

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE**

Final appraisal determination

**Cabazitaxel for hormone-refractory
metastatic prostate cancer previously
treated with a
docetaxel-containing regimen**

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 Cabazitaxel in combination with prednisone or prednisolone is not recommended for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
- 1.2 People currently receiving cabazitaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Cabazitaxel (Jevtana, Sanofi) is an antineoplastic drug that belongs to a class of drugs known as taxanes. It works by disrupting the

microtubular network that is essential for mitotic and interphase cellular functions, and therefore causes inhibition of cell division and cell death. It is administered by intravenous infusion.

- 2.2 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'.
- 2.3 The most commonly occurring adverse reactions are related to bone marrow suppression which include anaemia, leukopenia, neutropenia, and thrombocytopenia and gastrointestinal events such as diarrhoea. Other very common adverse reactions (reported in 10% or more patients receiving cabazitaxel in the TROPIC trial) include fatigue, nausea, vomiting, constipation, asthenia, haematuria, back pain, anorexia, pyrexia, dyspnoea, abdominal pain, dysgeusia, cough, arthralgia, and alopecia. Other common adverse reactions (reported in 1–10% of patients receiving cabazitaxel in the TROPIC trial) include peripheral oedema, decrease in body weight, peripheral neuropathy, dizziness, pain in extremities, and febrile neutropenia. Premedication with an antihistamine, a corticosteroid and an H₂ antagonist is indicated. Contraindications include hypersensitivity to taxanes, a neutrophil count of less than 1500/mm³ and hepatic impairment. For full details of side effects and contraindications, see the summary of product characteristics (SPC).
- 2.4 The cost of a 1.5 ml vial containing 60 mg cabazitaxel (40 mg/ml) is £3696 (excluding VAT; 'British national formulary' [BNF] edition 62). The average cost of one cycle of treatment is £3696 excluding VAT. The median number of cycles was six in the key clinical trial.

Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of cabazitaxel and a review of this submission by the Evidence Review Group (ERG; appendix B).

- 3.1 The manufacturer's submission presented evidence on clinical effectiveness from one phase III, randomised, open-label, multicentre trial (TROPIC) in men aged over 18 years with hormone-refractory metastatic prostate cancer, with an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and with evidence of disease progression during or after completion of docetaxel-containing treatment. Patients were randomised to cabazitaxel plus either prednisone or prednisolone, or to mitoxantrone plus either prednisone or prednisolone. Patients who were receiving therapy with luteinizing hormone-releasing hormone agonists were allowed to continue this. Patients in the cabazitaxel arm received premedication comprising an antihistamine, an anti-emetic, a corticosteroid and an H2-blocker (except cimetidine). Patients in the mitoxantrone arm received premedication with an anti-emetic only, with other premedications discretionary. Prophylactic treatment with granulocyte-stimulating factors was not permitted during the first cycle, but thereafter was allowed at the physician's discretion and was compulsory for patients with prolonged neutropenia (≥ 7 days) or neutropenia complicated by fever or infection.
- 3.2 Overall survival was the primary outcome of the TROPIC trial. Secondary outcomes included progression-free survival (with progression defined as a rise in prostate-specific antigen [PSA]

level, tumour progression, pain progression or death), time to tumour progression, overall response rate, PSA progression, pain response measures and safety.

- 3.3 The manufacturer provided the published results for the whole trial population after a median follow-up of 12.8 months, at which point 513 deaths had occurred. Final analyses had been planned after 511 deaths. An updated analysis was carried out when 585 deaths had occurred. The manufacturer presented the results for the primary outcome (overall survival) for the entire TROPIC population and for subgroups defined a priori by the following baseline characteristics: ECOG performance status (0 or 1 versus 2), whether or not disease was measurable using the Response Evaluation Criteria in Solid Tumors, number of prior chemotherapy regimens, age ≥ 65 years, geographical region, pain at baseline, whether PSA was rising at baseline or not (at least two consecutive increases relative to a reference value measured at least a week apart), time from last docetaxel treatment to randomisation, docetaxel dose, and time from last docetaxel treatment to progression. In a post-hoc analysis the manufacturer also presented overall survival and progression-free survival for the following three subgroups: patients with an ECOG performance score of 0 or 1 who had received > 225 mg/m² of docetaxel; European patients; and European patients with an ECOG performance score of 0 or 1 who had previously received ≥ 225 mg/m² of docetaxel. The manufacturer chose the latter group as the base case for health economic modelling. Evidence on the clinical effectiveness of cabazitaxel compared with mitoxantrone in the subgroups defined in the post-hoc analysis was considered by the manufacturer to be academic in confidence and therefore cannot be presented.

- 3.4 TROPIC enrolled 755 men (378 in the cabazitaxel arm and 377 in the mitoxantrone arm) from 26 countries. Patients were randomised to receive either cabazitaxel 25 mg/m² given intravenously over 1 hour, or mitoxantrone 12 mg/m² given intravenously over 15–30 minutes. Treatments were given on day 1 of each 21-day cycle and could be given for a maximum of ten cycles. All patients also received 10 mg per day of oral prednisolone. The protocol prohibited cabazitaxel for patients randomised to the mitoxantrone group; however, 12% of these patients were taking tubulin-binding drugs at the time of disease progression.
- 3.5 The published analysis of the intention-to-treat population of TROPIC reported a statistically significant improvement in median overall survival with cabazitaxel (15.1 months in the cabazitaxel arm compared with 12.7 months in the mitoxantrone arm; hazard ratio [HR] for death 0.70, 95% confidence interval [CI] 0.59 to 0.83, $p < 0.0001$). An updated analysis performed later when 585 deaths had occurred reported median survival values similar to the previous analyses (HR for death 0.72, 95% CI 0.61 to 0.84, $p < 0.0001$). The trend of improvement in overall survival with cabazitaxel was consistent in all subgroups defined a priori, except in patients who had received insufficient prior docetaxel therapy (< 225 mg/m² docetaxel) and those from countries outside North America or Europe.
- 3.6 In the published analysis of the intention-to-treat population of TROPIC, cabazitaxel was associated with a statistically significant improvement in median progression-free survival (with progression defined as a rise in PSA level, tumour progression, pain progression or death). Progression-free survival was 2.8 months in the cabazitaxel arm and 1.4 months in the mitoxantrone arm (HR 0.74, 95% CI 0.64 to 0.86, $p < 0.0001$).

- 3.7 None of the patients in the trial had a complete tumour response according to the Response Evaluation Criteria in Solid Tumors. The proportion of patients with a partial response, evaluated in 405 patients with measurable disease at baseline according to Response Evaluation Criteria in Solid Tumors, was 14.4% in the cabazitaxel arm compared with 4.4% in the mitoxantrone arm ($p = 0.0005$). Among the 755 patients in the intention-to-treat analyses, the median time to tumour progression (defined as the number of months from the date of randomisation to evidence of disease progression based on tumour measurements) was 8.8 months in the cabazitaxel arm compared with 5.4 months in the mitoxantrone arm (HR 0.61, 95% CI 0.49 to 0.76, $p < 0.0001$).
- 3.8 PSA response was measured only in patients with a baseline serum PSA concentration ≥ 20 micrograms per litre and was defined as a $\geq 50\%$ reduction in baseline PSA levels. The PSA response rate was 39.2% in the cabazitaxel group compared with 17.8% in the mitoxantrone group and was statistically significant in favour of cabazitaxel ($p = 0.0002$). PSA progression was defined as an increase of $\geq 25\%$ over nadir PSA concentration provided that the increase in the absolute PSA value was ≥ 5 micrograms per litre in patients with no PSA response, or $\geq 50\%$ over nadir in patients with a PSA response and patients in whom PSA response was not evaluated because baseline PSA value was < 20 micrograms per litre. The median time to PSA progression was 6.4 months in the cabazitaxel arm compared with 3.1 months in the mitoxantrone arm (HR 0.75, 95% CI 0.63 to 0.90, $p = 0.001$).
- 3.9 Pain response was defined as a reduction of ≥ 2 points from baseline median present pain intensity score on the McGill-Melzack scale with no concomitant increase in analgesic score, or a reduction of $\geq 50\%$ in analgesic use from baseline mean analgesic

score with no concomitant increase in pain for two consecutive evaluations conducted at least 3 weeks apart. Among 343 patients with a median present pain intensity score of ≥ 2 or mean analgesic score of ≥ 10 points at baseline, there was no statistically significant difference in pain response between the treatment arms (9.2% in the cabazitaxel arm and 7.7% in the mitoxantrone arm; $p = 0.63$).

