

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen

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

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see the [project documents](#)) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

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

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 22nd February 2016

Second Appraisal Committee meeting: 2nd March 2016

Details of membership of the Appraisal Committee are given in the project documents.

1 Recommendations

- 1.1 Cabazitaxel in combination with prednisone or prednisolone is not recommended within its marketing authorisation for treating hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen.
- 1.2 People whose treatment with cabazitaxel was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Cabazitaxel (Jevtana, Sanofi) is an antineoplastic drug in a class of drugs known as taxanes, which include 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 £3696 per vial (excluding VAT; 'British national formulary' [BNF edition 70]). The average cost of 1 cycle (administered as a 1-hour intravenous infusion every 3 weeks) of

treatment is £3696 excluding VAT. The summary of product characteristics does not limit the number of cycles; the median number of cycles was 6 in the key clinical trial which capped cycles at 10.

- 2.4 The company has agreed a patient access scheme with the Department of Health. If cabazitaxel had been recommended, this scheme would provide a simple discount to the list price of cabazitaxel with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.
- 2.5 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 previously treated with a docetaxel-containing regimen. Patients aged 18 years or older were randomised 1:1 to have either:

- 25 mg/m² of cabazitaxel intravenously every 3 weeks in combination with 10 mg prednisone (or prednisolone) orally for a maximum of 10 cycles or
- 12 mg/m² of mitoxantrone intravenously every 3 weeks with 10 mg prednisone (or prednisolone) orally for a maximum of 10 cycles.

The investigators capped the treatment for both drugs at a maximum of 10 cycles to minimise the risk of mitoxantrone-induced cardiac toxicity.

- 3.2 The company stated that mitoxantrone was equivalent to best supportive care. To support this statement, it referred to an article 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. In the absence of confirmation of death, 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 progression, pain progression, or death from any cause.

Statistical analysis

- 3.4 The company presented an updated analysis of TROPIC which 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) and

the per-protocol analysis for adverse events included only those patients who had at least 1 dose of the study treatment (n=742).

Baseline characteristics

3.5 In the intention-to-treat analysis, 378 patients were randomised to have cabazitaxel and 377 patients were randomised to have mitoxantrone. The median age of patients in the cabazitaxel group was 68 years and in the mitoxantrone group, 67 years. The percentage of patients with ECOG performance status of 0 or 1 was 92.6% in the cabazitaxel group and 91.2% in the mitoxantrone group. In the cabazitaxel group 71% of patients were previously treated with chemotherapy; this was 69% in the mitoxantrone group. None of the patients who entered the trial had previous treatment with enzalutamide or abiraterone.

Results of TROPIC

3.6 In the intention-to-treat analysis, median overall survival was 15.08 months (95% confidence interval [CI]: 13.96 to 16.49) in the cabazitaxel group and 12.78 months (95% CI: 11.53 to 13.73) in the mitoxantrone group. The difference was 2.3 months. The risk of death was statistically significantly lower in the cabazitaxel group than in the mitoxantrone group (hazard ratio [HR] 0.72; 95% CI 0.61 to 0.84; $p=0.0002$).

Subgroup of patients with an ECOG performance status of 0–1 who had had at least 225 mg/m² or more of docetaxel

3.7 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 ECOG performance status of 0–1 (lower scores reflect better function) who had had at least 225 mg/m² 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 the intention-to-treat population of 755 patients.

- 3.8 In the subgroup analysis median overall survival was 15.6 months (95% 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 (HR 0.69; 95% CI 0.57 to 0.82; $p < 0.001$).
- 3.9 In the subgroup analysis, progression-free survival was 2.76 months (95% CI: 2.43 to 3.12) in the cabazitaxel group and 1.41 months (95% CI: 1.35 to 1.84) in the mitoxantrone group. The difference was 1.41 months. The risk of progression was statistically significantly lower in the cabazitaxel group than in the mitoxantrone group (HR 0.76; 95% CI 0.65 to 0.89; $p = 0.001$).

Network meta-analysis

- 3.10 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 prednisone plus placebo.
- 3.11 The company noted that the definition of progression in TROPIC is 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.

