormone-relapsed prostate cancer and the doctor responsible for their care thinks that cabazitaxel is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 appraisal technology 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.

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.

Victoria Kelly
Technical Lead

Rosie Lovett
Technical Adviser

Jeremy Powell
Project Manager

Update information

August 2016: This guidance was re-issued after a change to the commercial arrangements in August 2016. This change did not affect cost effectiveness. The following sections of the guidance have been updated: recommendation 1.1; sections 2.3, 3.20, 3.34, 3.36, 4.19, 4.21, 4.32 and 5.4; and the table summarising the appraisal committee's key conclusions.

Minor changes since publication

November 2021: Guidance updated because the commercial arrangement has changed to a simple discount patient access scheme alone.

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