3.10 Pain progression was defined as an increase of ≥ 1 point in median present pain intensity from its nadir noted on two consecutive visits made 3 weeks apart, or an increase of $\geq 25\%$ in the mean analgesic score compared with the baseline score noted on two consecutive visits made 3 weeks apart, or need for local palliative radiotherapy. There was no significant difference in time to pain progression between the treatment arms ($p = 0.52$).

3.11 The most common adverse events in the TROPIC trial were neutropenia and its complications (febrile neutropenia and infections), and gastrointestinal toxicity (diarrhoea, nausea and vomiting). Cabazitaxel was associated with higher rates of \geq grade 3 neutropenia (82% compared with 58% in the mitoxantrone arm), and infections and febrile neutropenia (7.5% compared with 1.3% in the mitoxantrone arm). The clinical consequences of neutropenia were the most common cause of death in patients in the cabazitaxel arm (accounting for seven deaths compared with one death in the mitoxantrone arm). Following the consultation on the appraisal consultation document, the manufacturer provided data from the TROPIC trial on cardiac events and suggested that these data indicated a lack of clear evidence that cabazitaxel contributed to higher incidence of cardiac events in the cabazitaxel arm. The manufacturer also reported that an external cardiologist had evaluated the results of a phase I study

(TES10884) of the effect of cabazitaxel on the QT/QTc interval and concluded that there was no effect on ventricular repolarisation necessitating substantial risk–benefit considerations. The manufacturer indicated that it had not identified any new safety concerns related to cardiac toxicity in post-marketing reports on cabazitaxel safety. The manufacturer stated that an expert panel convened to review renal events in the seven completed studies of cabazitaxel concluded that most patients with renal failure had at least one concomitant risk factor (such as diarrhoea, dehydration, severe infection with or without septic shock, local obstruction/progression, medication known to be associated with renal events [for example, non-steroidal anti-inflammatory drugs, zoledronic acid, vancomycin, aminoglycoside], and radiocontrast media). The manufacturer stated that this makes it difficult to determine which factors contributed to renal failure in the cabazitaxel studies.

- 3.12 The manufacturer submitted a cohort Markov model that compared two treatment regimens in patients with hormone-refractory metastatic prostate cancer that had progressed after docetaxel treatment: cabazitaxel combined with prednisolone, and mitoxantrone combined with prednisolone. The model’s perspective was that of the NHS and personal social services. All future costs and benefits were discounted at a rate of 3.56%. Treatment was modelled over a lifetime (14.4 years) with a cycle length of 3 weeks. The model included three health states: stable disease, progressive disease and death. All patients entered the model in the stable disease state, from which transitions to progressive disease and death were possible. Once patients entered the progressive disease state, they would remain there until death.

3.13 For the base-case analysis, the manufacturer used survival data from a post-hoc subgroup analysis of European patients with an ECOG performance status of 0 or 1 who had previously received ≥ 225 mg/m² of docetaxel. Transition probabilities of moving from stable to progressive disease were calculated from data on progression-free survival. The transition probabilities of moving from stable or progressive disease to death were based on overall survival data. The model used data from Kaplan–Meier curves derived from TROPIC until the number of patients remaining in the trial was small, defined by the manufacturer as when there were no events over four consecutive cycles of treatment. After this, the manufacturer calculated transition probabilities from fitted parametric curves because it considered the data from Kaplan–Meier curves to be unreliable given the small number of remaining patients. In the base case the Kaplan–Meier data were used up to week 57 (19 cycles) for progression-free survival and week 111 (37 cycles) for overall survival. A Weibull distribution was used to estimate overall survival for both treatments. For progression-free survival, a Weibull distribution was fitted to the cabazitaxel data whereas a log-normal distribution was fitted to the mitoxantrone data. Following consultation on the appraisal consultation document, the manufacturer provided further justification for its decision to use the subgroup of European patients with an ECOG performance status of 0 or 1 who have previously received ≥ 225 mg/m² docetaxel in the base case. The manufacturer acknowledged that there was no a priori clinical rationale to expect different treatment effects in different geographical regions. The manufacturer noted that a test for interaction for treatment between the three groups (Europe, North America, and ‘other countries’) was not statistically significant. The manufacturer stated that a test for interaction was statistically significant when the European and

North American groups were combined and compared with 'other countries' ($p < 0.1$). The manufacturer noted that increasing the alpha value from 0.05 to 0.10 was usual for an interaction test because of the lack of power of the statistical interaction test often seen in subgroups. The manufacturer also noted the different rates of adverse reactions observed in different regions and interpreted this to reflect varying clinical management. The manufacturer was therefore of the view that the European subgroup is more generalisable to the UK population.

- 3.14 Treatment costs incurred during the stable disease state included the acquisition and administration costs for active treatment, the costs of premedication and concomitant medication, the costs of hospitalisation, tests and imaging, and physician time (over and above that needed for chemotherapy administration). Treatment costs were applied on a per cycle basis. The manufacturer included in the model the costs and disutilities of grade 3 adverse reactions in the stable disease state only, based on observations in the TROPIC trial. The manufacturer also applied a one-time transition cost when patients moved from the stable to the progressive disease state based on the cost of post second-line chemotherapies received by patients in TROPIC and an ongoing per cycle cost of best supportive care, concomitant medication and additional costs such as laboratory tests and hospitalisation. The manufacturer applied an end-of-life cost in the model when patients died.
- 3.15 Data on health-related quality of life were not collected in TROPIC. In the model, the manufacturer chose the utility value for patients with stable disease from an interim analysis of an ongoing single-arm, early access (before marketing authorisation) programme collecting EQ-5D data from patients receiving cabazitaxel for

metastatic prostate cancer in 9 of 12 UK centres active at that time. In the original model, the manufacturer used the mean utility value for patients in their second cycle of treatment for stable disease, and calculated the utility of the progressive disease state by applying a decrement of 0.07 (derived from Sullivan et al. 2007) to the utility value of stable disease. The manufacturer assumed that utility values within a health state were independent of time spent in the health state and stated that this is a widely accepted and commonly used assumption in oncology modelling. During the consultation on the appraisal consultation document, the manufacturer updated the model with utility values for stable disease derived from a second interim analysis of data from the early access programme. The updated utility value for the stable disease state was obtained by pooling utility values from patients in cycle 2 and cycle 4 of cabazitaxel treatment. This resulted in a slightly lower value which was slightly more precise (narrower confidence interval). The manufacturer acknowledged that the same patients may have been assessed at different times. The manufacturer also stated that at the time of the second interim analysis, few patients had progressive disease and this prevented any meaningful estimation of utility values for the progressive disease state from these data.