- 3.12 The results of 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.
- 3.13 The company advised that its network meta-analysis assumed that the trial populations, and control-group treatments, are 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

- 3.14 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 3.7) who had an ECOG performance status of 0–1 and previously had at least 225 mg/m² of docetaxel.
- 3.15 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 (using abiraterone or enzalutamide after docetaxel) the company compared cabazitaxel with abiraterone and cabazitaxel with enzalutamide.
- 3.16 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/m² every 3 weeks in combination with 10 mg/day of oral prednisolone.
- Cabazitaxel, 25 mg/m² every 3 weeks in combination with 10 mg/day of oral prednisolone.

Clinical parameters

3.17 To model time to disease progression and survival times for the subgroup (patients in TROPIC with an ECOG performance status of 0–1 and previously treated with at least 225 mg/m² of docetaxel), the company used a log-normal curve for time to progression and a Weibull curve for survival times. The company chose the parametric distributions based on statistical criteria and visual inspection. The company used the same parametric distributions for both the cabazitaxel and mitoxantrone arms of the model.

Health-related quality of life

3.18 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, 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.

3.19 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

3.20 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

- 3.21 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.
- 3.22 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). Cabazitaxel and mitoxantrone come in vials and a patient's dosage depends on body surface area. The company assumed that the mean body surface area was 1.9 m² (based on clinical opinion; the mean body surface area observed in TROPIC was 2.01 m²). It also assumed there was no drug wastage of cabazitaxel. In response to a clarification question from NICE before the Committee meeting, the company explained that it believes no cabazitaxel will be

wasted because 'patient-specific doses in the form of compounded IV [intravenous] bags of cabazitaxel can be supplied direct to NHS hospitals'.

- 3.23 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.

Company's base-case results and sensitivity analyses

- 3.24 The company's deterministic base case estimated that cabazitaxel (with patient access scheme discount) compared with mitoxantrone resulted in an incremental cost-effectiveness ratio (ICER) of £49,327 per quality-adjusted life year (QALY) gained (incremental costs £11,450, incremental QALYs 0.232). The probabilistic ICER, presented by the ERG, was £50,682 per QALY gained (incremental costs £11,829; incremental QALYs 0.233).
- 3.25 Following the factual accuracy check that preceded the Committee meeting, the company noted that its original base case assumed no wastage of mitoxantrone. This was an error, so the company submitted a new scenario assuming wastage of mitoxantrone but not cabazitaxel. The deterministic ICER reduced from £49,327 to £48,256 per QALY gained (incremental costs £11,202; incremental QALYs 0.23).
- 3.26 In its deterministic sensitivity analyses, the company varied the utility values, time horizon, discount rates, method for extrapolating overall survival data, and the percentage of patients who have best supportive care after disease progression. The company stated that the model was most sensitive to the utility value for the progressive-disease health state.

Company's scenario analyses

- 3.27 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 cabazitaxel are offered by their respective companies to the NHS with discounts, these are confidential and not known to Sanofi. These scenario analyses used the intention-to-treat population of TROPIC. The company assumed that patients take enzalutamide and abiraterone until disease progression or death, whereas patients use cabazitaxel for up to 10 cycles.

- 3.28 The company took the hazard ratios reflecting the effectiveness of cabazitaxel compared with abiraterone or enzalutamide 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.
- 3.29 Because of the confidential discounts the ERG recalculated the company's scenario analyses using the patient access scheme discounts for cabazitaxel, enzalutamide and abiraterone.

Evidence Review Group Key Issues

Network meta-analysis

- 3.30 The ERG agreed with the company's concerns about the assumptions made in the company's network meta-analysis (see section 3.13). 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 significant difference between any of the treatments in either overall survival or radiographic progression-free survival.

3.31 The ERG also noted that the company used hazard ratios for the 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.

Economic model

3.32 The ERG noted that in NICE's 2012 technology appraisal guidance on [cabazitaxel](#) the Committee preferred the piecewise approach for extrapolating TROPIC trial data to other 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 therefore 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. This scenario reduced the company's base-case ICER comparing cabazitaxel with mitoxantrone from £49,327 to £48,543 per QALY gained. 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. However, the ERG could not use the same piecewise curves in its exploratory analysis because the company had not provided full details of its approach.

Following the factual accuracy check that preceded the Committee

meeting, the company submitted a new analysis using the ERG's preferred assumptions (see section 3.39) and using the piecewise curve. The results reduced the ERG's exploratory ICER (assuming that no cabazitaxel is wasted) from £51,308 to £50,195 per QALY gained.