- 3.16 Following consultation on the appraisal consultation document, the manufacturer provided additional references to justify the utility values assumed for stable and progressive disease states. According to the manufacturer a review of literature on health utilities in cancer by Pickard et al. (2007a) identified only one of the nine utility values reported in prostate cancer to be less than 0.75. The manufacturer noted that these values were not comparable to the early access programme data because they included utility in

the early stages of prostate cancer. In support of its calculation of utility values for the progressive disease state, the manufacturer cited a retrospective analysis (Pickard et al. 2007b) which calculated the minimally important difference in EQ-5D score (defined as the smallest change in a patient-reported outcome measure that is perceived by the patient as beneficial or that would result in a change in a treatment). The analysis was of cross-sectional data from 534 cancer patients receiving chemotherapy with 11 types of cancer, including advanced (stage 3 or 4) cancer of the bladder, brain, breast (women only), colon/rectum, head/neck, liver/pancreas, kidney, lung, lymphoma, ovary (women only), and prostate (men only). A minimally important difference in EQ-5D score for the UK population ranged from 0.08 to 0.16 or 0.09 to 0.16 depending on whether a distribution-based or anchor-based approach was used (Pickard et al. 2007b). The manufacturer considered these figures to be in line with the 0.07 decrement applied to the utility for stable disease to generate the figure for the progressive disease state. Pickard 2007b reported an overall mean utility of 0.72 in people with a mixture of different stage 3 or 4 cancers calculated by the UK tariff. In addition, the manufacturer stated that a registry study (PROTREAT), collecting EQ-5D data in people with hormone refractory prostate cancer prior to initiation of second-line therapy, reported a mean utility value of 0.696 for patients with an ECOG of 0-1.

- 3.17 In the manufacturer's base-case population, treatment with cabazitaxel was associated with a total incremental cost of £22,325 and an additional gain of 0.298 quality-adjusted life years (QALYs), which resulted in an incremental cost-effectiveness ratio (ICER) of £74,908 per QALY gained. In response to a request for clarification from the ERG, the manufacturer made a number of changes to the

model (including correcting the total number of inpatient days per episode of neuropathy, the value for disutility for pulmonary embolism and the minor change to the calculation of QALY losses associated with adverse reactions). These changes increased the base-case ICER to £74,938 per QALY gained.

3.18 The manufacturer assessed the robustness of the ICER by conducting one-way deterministic sensitivity analyses which included increasing and decreasing the utility value associated with stable and progressive disease by 20%, increasing and decreasing by 50% the costs associated with the stable disease and progressive disease states, varying the use of granulocyte-colony stimulating factor, excluding the disutility associated with adverse reactions, using a time horizon of between 1 and 10 years, using alternative discount rates for cost and varying health-related benefits. These analyses demonstrated that the ICER was particularly sensitive to the utility value assigned to the progressive disease state and also to the time horizon. Assuming a 20% lower utility value for the progressive disease state increased the ICER from £74,908 to £88,878 per QALY gained. Shortening the time horizon to 3 years or less increased the ICER to over £93,000 per QALY gained. The probabilistic sensitivity analysis showed that the probability of cabazitaxel being cost effective ranged from 9.4% at a threshold of £60,000 to 75.4% at a threshold of £90,000.

3.19 The manufacturer also conducted several scenario analyses which included:

- an alternative curve fitting (that is, statistical extrapolations for the curves representing overall survival and progression-free survival by including parametric distributions for overall survival

and progression-free survival during the trial period), which led to an ICER of £82,905 per QALY gained

- a Weibull instead of log-normal distribution for progression-free survival in the mitoxantrone arm, which led to an ICER of £74,786 per QALY gained
- an alternative utility decrement of 0.085 (Sandblom et al. 2004) instead of 0.07 in the base case for progressive disease, which led to an ICER of £76,171 per QALY gained
- UK-specific rates of use of granulocyte-colony stimulating factor after treatment with cabazitaxel (rather than the use in TROPIC), which led to an ICER of £74,387 per QALY gained
- equivalent costs for progressive disease in both arms, which led to an ICER of £68,210 per QALY gained
- an assumption that patients share vials of cabazitaxel, which lead to an ICER of £60,928 per QALY gained
- an assumption that the cost of post second-line treatment is in accordance with an audit from the UK instead of the TROPIC trial, which led to an ICER or £75,972 per QALY gained.

3.20 In addition to the population (subgroup) chosen for the base case, the manufacturer also calculated three additional ICERs for:

- the whole population enrolled in TROPIC (£87,684 per QALY gained)
- for European patients in TROPIC regardless of ECOG status or previous docetaxel treatment (£84,540 per QALY gained)
- for all TROPIC patients with an ECOG performance score of 0 or 1 who received ≥ 225 mg/m² of docetaxel (£82,538 per QALY gained).

3.21 The ERG was content with the methodological quality of TROPIC but noted that the trial was not powered to detect differences in the

incidence of specific adverse reactions. The manufacturer noted that this is the case in most registration trials. The ERG stated that because of the stringent management of adverse reactions in the trial, the incidence of adverse reactions associated with cabazitaxel is likely to be higher in clinical practice in the UK. The ERG also stated that the trial provided insufficient information on the cardiac and renal complications associated with cabazitaxel. The ERG critiqued the additional information presented by the manufacturer and the comments received from clinicians following the consultation related to cardiac and renal safety. The ERG agreed that there appear to be no issues related to cardiac and renal toxicity additional to those included in the current safety profile.

- 3.22 In the ERG's view the manufacturer's model was robust and transparent, allowing variables to be altered and the variability and uncertainty in the model to be assessed.
- 3.23 The ERG's view was that the population used by the manufacturer in the base case was inappropriate because there was no clinical reason to assume that the results in patients recruited at European centres would differ from those in patients recruited in non-European countries. In response to the ERG's request for clarification, the manufacturer reported that there was no statistical heterogeneity in treatment effect across the three regions (Europe, North America and other countries) among the whole intention-to-treat population of TROPIC ($p = 0.1535$) as well as among the patients with ECOG performance scores of 0 or 1 who also received $\geq 225 \text{ mg/m}^2$ of docetaxel ($p = 0.4098$). The ERG therefore suggested that the population most clinically relevant to the UK was all patients in TROPIC who received $\geq 225 \text{ mg/m}^2$ of first-line docetaxel and who had an ECOG performance score of 0 or 1. The ERG examined the justification presented by the

manufacturer for their choice of base-case population during the consultation. The ERG reiterated the need for a clinical rationale for assuming regional differences in the relative survival advantage and noted that there was none. The ERG commented that the statistical test of interaction for the combined European and North America groups compared with 'other countries' is not a proof of statistically significant difference by region because the manufacturer did not explore other possible regional combinations. The ERG noted that the manufacturer's justification of the analysis by region was to reflect regional differences in clinical management and therefore adverse reactions. However, the ERG commented that differences in the rate of adverse reactions between regions could not be attributed only to different clinical management, because there may also have been differences in patient demographics (for example, age and the duration of metastatic disease). It is therefore difficult to conclude that regional differences in the rate of adverse reactions are not the result of other demographic variables which were not explored in a multivariate regression analysis. Moreover, the ERG noted that the rate of adverse reactions for North America is closer to that for 'other countries' than for Europe, which does not support combining the North American and European groups based on the incidence of adverse reactions.

- 3.24 The ERG stated that the manufacturer's choice of 38 cycles as the time to replace Kaplan–Meier data on overall survival in the model with a fitted parametric curve was based on an arbitrary decision rule. The ERG further noted that the ICER was sensitive to the time point at which this change was made, with the ICER varying from £72,184 to £90,786 per QALY gained. The ERG also noted that the Kaplan–Meier curves provide the most accurate reflection of the

trial, but are less generalisable to other populations who are eligible for treatment. The ERG commented that mathematical models are used for generalising results from one population to another because they assume an underlying trend and minimise the impact of chance observations that could occur in a study population. The ERG stated that the use of parametric curves throughout would be more appropriate.

3.25 In response to the ERG's request for clarification, the manufacturer conducted a scenario analysis in which patients who died within 30 days of randomisation were excluded. The ERG believed that these deaths could have been prevented with more vigilant treatment of neutropenia. In the intention-to-treat population three patients in the mitoxantrone arm (0.8%) and eight patients in the cabazitaxel arm (2.1%) died within the first month of randomisation, whereas in the manufacturer's base-case population only one patient in the mitoxantrone arm (0.6%) and two patients in the cabazitaxel arm (1.1%) died within the first month of randomisation. When these patients were removed from the analysis the manufacturer's base-case ICER increased from £74,908 to £78,319 per QALY gained.

3.26 The ERG expressed concern about imprecision in the utility estimates for the stable disease state, as reflected by the wide confidence intervals for these estimates. The ERG noted that the utility value for stable disease incorporated in the model was similar to the age-matched utility values observed in the general population, which the ERG thought to be implausible. The ERG also noted that the utility values for stable disease and progressive disease were sampled independently in the probabilistic sensitivity analyses, which led to the utility value for progressive disease being higher than the utility for stable disease in some instances.

The ERG considered this implausible. The ERG noted the published references presented by the manufacturer to support the utility decrement applied to stable disease on progression for a variety of cancers. The ERG agreed with the manufacturer's comment that these additional references have limited relevance to this population.

- 3.27 The ERG performed exploratory analyses using the manufacturer's model, but using a population that the ERG considered to be clinically relevant to the UK (that is, all TROPIC patients [not only European patients] who received ≥ 225 mg/m² of first-line docetaxel and who had an ECOG performance score of 0 or 1). The deterministic ICER for this population was £82,538 per QALY gained. The ERG then amended the manufacturer's model by using parametric curves for the entire time horizon in the model, calculating the utility for progressive disease by applying a mean decrement of 0.07 to the utility of stable disease and applying an arbitrarily defined standard deviation of 0.02 to the decrement. The ERG also corrected a minor error in the discount rate. The combined impact of all these amendments was to increase the ICER to £89,476 per QALY gained.
- 3.28 The ERG performed a number of sensitivity analyses to test the robustness of the ERG's base-case ICER when plausible changes in assumptions were made. The use of alternative utility values for stable disease had the greatest impact on the ERG's base-case ICER. Assuming the value for utility that reflected the lower limit of the 95% confidence interval for stable disease increased the ERG's base-case ICER from £89,476 to £111,719 per QALY gained. Assuming the value that reflected the upper limit of the 95% confidence interval decreased the ICER to £74,620 per QALY gained. In addition, assuming that the decrement between the utility

value of stable disease and progressive disease was 0.085 (reported by Sandblom et al. 2004) increased the ERG's base-case ICER from £89,476 to £90,865 per QALY gained.

Additional analysis submitted by the manufacturer during consultation

3.29 Following the consultation on the appraisal consultation document, the manufacturer presented a number of exploratory analyses addressing some of the concerns raised by the Committee. The manufacturer submitted updated utility values for the stable disease state from the second interim analysis of the early access programme, used values reflecting usage of post second-line chemotherapy in the UK (lower than observed in the TROPIC trial) and corrected a minor error in the discount rate. Collectively, these amendments are now referred to as the manufacturer's revised base-case model.

3.30 In the revised base-case model using the manufacturer's base-case population, cabazitaxel was associated with a total incremental cost of £22,649 and a QALY gain of 0.290, resulting in an ICER of £78,016 per QALY gained compared with mitoxantrone. The manufacturer also presented revised ICERs for different populations: that is, all patients in TROPIC with ECOG performance score of 0 or 1 who had received ≥ 225 mg/m² prior docetaxel therapy (£86,008 per QALY gained), European patients regardless of ECOG performance status and previous docetaxel therapy (£87,348 per QALY gained) and all patients in TROPIC (£91,134 per QALY gained).

3.31 The manufacturer also presented several univariate sensitivity analyses for its revised base-case model. These included:

- varying the utility value of stable and progressive disease by increasing and decreasing them by 20% (assuming a 20%

increase in utility values for both stable and progressive disease decreased the ICER from £78,016 to £64,104 per QALY gained; decreasing utility values by 20% increased the ICER to £99,640 per QALY gained

- reducing the utility decrement of 0.07 between stable and progressive disease by 20% gave an ICER of £76,794 per QALY gained; increasing this utility decrement by 20% gave an ICER of £79,277 per QALY gained
- using a utility decrement of 0.085 (Sandblom et al. 2004) increased the ICER from 78,016 per QALY gained in the base case to £79,369 per QALY gained
- using the lower level of the 95% confidence interval for the utility value of stable disease increased the ICER to £83,438 per QALY gained; using the upper level of the 95% confidence interval decreased the ICER to £73,255 per QALY gained
- applying parametric curve fitting throughout in both arms for overall survival data in both the arms from the beginning of treatment to the point at which the last person is alive; this increased the base-case ICER from £78,016 to £86,373 per QALY gained
- applying a Weibull distribution instead of log-normal distribution for progression-free survival data of the mitoxantrone arm increased the base-case ICER from £78,016 to £85,935 per QALY gained
- varying the time horizon from 1 to 10 years; the ICER decreased as the time horizon increased.

3.32 The manufacturer used a number of different mathematical approaches to extrapolate trial data to estimate the modelled extension in overall survival with cabazitaxel. This included a 'conservative approach' which used only Kaplan–Meier (that is,

trial) data up to the point at which the last death within the study was observed (at 26.9 months in the mitoxantrone arm). The manufacturer also modelled scenarios in which the Kaplan–Meier data were used for the trial period followed by linear extrapolation censored at different time-points which assumed that all patients in both arms had died at 33, 40 and 50 months. The mean overall survival gain for the manufacturer’s preferred base-case population (European patients with an ECOG performance status of 0 to 1 who had received ≥ 225 mg/m² first-line docetaxel) was estimated to be 3 months when the manufacturer assumed no patient survived beyond the trial period. The mean overall survival gain was 3.7, 4.3 and 5.3 months when patients were censored at 33, 40 and 50 months respectively. Similar analysis presented for all patients with an ECOG performance status of 0 or 1 who had received ≥ 225 mg/m² first-line docetaxel (the ERG base-case population) estimated the mean overall survival gain to be 3.3, 3.8 and 4.7 months when patients were censored at 33, 40 and 50 months respectively.

- 3.33 The manufacturer also performed a ‘piecewise analysis’ for overall survival data by fitting different survival curves over different time periods using a diagnostic graph. A plot of transformed survival against time demonstrated that the Weibull distribution appeared appropriate for the entire curve in the mitoxantrone arm, and that in the cabazitaxel arm different shapes were observed before and after 2.2 months, suggesting two different curves would be appropriate for these periods. Because no deaths occurred between 2.1 months and 2.2 months in the cabazitaxel arm, 2.1 months (corresponding to the third cycle of cabazitaxel treatment) was chosen by the manufacturer as a cut-off point. The manufacturer used Kaplan–Meier data for the initial period of

2.1 months and a Weibull parametric curve after 2.1 months for surviving patients. A similar plot for the subgroup of all patients with an ECOG performance status of 0 or 1 who had received ≥ 225 mg/m² first-line docetaxel (the ERG's base-case population) showed the same result and the same procedure was adopted for 'piecewise analysis' in this subgroup. Mean overall survival gains estimated using the piecewise analysis for both populations were submitted by the manufacturer as academic in confidence and therefore cannot be presented. The ICER resulting from the piecewise analysis for the manufacturer's base-case population was £77,765 per QALY gained and for the ERG's base-case population £87,518 per QALY gained.

3.34 The manufacturer also presented 'partitioned analyses' of overall survival data using three alternative functions:

- a Weibull curve and a log-logistic curve
- two Weibull curves
- three Weibull curves.

The manufacturer presented the mean overall survival as academic in confidence, and did not report an ICER for the partitioned analyses.

3.35 The ERG noted that the revised model submitted by the manufacturer after consultation on the appraisal consultation document did not incorporate the most recent survival data from the follow-up after the trial (after 585 people had died). The ERG also noted that the manufacturer presented only deterministic, but not probabilistic, results for the updated model.