3.33 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 base-case deterministic ICER comparing cabazitaxel with mitoxantrone from £49,327 to £50,370 per QALY gained.

3.34 The ERG advised that the modelled utility value for progressive disease was uncertain because it was based on data from only 25 people. Based on sensitivity analyses, the ERG advised that the model was sensitive to the utility value for the progressed disease health state. The ERG concluded that, because there was limited evidence to inform the utility value for this health state, the results of the model were uncertain.

3.35 The company included a disutility in the 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. Removing this disutility increased the ICER comparing cabazitaxel with mitoxantrone from £49,327 to £49,691 per QALY gained.

3.36 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 increased the ICER comparing cabazitaxel with mitoxantrone from £49,327 to £51,675 per QALY gained.

3.37 The ERG highlighted that 3 different estimates were available for the costs of treatment in the progressed-disease health state. The most expensive estimate (£1767.02) was based on the mitoxantrone group in the TROPIC trial. The least expensive estimate (£1192.81) was based on the cabazitaxel group in TROPIC. The third estimate was from a UK clinical audit (£1364.07). The company's model 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 reduced the ICER comparing cabazitaxel with mitoxantrone from £49,327 to £48,908 per QALY gained.

3.38 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. The ERG did an analysis which

assumed that a cycle of treatment with cabazitaxel would need the cost of a vial of cabazitaxel. This increased the ICER comparing cabazitaxel with mitoxantrone (the results are confidential and cannot be reported here).

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

- Do not model stopping treatment for reasons other than disease progression.
- 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 to model the costs of post-progression treatment and the proportion of patients who have best supportive care.

3.40 The ERG presented 2 exploratory base cases.

- When assuming that cabazitaxel is wasted (the ERG's preferred assumption), the ICER for cabazitaxel compared with mitoxantrone was over £55,000 per QALY gained (the precise results are confidential and cannot be reported here).
- Assuming no cabazitaxel is wasted, the ERG's deterministic ICER comparing cabazitaxel with mitoxantrone was £51,308 per QALY gained (incremental costs £11,823; incremental QALYs 0.23). The probabilistic ICER was £51,849 per QALY gained (incremental costs £15,064; incremental QALYs 0.23).

Of all the changes to the model made by the ERG, cabazitaxel wastage had the biggest impact on the ICER.

3.41 The ERG also did deterministic sensitivity analyses showing that its own estimates of cost effectiveness were sensitive to the method for extrapolating clinical effectiveness data and the utility value for progressive disease.

Cabazitaxel compared with enzalutamide, abiraterone and best supportive care

- 3.42 The ERG did a fully incremental analysis comparing cabazitaxel with enzalutamide, abiraterone and best supportive care (represented by mitoxantrone in TROPIC). The ERG used its random-effects network meta-analysis (see section 3.30) 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).
- 3.43 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. 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.
- 3.44 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 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 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 population) 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.

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, best supportive care, and abiraterone (currently available through the Cancer Drugs Fund). 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 patients in the NHS if cabazitaxel were not available). The Committee discussed radium-223 dichloride which was listed in the scope. It heard from the clinical experts at the

Committee meeting 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 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. The Committee noted that radium-223 dichloride had been widely used through the Cancer Drugs Fund and was now recommended in a NICE [Final Appraisal Determination](#) for people with symptomatic bone metastases and no known visceral metastases. 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. The Committee discussed additional comparators, noting that abiraterone or enzalutamide were options only for patients who had not taken either of these drugs previously. The Committee concluded that:

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

4.3 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 give an extension to life, even if short, and the hope that this offers.

The Committee also heard that patients want treatments that improve quality of life. The Committee further 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

- 4.4 The Committee considered the clinical-effectiveness evidence submitted by the company (see section 3.6). 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 previous treatments received by patients in TROPIC 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 accepted this, but noted the uncertainty in generalising the magnitude of benefit observed in TROPIC to the population in England. Overall, it concluded that TROPIC provided estimates of efficacy that were generalisable to the NHS in England.
- 4.5 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/m² 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/m² or more of docetaxel is the minimum dose used in clinical practice. The Committee concluded that this subgroup is closest in characteristics to the patients who would be offered cabazitaxel through the NHS in England.