3.36 The ERG agreed that a mean overall survival gain of at least 3 months in people with hormone-refractory metastatic prostate

cancer treated with cabazitaxel compared with those treated with mitoxantrone had been robustly demonstrated by mathematical exploration of survival data for the manufacturer's base-case population.

3.37 The ERG was content with the methodology and execution of the piecewise analysis and noted that the piecewise analysis also minimised the impact of the early deaths (within 30 days of randomisation). However, the ERG hypothesised that because the early deaths also affected the mitoxantrone arm, the manufacturer should have applied a similar piecewise fitting to the mitoxantrone arm. The ERG noted that applying the piecewise approach to both arms would increase the ICER by approximately £2000 per QALY gained for the manufacturer's base-case population and would be likely to have the same impact on the ICER for ERG's base-case analysis. The ERG noted that the reduction in the ICER for the manufacturer's base-case population with the piecewise analysis (compared with the single Weibull fit presented in the original submission) arises because the new Weibull estimates slightly reduce the probability of death in the tail of the distribution.

3.38 With respect to the partitioned analyses provided by the manufacturer, the ERG commented that the manufacturer did not provide enough information for a detailed critique and did not report any ICER estimates. The ERG also noted that when fitting the best curve one should take into consideration the number of parameters, as more parameters will improve the fit, but may not do so sufficiently to justify using an additional parameter, that is, may lead to increase unreliability of extrapolation beyond the trial period.

- 3.39 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of cabazitaxel, having considered evidence on the nature of hormone-refractory metastatic prostate cancer and the value placed on the benefits of cabazitaxel by people with the condition, those who represent them, and clinical specialists, and also considered the comments received during consultation. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the place of cabazitaxel in the clinical pathway of care for people with hormone-refractory metastatic prostate cancer. The Committee noted that the other treatments used in clinical practice do not have a marketing authorisation for hormone-refractory metastatic prostate cancer that has progressed after docetaxel treatment. The Committee heard from clinical specialists that the main treatment options for patients whose disease progresses after first-line docetaxel include cabazitaxel, mitoxantrone and re-treatment with docetaxel, although the latter is not recommended by current NICE guidance. Other chemotherapy regimens used in this setting are 5-fluorouracil, cyclophosphamide, carboplatin and etoposide. The Committee heard from the clinical specialists that they would be very unlikely to offer cabazitaxel to patients with an ECOG performance score of 2, even though these patients had not responded differently from patients with ECOG scores of 0 or 1 in the TROPIC trial, because these people will not be fit enough to tolerate further chemotherapy. The Committee also

heard from the clinical specialists and the NHS commissioning expert that access to cabazitaxel varies by region when it is made available through local cancer drug funds.

- 4.3 The Committee heard from the patient experts that the most important benefits of cabazitaxel were the extension to life, even if short, and the hope that this offers. The Committee further heard that patient experts are aware that cabazitaxel is associated with serious adverse reactions and that it would not be suitable for some patients who are not fit for chemotherapy. The Committee heard that people with prostate cancer in England and Wales are becoming increasingly concerned about what they perceive to be unequal access to treatment with cabazitaxel as provided through the Cancer Drugs Fund.

Clinical effectiveness

- 4.4 The Committee considered the evidence submitted by the manufacturer on the clinical effectiveness of cabazitaxel. The Committee noted that the evidence was based on a large, multinational, phase III, randomised trial (TROPIC, n=755) comparing cabazitaxel plus prednisone or prednisolone with mitoxantrone plus prednisone or prednisolone. The Committee noted that the manufacturer excluded from its submission the other comparators listed in the scope, and considered mitoxantrone to be the most relevant comparator based on evidence from the clinical specialists. The Committee noted that, as an open-label study, TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival, such as pain and deterioration in symptoms. The Committee heard from the manufacturer that blinding was not possible because of differences in the rate of infusion and colour of the drugs being compared. The Committee considered the generalisability of TROPIC to clinical

practice in the UK. The Committee considered the way progression-free survival was defined in TROPIC; that is, to include rise in PSA concentration and level of pain. The Committee heard from the clinical specialists that in clinical practice a rise in PSA concentration would not, on its own, be considered an indication to stop treatment with cabazitaxel; instead, the decision to stop cabazitaxel is based on a combination of clinical factors, primarily progression of symptoms. The Committee heard from the clinical specialists that participants in TROPIC were in many ways similar to those who would receive cabazitaxel treatment in the UK. The Committee concluded that the trial results would be generalisable to the UK. The Committee also considered the appropriateness of limiting cabazitaxel treatment to ten cycles. The Committee heard from the manufacturer that ten cycles was chosen because mitoxantrone is limited to ten cycles because of its cumulative effect on cardiac toxicity. The Committee was aware that the median number of cycles received by patients in TROPIC was six and that in clinical practice few patients would receive more than ten cycles because most would have disease that had progressed, would have experienced adverse reactions, or would have died. The Committee also noted that clinicians commonly discuss with patients their response to cabazitaxel treatment after six cycles and a decision whether to continue treatment is made on this basis. The Committee concluded that the population in TROPIC is generalisable to the UK and that the assumption that most patients would receive six cycles of treatment and that no patient would receive more than ten cycles is appropriate.

- 4.5 The Committee discussed the published results for the entire TROPIC population, noting that cabazitaxel is associated with a statistically significant improvement in overall survival and

progression-free survival compared with mitoxantrone. The Committee heard from the clinical specialists that the effectiveness of cabazitaxel in TROPIC was consistent with that seen in clinical practice in the UK. The Committee concluded that the evidence demonstrated that cabazitaxel is an effective second-line treatment for hormone-refractory metastatic prostate cancer.

- 4.6 The Committee considered the appropriateness of the manufacturer's base-case population (the post-hoc subgroup from TROPIC that comprised European patients with an ECOG performance score of 0 or 1 who had received ≥ 225 mg/m² of prior docetaxel therapy), which the manufacturer considered to be the most representative of the UK population. The Committee agreed that in order to accept that a treatment effect would differ among subgroups, an a priori clinical rationale justifying this would be needed with statistical tests for interaction between patients with or without the characteristics that define the different subgroups.
- 4.7 The Committee considered limiting the subgroup to European patients. The Committee noted that the clinical specialists considered there to be no difference in the effectiveness of cabazitaxel by geographical region, and the clinical specialists commented that clinicians in other European centres manage adverse reactions in a similar way to clinicians in the UK. The Committee discussed the comments received from the manufacturer during consultation. The Committee was aware that the manufacturer found no statistically significant differences in treatment by geographically defined subgroup when it compared Europe, North America, and 'other countries'. The Committee was aware that no results related to subgroup analyses by geographic area had been included in the main publication of the TROPIC trial (de Bono et al. 2010). The manufacturer explained that evaluating

effectiveness by geographic area was defined in the statistical plan a priori, but could not explain why the results of subgroups by region were excluded from this final publication of the TROPIC trial, which contained the results of the other pre-defined subgroups. The Committee was also aware that during the consultation the manufacturer had demonstrated the statistical interaction of a new subgroup, which combined North American with European patients and compared this with patients from other countries. This showed that interaction for treatment by region was statistically significant at 10% alpha level. The Committee noted that the manufacturer did not present an ICER for this subgroup (European and North American patients). The Committee noted the ERG's comment that the manufacturer had not analysed other regional combinations. The Committee considered that exploring interactions between other regional combinations was important before concluding that overall survival was statistically significantly different across some regions. The Committee did not consider there to be a difference in the effectiveness of cabazitaxel treatment between European patients and other patients in the TROPIC trial, and therefore concluded that it is not appropriate to restrict the base-case population to patients in TROPIC recruited at European centres.