4.6 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 UK marketing authorisation for treating metastatic hormone-relapsed prostate cancer, as the comparator in the pivotal trial. The clinical experts noted 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 the results of the Green et al. (2015) study (see section 3.2) that showed no statistically significant difference in overall survival between mitoxantrone and prednisone. 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.

4.7 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/m² or more of docetaxel. The results showed that cabazitaxel prolonged survival and progression-free survival compared with mitoxantrone (see section 3.8 and 3.9). The Committee was aware that this analysis was done in 2010 when 585 deaths had occurred, and that these results had been available to the Committee for NICE's 2012 technology appraisal of [cabazitaxel](#). The Committee recognised that

5 years had passed since this analysis was done. 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/m² 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.

- 4.8 The Committee considered the company's network meta-analysis comparing cabazitaxel with best supportive care, abiraterone and enzalutamide. The results showed that cabazitaxel improved overall survival and radiographic progression-free survival compared with best supportive care (section 3.12). It also showed that radiographic progression-free survival was shorter with cabazitaxel than with enzalutamide. 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 not be robust because of potential differences between trials in populations and control treatments.

- The company used a fixed-effects model; the ERG advised 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 this assumption was violated in the abiraterone trial (see section 3.31).

4.9 The Committee considered the results of the ERG's revised network meta-analysis using a random-effects model (see 3.30). It showed no difference between the 3 treatments in overall survival or radiographic progression-free survival. The Committee noted that there was a lack of 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. Overall, the Committee agreed that there were problems with the network meta-analysis and the results were highly uncertain. However, the Committee accepted that in the absence of more robust evidence, the random-effects network meta-analysis gave the best estimate of the effectiveness of cabazitaxel compared with abiraterone and enzalutamide. The Committee concluded that cabazitaxel, abiraterone and enzalutamide all had a similar effect on overall survival and radiographic progression-free survival.

Cost effectiveness

4.10 The Committee considered the company's economic model, noting that it was a partitioned-survival model (that is, the transitions between health states are 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/m² 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 the intention-to-treat population of TROPIC because this was the population in the network meta-analysis. The Committee concluded that the company's model was acceptable, but it should have included radium-223 as a comparator.

- 4.11 The Committee considered the estimates of overall survival in the company's model (see section 3.17), noting that in its 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 affect the predicted survival times if using a single extrapolation curve. The Committee was aware that, in response to a clarification question before the Committee meeting, the company presented a scenario analysis that used a piecewise extrapolation for cabazitaxel (see section 3.32). The piecewise extrapolation used the observed Kaplan–Meier curve from TROPIC for the first 2.1 months and a Weibull curve thereafter. This scenario reduced the company's deterministic base-case incremental cost-effectiveness ratio (ICER) from £49,327 to £48,543 per quality-adjusted life year (QALY) gained. The Committee heard from the company that 2.1 months was chosen because the trial protocol was altered at this point to allow granulocyte-colony stimulating factor prophylaxis, which reduced the number of deaths from neutropenia. The Committee accepted that the choice of 2.1 months as the time point for changing distribution was rational and clinically plausible. The Committee heard that the ERG preferred the piecewise approach rather than a single

Weibull curve. The Committee concluded that a piecewise curve was the most appropriate method for modelling overall survival with cabazitaxel.

4.12 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 3.18). 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) which means 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; however, the Committee noted that this minimally affected the ICER. The Committee acknowledged the limitations to 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.

4.13 The Committee considered the cost of drugs in the model, noting that the company used the British national formulary (BNF) price for mitoxantrone. The Committee considered that electronic marketing information tool (eMIT) prices 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 it noted that the ERG's exploratory analyses had done this.

- 4.14 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 model 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.
- 4.15 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 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 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.
- 4.16 The Committee considered the duration of treatment with cabazitaxel in the company's economic model. The Committee noted that the company had modelled a maximum of 10 cycles of treatment with cabazitaxel. It heard from the company that in TROPIC the median number of cycles administered was 6. The Committee heard from the clinical experts that in clinical practice patients routinely receive no more than 10 cycles. The Committee was aware that the marketing authorisation for cabazitaxel

does not specify a maximum number of cycles of treatment. The Committee accepted the evidence from clinical experts and recognised that the trial median treatment duration is 6 cycles, but concluded that uncertainty in this estimate increased the uncertainty in the model results.