- 4.8 The Committee considered limiting the subgroups to those who had received at least 225 mg/m² docetaxel as first-line therapy. The Committee heard from the manufacturer that best practice guidelines recommend this dose of previous docetaxel therapy. The Committee also noted that the inclusion criteria for TROPIC had been changed to reflect this dose and that only 59 patients in TROPIC had received lower-dose docetaxel therapy. The Committee also heard from the clinical specialists that it is appropriate for patients to receive at least 225 mg/m² of docetaxel

and gain the full benefit of first-line treatment before going on to second-line treatment with cabazitaxel. The Committee therefore considered that restricting the base-case population to the subgroups who had received at least 225 mg/m² of docetaxel was appropriate.

4.9 The Committee considered limiting the subgroups to those with an ECOG performance score of 0 or 1, the results of which were presented in the final published report of the trial but without a test for heterogeneity. The Committee heard from the clinical specialists that in patients with hormone-refractory metastatic prostate cancer, ECOG is routinely used to assess performance and the ECOG relates directly to whether patients are likely to tolerate further chemotherapy. The Committee heard from the clinical specialists that patients with an ECOG performance score of 2 would not be fit enough for chemotherapy, and therefore considered the restriction to ECOG performance scores of 0 or 1 to be appropriate. The Committee concluded that the most appropriate base-case population for this appraisal is all patients in TROPIC who received at least 225 mg/m² of docetaxel and had an ECOG performance score of 0 or 1.

4.10 The Committee considered the evidence on adverse reactions associated with cabazitaxel. It noted that haematological events and diarrhoea were major concerns. The Committee heard from the clinical specialists that most cases of neutropenia were identified during routine blood tests but that only those that developed into febrile neutropenia or neutropenic sepsis were of particular concern to clinicians and patients. The Committee noted that the incidence of neutropenia was lower among participants recruited at European centres than other centres. The Committee heard from the clinical specialists that clinicians in the UK follow best practice guidelines

for managing neutropenia and, as a result, few patients in the UK develop febrile neutropenia or neutropenic sepsis. The Committee was initially concerned that in TROPIC more participants in the cabazitaxel arm died from cardiac and renal complications than in the mitoxantrone arm. The Committee considered data from three sources presented by the manufacturer after consultation:

- the result of studies evaluating cardiac toxicity associated with cabazitaxel
- the conclusions of a review by an expert panel of renal events observed with cabazitaxel
- post-marketing safety data.

The Committee concluded that there is no evidence of additional risk other than that included in the SPC and that the health economic model adequately reflected the disutility associated with adverse reactions.

Cost effectiveness

- 4.11 The Committee considered the manufacturer's economic model, the assumptions on which the parameters in the model were based, and the critique and exploratory analyses performed by the ERG. The Committee concluded that the structure of the submitted Markov model was acceptable.
- 4.12 The Committee considered the transition probabilities that reflected the simulated population moving between different states in the model. The Committee noted that the calculated transition probabilities from either the stable disease or progressive disease state to the death state were based on Kaplan–Meier data from TROPIC for overall survival until completion of 37 cycles of treatment. After this the model used parametric curves. The

Committee noted that the ICER was sensitive to the time point chosen to replace Kaplan–Meier survival curves with parametric curves, and that the time point chosen by the manufacturer produced a relatively favourable ICER. The Committee considered the ERG’s concerns that Kaplan–Meier curves are specific to the TROPIC population and that parametric curves are more likely to generate transition probabilities more generalisable to patients other than those enrolled in TROPIC. The Committee noted that the application of fitted parametric curves increased the manufacturer’s base-case ICER from £74,900 to £82,900 per QALY gained. The Committee concluded that the fitted parametric curves are more generalisable to the population outside the trial.

- 4.13 The Committee considered an analysis by the manufacturer at the clarification stage in which early deaths (within 30 days of randomisation) were excluded from survival data to adjust for deaths attributed to treatment-induced neutropenia. The Committee noted the amendment of the TROPIC protocol regarding treating neutropenia and adjusting the dose of cabazitaxel. The Committee also noted that no early deaths were reported after this protocol amendment from any geographical region. The Committee concluded that preventing deaths from neutropenia depends on adhering to the dose adjustments of cabazitaxel specified in the SPC, and does not depend on the geographical region. The Committee considered that removing data related to patients who died within 30 days of randomisation from the analysis increased the ICER, whereas one might have expected the reverse given that cabazitaxel led to some early deaths, but overall extended life. The Committee noted the ERG’s comment that the likely reason for this increase in the ICER was that the parameters for the Weibull distributions fitted to the overall survival data had altered, reducing

the difference between cabazitaxel and mitoxantrone in the tail of the curve. This resulted in a difference between the mean survival within the cabazitaxel and the mitoxantrone arms. The Committee further concluded that with better management of neutropenia these early deaths could be avoided. If the costs of treating people not dying within 30 days were included in the model for the stable and progressive disease states the ICER would probably be slightly higher than estimated.

4.14 The Committee noted that the manufacturer based the utility value for the stable disease state on a small selected sample of patients (number is academic in confidence) and that the value had a wide confidence interval. The Committee understood that this utility value was similar to the utility value observed in the age-matched general population. The Committee agreed this to be implausible because people with metastatic prostate cancer refractory to docetaxel treatment would be expected to have a poorer quality of life. The Committee also agreed that patients who participate in trials may be healthier than other patients for whom cabazitaxel might be appropriate, because to participate in studies involves time and travel to hospital. The Committee also noted that open label designs such as in the early access programme bias results towards a beneficial effect as the outcomes are based on patient's self assessment.

4.15 The Committee considered the utility value of stable disease from the second interim analysis of the early access programme submitted by the manufacturer during the consultation. The Committee welcomed the manufacturer's commitment and efforts to obtaining EQ-5D utility data in accordance with the reference case, because none had been collected during the TROPIC trial. However, the Committee had concerns related to the analysis:

- There were markedly fewer patients assessed in cycle 4 of the second interim analysis than in cycle 2 of the first interim analysis. The Committee noted that the manufacturer had not explored the reason for this.
- The Committee was also concerned that the manufacturer had pooled values for patients who had participated in the early access programme from cycle 2 and cycle 4, and insofar as their disease had not progressed at cycle 4, their disease may have been milder and their utility values higher than that of typical patients with hormone-refractory metastatic prostate cancer.
- The early access programme study has not finished and the methodology of data collection and analysis of the early access programme have not been subjected to scientific scrutiny (peer review).

Therefore, the Committee was concerned about the uncertainty around the utility value and whether the utility value as calculated from the early access programme could be applicable to the wider population with hormone-refractory metastatic prostate cancer refractory to docetaxel treatment.

- 4.16 The Committee considered additional references provided by the manufacturer during consultation in support of the utility value for stable disease incorporated in the model. The Committee noted that studies included in the review by Pickard et al. (2007a) of health utilities in prostate cancer are in general related to the early stages of prostate cancer and only a small number of patients in a few studies could be assumed to have hormone-refractory metastatic prostate cancer which has progressed after first-line therapy. The Committee also considered the mean utility value of

0.72 was derived from 534 patients with a variety of different types of advanced (stage 3 or 4) cancers (Pickard et al. 2007b) of whom only 50–52 had stage 3 or 4 prostate cancer. The Committee questioned how applicable the studies by Pickard were to the population considered in this appraisal. The Committee further noted that the PROTREAT study indicated lower utility values than the baseline utility values from the second interim analysis of the early access programme. The Committee concluded that there remains considerable uncertainty around the utility value for stable disease incorporated in the model, that this utility value was likely to be overestimated, and that, consequently, the ICER was likely to be underestimated.

- 4.17 The Committee then considered the decrement applied to the utility of the stable disease state to calculate the utility of the progressive disease state. The Committee noted that applying a constant utility over the model time horizon would not capture the natural deterioration in quality of life after disease has progressed. The Committee heard from the clinical specialists that it is difficult to determine the difference in quality of life between stable and progressive disease because symptoms vary across patients (for example, some patients with bone metastases sustain fractures that cause considerable pain and loss of independence, whereas other patients with bone metastases have no such fractures). The Committee concluded that, on average, patients with progressive disease feel less well and have a worse quality of life than those with stable disease, and that a utility decrement of 0.07 between stable and progressive disease underestimates the difference in quality of life between the two health states. The Committee was aware that the choice of utility value for progressive disease had an impact on the ICER, and that changing this parameter by 20%

either way resulted in ICERs between £65,000 and £89,000 per QALY gained (from manufacturer's base case). The Committee also noted that using a slightly larger utility decrement of 0.085 for progressive disease increased the ICER from the ERG's original base case of £89,500 to £90,900 per QALY gained. The Committee considered the additional reference (Pickard et al. 2007b) provided by the manufacturer during consultation in support of the utility decrement of 0.07 for the difference in quality of life between stable and progressive disease in the economic model. The Committee concluded in light of evidence from the manufacturer on the minimally important difference in EQ-5D score (section 3.16) that the utility decrement associated with progressive disease in the economic model of 0.07 was likely to be too low and that this would underestimate the ICER.

4.18 The Committee considered the assumptions related to resource use in the manufacturer's original model. The Committee heard from the clinical specialists that in the TROPIC trial the proportion of patients who had received post second-line chemotherapy seems higher than they would have expected (designated as academic in confidence in the manufacturer's submission and therefore not presented here) and that the lower proportion of patients receiving post second-line chemotherapy from a UK audit (also academic in confidence) seemed more realistic. The Committee was aware that using the more realistic UK audit values would marginally increase the ICER. The Committee was content that in the revised model submitted after consultation the manufacturer used the rate of post second-line chemotherapy from the UK audit.

4.19 The Committee also heard from the clinical specialists that in clinical practice all patients experiencing febrile neutropenia would

need hospitalisation, an assumption not included in the manufacturer's original model or in its revised model. The Committee noted the manufacturer's comment that assuming all patients were admitted to hospital would increase the base-case ICER by £254 per QALY gained. The Committee agreed that this would increase the ICER marginally.

4.20 The Committee considered a sensitivity analysis indicating that the ICER would decrease if patients shared vials. However, the Committee heard from the clinical specialists that because the number of patients treated at each centre is small, and because cabazitaxel has a short shelf life once opened, vial sharing is not feasible in the clinical setting. The Committee therefore concluded that the ICER based on vial sharing of cabazitaxel is not relevant in clinical practice in the UK.

4.21 The Committee considered the revised economic model presented by the manufacturer following the consultation and the critique provided by the ERG. The Committee was disappointed that the additional analysis was not based on the most recent survival data (in which 588 deaths had occurred).

4.22 The Committee considered the different mathematical methods of curve fitting based on the piecewise and partitioned analysis presented by manufacturer during consultation. The Committee discussed the relative merit of using a piecewise analysis. The Committee heard from the ERG that both the piecewise and the partitioned methods of curve fitting were more plausible than the method provided in the original model (which used the Kaplan–Meier data until they were considered unreliable and a single Weibull fit). The Committee concluded that the piecewise approach was reasonable. The Committee was aware that the piecewise

curve fitting had not used more than two pieces. The Committee noted that the piecewise approach resulted in somewhat higher ICERs for the manufacturer's base-case population than the original model submitted by the manufacturer. The Committee heard from the ERG that piecewise analysis would likely minimise the impact of early deaths from cabazitaxel-induced neutropenia, and it would therefore not be appropriate to remove early deaths from the piecewise analysis. The Committee was aware that the ERG was not able to fully assess the partitioned analysis because the manufacturer did not provide adequate information. It further noted that the corresponding ICERs were also not presented by the manufacturer for the partitioned analysis. The Committee heard from the manufacturer at the second Committee meeting that the probabilistic ICER for the manufacturer's base-case population for the partitioned analysis was £78,822 per QALY gained. The Committee concluded that of all the methods of curve fitting, it considered the piecewise analysis the most appropriate, and that this led to an ICER of £87,518 per QALY gained for its preferred base-case population (all patients with an ECOG performance status of 0 or 1 who had received at least 225mg/m² of docetaxel). The Committee therefore concluded that an ICER of £87,500 per QALY gained provided the starting point for discussions on the most plausible ICER. The Committee felt that uncertainty remained with regard to the most plausible ICER, and that the following factors would be likely to increase the ICER:

- a lower utility value for stable disease
- a larger difference in quality of life between stable and progressive disease
- a model which includes the costs for hospitalisation in all patients with febrile neutropenia

- fitting the mitoxantrone curve using a piecewise approach.

4.23 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with 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.

4.24 The Committee discussed whether cabazitaxel fulfilled the criteria for consideration as a life-extending end-of-life treatment. For hormone-refractory metastatic prostate cancer that has progressed after first-line treatment, the Committee agreed that the first criterion related to life expectancy was fulfilled, because estimates of life expectancy from trials with best supportive care in this setting were less than 15 months. The Committee understood from the estimates provided by the manufacturer and the ERG that there are about 7000 people with hormone-refractory metastatic prostate cancer in England and Wales, and that the number of people who

receive second-line chemotherapy is less than 2000. The Committee agreed that the patient population for which cabazitaxel has a marketing authorisation is small. The Committee considered the degree to which cabazitaxel extended life. It noted that in the manufacturer's original model the median overall survival gain was 2.4 months in the TROPIC population, that the mean overall survival gain estimated using the model was 4.2 months, and that this modelled survival gain was dependent on the curve fitting used. The Committee considered whether the extension to mean overall survival associated with cabazitaxel used in the model was robust. The Committee noted that the manufacturer had presented an extensive range of different mathematical methods for extrapolating overall survival for the manufacturer's base-case population, all of which resulted in an extension of life of 3 months or greater. In the Committee's view, the most conservative estimate (in which no survival benefit was assumed beyond the trial period and which showed a mean increased overall survival of 3 months), underestimated the true survival benefit of cabazitaxel. The Committee concluded that a mean improvement of greater than 3 months in mean overall survival had been robustly demonstrated and that therefore the end-of-life criteria were met. The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources.

- 4.25 The Committee discussed whether there were any equality issues that required consideration in this appraisal. The Committee understood that people who have proposed, started or completed

male to female gender reassignment can develop prostate cancer. The Committee therefore concluded that this appraisal should refer to people rather than to men. Furthermore, the Committee had been made aware that people with prostate cancer who have proposed, started or completed male to female gender reassignment may find it uncomfortable to attend male urology clinics. However, the Committee agreed that the treatment of prostate cancer would be likely to be provided in oncology clinics, and that it was outside the remit of a technology appraisal to address this issue.

- 4.26 The Committee considered whether cabazitaxel is an innovative technology. It heard from the manufacturer 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.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
	Cabazitaxel in combination with prednisone or prednisolone is not recommended for people with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.	1.1
	The Committee considered the incremental cost-effectiveness ratio (ICER) of £87,500 per quality-adjusted life year (QALY) gained as the starting point for its decision. The Committee further noted that there remains considerable uncertainty in the robustness of this ICER because the utility values that were used in the model were based on unpublished data from an interim analysis of a small number of patients, and the costs associated with the management of febrile neutropenia were underestimated in the model. The Committee therefore concluded that the most plausible ICER would be above £87,500 per QALY gained. The Committee agreed that cabazitaxel was an effective, life-extending treatment but the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources.	4.22 4.24
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from clinical specialists that the main treatment options for patients whose disease progresses after first-line docetaxel include cabazitaxel, mitoxantrone and re-treatment with docetaxel, although the latter is not recommended by current NICE guidance. Other chemotherapy regimens used in this setting are 5-fluorouracil, cyclophosphamide, carboplatin and etoposide.	4.2