- 4.17 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 hospitals per milligram. Under the proposed system, the NHS would order the number of milligrams of cabazitaxel needed per patient and the company would make this available to the NHS hospital in a compounded intravenous bag for each patient. The company advised that the proposed arrangement means that cabazitaxel would be provided so that only the milligrams used would be invoiced to the NHS provider. The Committee asked the company to provide further details of the scheme and to confirm that NHS England believed it appropriate to supply and purchase cabazitaxel in this way. The Committee concluded that, to reflect current practice, the economic model should include wastage of cabazitaxel and mitoxantrone.
- 4.18 The Committee discussed the cost effectiveness of cabazitaxel, noting that the appropriate comparators depend on which treatments patients had had before (see section 4.2). It also noted that all analyses were limited because they did not include radium-223 dichloride, which it agreed was a relevant comparator.
- 4.19 For people who previously had abiraterone or enzalutamide, the Committee discussed the cost effectiveness of cabazitaxel (including the confidential patient access scheme discount) compared with mitoxantrone (a proxy for best supportive care). The Committee noted that the company's base-case probabilistic ICER (assuming no wastage of cabazitaxel) was £50,700 per QALY gained. The Committee agreed that it

preferred to use probabilistic rather than deterministic ICERs, because probabilistic analyses reflect the uncertainty around the mean health and cost inputs in the model. The Committee concluded that it preferred the ERG's probabilistic exploratory analysis because it:

- did not use a utility value of 0 for the final 3 months of life (see section 4.12)
- used the eMIT price for mitoxantrone (see section 4.13)
- did not model stopping treatment for reasons other than disease progression, death or reaching the maximum number of treatment cycles (see section 4.14)
- used a UK audit to inform post-progression resource use and treatment choice, for all patients in the model (see section 4.15).

The Committee noted that the ERG's probabilistic analysis, assuming cabazitaxel waste, gave an ICER for cabazitaxel compared with mitoxantrone of over £55,000 per QALY gained (the results are confidential and cannot be reported here). The Committee noted that the ERG's analysis used a Weibull curve to extrapolate overall survival with cabazitaxel, whereas the Committee preferred a piecewise analysis (see section 4.11). The Committee was aware that one of the company's analyses combined piecewise curve fitting with the ERG's assumptions (see section 3.32), and it noted that this slightly decreased the deterministic ICER, however this analysis did not include cabazitaxel waste, which is the Committee's preferred assumption. The Committee concluded that the most plausible ICER for cabazitaxel compared with mitoxantrone, including cabazitaxel waste and the ERG's assumptions, was over £55,000 per QALY gained. It further concluded that, if the company could guarantee cabazitaxel would be supplied without wastage, the most plausible ICER would be £51,800 per QALY gained.

4.20 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. Abiraterone and enzalutamide both have confidential patient access schemes and, to avoid disclosing the level of discount, the detailed results of these analyses cannot be reported here. The Committee was aware that the company had submitted scenario analyses comparing cabazitaxel with abiraterone and, separately, enzalutamide. However, the Committee preferred to use the ERG's analysis because it: included best supportive care as a comparator; was fully incremental; used a random-effects network meta-analysis; and included the Committee's preferred assumptions. The Committee considered the results of the ERG's incremental analysis that showed that cabazitaxel was extendedly dominated by enzalutamide 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 acknowledged the limitations of the network meta-analysis but concluded that cabazitaxel was not a cost-effective use of NHS resources for people not previously treated with enzalutamide or abiraterone.

End-of-life considerations

4.21 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.

4.22 The Committee considered the end-of-life criteria separately for 2 groups: people who had had abiraterone or enzalutamide before docetaxel, and 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.

4.23 For people who had abiraterone or enzalutamide before docetaxel 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/m² or more 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 1690 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.

- 4.24 The Committee considered each end-of-life criterion in turn for people who had not had enzalutamide or abiraterone. For the short life-expectancy criterion, 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 as 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 be longer, the short life-expectancy criterion was met. For the extension-to-life criterion it 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 4.23. 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.