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?	<p>The Committee heard from the patient experts about the potential benefits of cabazitaxel treatment. The patient experts considered that the most important benefits of cabazitaxel were the extension to life, even if for a short time, and the hope that this offers.</p> <p>The Committee heard from the manufacturer 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>	4.3 4.26
What is the position of the treatment in the pathway of care for the condition?	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'	2.2, 4.2
Adverse effects	The Committee noted that haematological adverse events and diarrhoea were major concerns. The Committee noted that the incidence of neutropenia was lower among participants recruited at European centres than other centres. The Committee was concerned that in TROPIC more participants in the cabazitaxel arm died from cardiac and renal complications than in the mitoxantrone arm. The Committee considered three sources of data presented by the manufacturer after consultation: the results of studies evaluating cardiac toxicity associated with cabazitaxel; the conclusions of a review by an expert panel of renal events observed with cabazitaxel; and post-marketing safety data. It concluded that there is no evidence of additional risk other than that included in the SPC.	4.10
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Evidence of clinical effectiveness comes from an open-label randomised controlled trial (TROPIC) in men aged over 18 years with hormone-refractory metastatic prostate cancer and an	3.1, 4.4

	Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, with evidence of disease progression during or after completion of docetaxel-containing treatment.	
Relevance to general clinical practice in the NHS	The Committee concluded that the trial results would be generalisable to the UK.	4.4
Uncertainties generated by the evidence	The Committee noted that, as an open-label study, TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival, such as pain and deterioration in symptoms.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee concluded that the most appropriate base-case population for this appraisal is all patients in TROPIC who received at least 225 mg/m ² of docetaxel of docetaxel and had an ECOG performance score of 0 or 1.	4.7, 4.8, 4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	<p>The published analysis of the intention-to-treat population of TROPIC reported a statistically significant improvement in median overall survival with cabazitaxel (15.1 months in the cabazitaxel arm compared with 12.7 months in the mitoxantrone arm; hazard ratio [HR] for death 0.70, 95% confidence interval [CI] 0.59 to 0.83, p<0.0001). Progression-free survival was 2.8 months in the cabazitaxel arm and 1.4 months in the mitoxantrone arm (HR 0.74, 95% CI 0.64 to 0.86, p<0.0001).</p> <p>The Committee concluded that the evidence demonstrated that cabazitaxel is an effective second-line treatment for hormone-refractory metastatic prostate cancer.</p>	3.5, 3.6 4.5

Evidence for cost effectiveness		
<p>Availability and nature of evidence</p>	<p>The manufacturer submitted a cohort Markov model that compared cabazitaxel plus prednisone or prednisolone with mitoxantrone plus prednisone or prednisolone in patients with hormone-refractory metastatic prostate cancer that had progressed after docetaxel treatment. Treatment was modelled over a lifetime (14.4 years) with a 3-week cycle length. The model included three health states: stable disease, progressive disease and death.</p> <p>The Committee considered the structure of the submitted Markov model to be acceptable.</p>	<p>3.12</p> <p>4.12</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that there remains considerable uncertainty in the robustness of manufacturer's base-case ICER because effectiveness data were from a post-hoc subgroup from TROPIC without any plausible clinical or statistical rationale, the model used data from Kaplan–Meier curves to calculate transition probabilities (until the small number of patients made the curve erratic and parametric curves were used) making results less generalisable to the population outside the trial, the utility values were based on unpublished data from an interim analysis of a small number of patients, and the costs associated with managing febrile neutropenia were underestimated.</p>	<p>4.9, 4.12, 4.14, 4.15, 4.19</p>
<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 Committee noted that the ICERs were sensitive to the absolute and relative difference in the utility for stable disease and progressive disease. The Committee concluded that there remains considerable uncertainty as to the validity of the utility data incorporated in the model.</p> <p>None identified</p>	<p>4.14 4.15 4.16 4.17</p>

Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	–
What are the key drivers of cost effectiveness?	The Committee noted the ICER was very sensitive to the time point chosen to replace Kaplan–Meier survival curves with parametric curves, and the utility values assigned to the stable and progressive disease states.	4.12, 4.14, 4.15, 4.16, 4.17
Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that the most plausible ICER would be above £87,500 per QALY gained. The Committee further noted that there remains considerable uncertainty in the robustness of this ICER because the utility values that were used in the model were based on unpublished data from an interim analysis of a small number of patients, and the costs associated with managing febrile neutropenia were underestimated.	4.22
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	–
End-of-life considerations	The Committee considered the criteria related to short life expectancy (less than 24 months) without treatment and the small patient population (less than 2000) to be met. The Committee agreed that the estimate of a mean extension to life of 3 or more months could be considered sufficiently robust. However, the Committee considered that the additional weight needed to bring the ICER into the range considered a cost-effective use of NHS resources was too great.	4.24
Equalities considerations and social value judgements	The Committee concluded that the recommendations should refer to people rather than men to include people who have proposed, started or completed gender reassignment.	4.25

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- Prostate cancer: diagnosis and treatment. NICE clinical guideline 58 (2008). Available from www.nice.org.uk/guidance/CG58
- Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. NICE technology appraisal guidance 101 (2006). Available from www.nice.org.uk/guidance/TA101
- Improving outcomes in urogenital cancers: the manual. NICE cancer service guidance (2002). Available from www.nice.org.uk/guidance/CSGUC

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Abiraterone for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy. NICE technology appraisal in preparation (publication expected May 2012). More information available from www.nice.org.uk/guidance/TA/Wave26/4

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in February 2015. 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
December 2011

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Michael Boscoe

Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director - Pharmaceuticals & Personal Health, Oral Care Europe

Mrs Eleanor Grey

Lay member

Dr Neil Iosson

General Practitioner

Mr Terence Lewis

Lay member

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Dr Florian Alexander Ruths

Consultant Psychiatrist and Cognitive Therapist at the Maudsley Hospital,
London

Mr Navin Sewak

Primary Care Pharmacist, NHS Hammersmith and Fulham

Mr Roderick Smith

Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group
(PenTAG), University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology,
University of Birmingham

Mr Tom Wilson

Director of Contracting and Performance, NHS Tameside and Glossop

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser (delete if there is no technical adviser) and a project manager.

Anwar Jilani

Technical Lead

Eleanor Donegan

Technical Adviser

Jeremy Powell

Project Manager

Appendix B: Sources of evidence considered by the Committee

- A The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR), The University of Sheffield:
- Stevenson M, Lloyd Jones M, Kearns B et al. Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer, August 2011).
- B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.
- I Manufacturer/sponsor
- Sanofi-aventis
- II Professional/specialist and patient/carer groups:
- British Uro-Oncology Group
 - Equalities National Council
 - Macmillan Cancer Support
 - Prostate Cancer Charity
 - Prostate Cancer Support Federation
 - Royal College of Nursing
 - Royal College of Physicians
- III Other consultees:
- Department of Health
 - NHS Warwickshire

- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency
- MRC Clinical Trials Unit
- Prostate Action

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on cabazitaxel by providing oral evidence to the Committee. They were also invited to comment on the ACD.

- Dr Simon Crabb, Senior Lecturer and Honorary Consultant in Medical Oncology, nominated by Royal College of Physicians – clinical specialist.
- Dr Heather Payne, Consultant in Clinical Oncology, nominated by British Uro-Oncology Group – clinical specialist.
- Lauren Wiggins, Senior Information and Support Nurse Specialist, nominated by the Prostate Cancer Charity – clinical specialist.
- George Goldsmith, nominated by the Prostate Cancer Support Federation – patient expert.
- Ruth Holdaway, Director of Operations, the Prostate Cancer Charity, nominated by the Prostate Cancer Charity – patient expert.

- D The following individual was nominated as NHS Commissioning expert by the selected PCTs allocated to this appraisal. She gave her expert/NHS commissioning personal view on cabazitaxel by attending the initial Committee discussion and providing written evidence to the Committee. She was also invited to comment on the ACD.
- Suzanne Heafield, selected by NHS Warwickshire – NHS Commissioning expert
- E Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.
- Sanofi-aventis