- 4.25 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 the treatment adds demonstrable and distinctive benefits of a substantial nature that have not already been adequately captured in the QALY measure.
- 4.26 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 about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Committee conclusions

- 4.27 The Committee considered the use of cabazitaxel in people with metastatic hormone-relapsed prostate cancer who have been previously treated with abiraterone or enzalutamide and then docetaxel. The Committee acknowledged that cabazitaxel was a clinically effective treatment that prolonged life and was valued by patients. It noted that this population could be considered under the supplementary advice to the Committee on end-of-life treatments. The Committee was aware that the most plausible ICER for the comparison with mitoxantrone was over £55,000 per QALY gained. The Committee concluded that, even when

applying the maximum weighting to the QALY that is possible under the end-of-life considerations, the ICER for cabazitaxel did not fall within the range representative of a cost-effective treatment. The Committee further concluded that even if the company supplied cabazitaxel with no waste, the ICER would still fall outside the range representative of a cost-effective treatment.

4.28 The Committee considered the use of cabazitaxel in people with metastatic hormone-relapsed prostate cancer who have not been previously treated with abiraterone or enzalutamide. It noted that this population could not be considered under the supplementary advice to the Committee on end-of-life treatments. The Committee noted that cabazitaxel was extendedly dominated by enzalutamide and best supportive care. The Committee concluded that cabazitaxel did not represent a cost-effective use of NHS resources.

4.29 The Committee concluded that cabazitaxel in combination with prednisone or prednisolone is not recommended within its marketing authorisation for treating hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title: Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen	Section
Key conclusion		
Cabazitaxel in combination with prednisone or prednisolone is not recommended for treating hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen.		1.1
In the relevant subgroup for the appraisal (that is, people with an		4.7

<p>ECOG performance score of 0 or 1 who had had 225 mg/m² or more of docetaxel), the Committee concluded that cabazitaxel compared with mitoxantrone improves overall survival.</p>	
<p>Despite concerns about the network meta-analysis, the Committee concluded that cabazitaxel, abiraterone and enzalutamide all had a similar effect on overall survival.</p>	4.9
<p>The Committee considered the use of cabazitaxel in people with metastatic hormone-relapsed prostate cancer who have been previously treated with abiraterone or enzalutamide and then docetaxel. The most plausible ICER for the comparison with mitoxantrone was over £55,000 per QALY gained (the results are confidential and cannot be reported here). The Committee concluded that, even when applying the maximum weighting to the QALY that is possible under the end-of-life considerations, the ICER for cabazitaxel did not fall within the range representative of a cost-effective treatment.</p>	4.27
<p>The Committee considered the use of cabazitaxel in people with metastatic hormone-relapsed prostate cancer who have not been previously treated with abiraterone or enzalutamide. The Committee noted that cabazitaxel was extendedly dominated by enzalutamide and best supportive care. The Committee concluded that cabazitaxel did not represent a cost-effective use of NHS resources.</p>	4.28
<p>Current practice</p>	

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>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</p>	<p>4.1</p>
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The company stated that cabazitaxel has been specifically 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 already been adequately captured in the QALY measure.</p>	<p>4.25</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>For people who had treatment with abiraterone or enzalutamide before docetaxel, the relevant comparators for cabazitaxel are radium-223 dichloride and best supportive care.</p> <p>For people who have not had treatment with abiraterone or enzalutamide, the relevant comparators for cabazitaxel are abiraterone, enzalutamide, radium-223 dichloride and best supportive care.</p>	<p>4.2</p>
<p>Adverse reactions</p>	<p>The summary of product characteristics lists anaemia, leukopenia and neutropenia as the 3 most common adverse reactions.</p>	<p>2.2</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>TROPIC was a large, open-label, multinational, phase III, randomised trial comparing cabazitaxel plus prednisone or prednisolone with mitoxantrone plus prednisone or prednisolone.</p>	<p>4.4</p>

<p>Relevance to general clinical practice in the NHS</p>	<p>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/m² or more of docetaxel. The Committee agreed that this subgroup is closest in characteristics to patients in England who would be offered cabazitaxel.</p>	<p>4.5</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee noted that TROPIC was conducted before abiraterone and enzalutamide were available in clinical practice in the NHS, 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.</p>	<p>4.4</p>

	<p>The Committee considered the company’s network meta-analysis comparing cabazitaxel with best supportive care, abiraterone and enzalutamide. It noted the critique by the company and the ERG and concluded that the network meta-analysis may not be robust because of potential differences between trials in populations and control treatments, and because the proportional hazards assumption was violated.</p>	<p>4.8, 4.9</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>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/m² or more of docetaxel. Within this population, no subgroups were identified.</p>	<p>4.5</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>Median overall survival was 15.6 months (95% 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, hazard ratio [HR] 0.69; 95% CI 0.57 to 0.82; p<0.001).</p> <p>The 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.</p>	<p>3.8</p> <p>4.9</p>

<p>How has the new clinical evidence that has emerged since the original appraisal TA255 influenced the current recommendations?</p>	<p>For the present appraisal, the company's submission used an analysis of the TROPIC trial that was done in 2010 when 585 deaths had occurred. These results had been available to the Committee for TA255. 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 TA255.</p>	<p>2.5, 3.4, 4.12</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company's economic model was 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/m² or more of 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 population of TROPIC.</p>	<p>4.10</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The company's model excluded radium-223, which was a relevant comparator.</p> <p>The company did not include cabazitaxel drug wastage in its economic model because it has proposed a new system in which the drug will be supplied to NHS hospitals per milligram. In the proposed system the NHS would order the number of milligrams of cabazitaxel needed per patient and the company would make this available to the NHS hospital in a compounded intravenous bag for each patient. The Committee asked the company to provide further details of the scheme. The Committee concluded that to reflect current practice, the economic model should include wastage of cabazitaxel.</p> <p>There were additional uncertainties in the modelling which had a smaller impact on the ICER.</p>	<p>4.2, 4.10</p> <p>4.17</p> <p>4.11- 4.17</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p>	<p>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.</p>	<p>4.12</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>Of all the changes to the model made by the ERG, cabazitaxel wastage had the biggest impact on the ICER.</p>	<p>3.40</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>For people who previously had abiraterone or enzalutamide the Committee concluded that the most plausible ICER for cabazitaxel compared with mitoxantrone, including cabazitaxel waste and the ERG's assumptions, was over £55,000 per QALY gained (the results are confidential and cannot be reported here). It further concluded that, if the company provided cabazitaxel without waste, the most plausible ICER would be £51,800 per QALY gained.</p> <p>For people who have not previously had abiraterone or enzalutamide, cabazitaxel was extendedly dominated by best supportive care and enzalutamide.</p>	<p>4.19</p> <p>4.18</p>
<p>How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA255) influenced the current recommendations?</p>	<p>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 and the company has agreed a new patient access scheme.</p>	<p>2.5</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>The PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.</p>	<p>4.26</p>

<p>End-of-life considerations</p>	<p>The Committee considered the end-of-life criteria separately for the 2 groups outlined in section 4.2. The Committee could not assess whether cabazitaxel met the extension to life criterion relative to radium-223 dichloride because it had not been presented with analyses that compared the clinical effectiveness of cabazitaxel and radium-223 dichloride.</p>	<p>4.22</p>
	<p>For people who had abiraterone or enzalutamide before docetaxel the Committee concluded that the end-of-life criteria were met.</p>	<p>4.23</p>
	<p>For people who had not had enzalutamide or abiraterone before, the short life expectancy criterion and small population size criterion were met. For the extension-to-life criterion, the network meta-analysis showed no statistically significant difference in overall survival between cabazitaxel, abiraterone and enzalutamide. In addition the company stated 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 and that cabazitaxel did not meet the criteria for end-of-life consideration, in the group of people not previously treated with abiraterone or enzalutamide.</p>	<p>4.24</p>

<p>Equalities considerations and social value judgements</p>	<p>No equality issues were raised.</p>	
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5 Related NICE guidance

Further information is available on the [NICE website](#).

Published

- [Prostate cancer: diagnosis and treatment](#). NICE clinical guideline 175 (2014).
- [Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen](#). NICE technology appraisal guidance 316 (2014).
- [Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen](#). NICE technology appraisal guidance 259 (2012).
- [Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen](#). NICE technology appraisal guidance 255 (2012).
- [Docetaxel for the treatment of hormone-refractory metastatic prostate cancer](#). NICE technology appraisal 101 (2006).

Under development

- Abiraterone acetate for the treatment of metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. NICE technology appraisal guidance. The date of publication is to be confirmed.
- Enzalutamide for the treatment of metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. NICE technology appraisal guidance (publication expected January 2016)

- Radium-223 dichloride for treating metastatic hormone-relapsed prostate cancer with bone metastases. NICE technology appraisal guidance (publication expected January 2016)

6 Proposed date for review of guidance

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

Amanda Adler
Chair, Appraisal Committee
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