NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

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

The Department of Health asked the National Institute for Health and Clinical Excellence (NICE) to produce guidance on using cabazitaxel in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists 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 draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see appendix B) and the public. This document should be read along with the evidence base (the evaluation report), which is available from www.nice.org.uk

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 provisional 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 gender, race, disability, age, sexual orientation, religion or belief?

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 and Wales.

For further details, see the 'Guide to the technology appraisal process' (available at www.nice.org.uk).

The key dates for this appraisal are:

Closing date for comments: 21 October 2011

Second Appraisal Committee meeting: 1 November 2011

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

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1 Appraisal Committee's preliminary recommendations

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.

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 like diarrhoea. Other very common adverse reactions include fatigue, nausea, vomiting, constipation, asthenia, haematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnoea, abdominal pain, dysgeusia, cough, arthralgia, and alopecia. 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 is £3696 excluding VAT (based on the manufacturer's submission). The average of cost of one cycle of treatment is £3696 excluding VAT. The median number of cycles in the key clinical trial was 6. 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 and an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, with evidence of disease progression during or after completion of docetaxel-containing treatment. Patients were randomised to cabazitaxel plus prednisone or prednisolone, or to mitoxantrone plus prednisone or prednisolone. Patients who were receiving luteinizing hormone-releasing hormone agonist therapy were allowed to continue it. 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 (lasting ≥ 7 days) neutropenia 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 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 duration of 12.8 months, at which point 513 deaths had occurred (having planned for final analyses after 511 deaths). An updated analysis was carried out almost 6 months later, when 585 deaths had occurred. The manufacturer presented the results for the primary end point, 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 rising at baseline or not, time from last docetaxel treatment to randomisation, docetaxel dose and time of progression from last docetaxel treatment. The manufacturer also presented overall survival and progression-free survival for three subgroups defined post hoc: patients with an ECOG performance score of 0 or 1 who had received > 225 mg/m^2 of docetaxel; European patients; and European patients with an ECOG performance score of 0 or 1 who had previously received

≥ 225 mg/m^2 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 post hoc 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/m^2 given intravenously over 1 hour, or mitoxantrone 12 mg/m^2 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 almost 6 months later reported median survival values identical 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 of the subgroups defined a priori except in patients who had received insufficient prior docetaxel therapy 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 people who had 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 0.49–0.76, $p < 0.0001$).

3.8 PSA response was measured only in patients with a baseline serum PSA concentration ≥ 20 micrograms per litre and was defined as a ≥ 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 ≥ 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 ≥ 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 0.63–0.90, 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 ≥ 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 ≥ 25% in the mean analgesic score compared with the baseline score noted on two consecutive visits made 3 weeks apart, or requirement 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 ≥ grade 3 neutropenia (82% compared with 58% in the mitoxantrone arm), and infections and febrile neutropenia (28% compared with 5% 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).

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 either prednisone or prednisolone, and mitoxantrone combined with either prednisone or prednisolone. The model's perspective was that of the NHS/personal social services. All future costs and benefits were discounted at a rate of 3.5%. Treatment was modelled over a lifetime (15 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 that included European patients with an ECOG performance status of 0 or 1 who had previously received ≥ 225 mg/m^2 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 study was small. After this time, the manufacturer calculated transition probabilities from fitted parametric curves as it considered the data from Kaplan-Meier curves from a small number of patients to be unreliable. In the base case the Kaplan-Meier data were used up until week 57 (19 cycles) for progression-free survival and week 111 (37 cycles) for overall survival. A Weibull distribution was used to estimate the overall survival rates for both treatments. For progression-free survival rates a Weibull distribution was fitted to

the cabazitaxel data whereas a log-normal distribution was fitted to the mitoxantrone data.

3.14 Treatment costs incurred during the stable disease state included the acquisition and administration costs of active treatment, the costs of premedication before treatment and concomitant medication during treatment. The manufacturer included in the model the costs and disutilities of grade 3 adverse events in the stable disease state only, based on observations in TROPIC. 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 best supportive care and a mix of post second-line chemotherapies received by patients in TROPIC. The manufacturer applied an end-of-life cost when modelled 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) program collecting EuroQol 5-Dimension (EQ-5D) data from patients receiving cabazitaxel treatment for metastatic prostate cancer in nine UK centres. The manufacturer calculated the utility of the progressive disease state by applying a decrement derived from the literature 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.

3.16 In the 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. During the clarification step between the Evidence Review Group (ERG) and the manufacturer, 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 incidence of adverse events). These changes increased the base-case ICER to £74,938 per QALY gained.

3.17 The manufacturer conducted one-way deterministic sensitivity analyses by varying parameters in the model to assess the robustness of the ICER. 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.

3.18 The manufacturer also conducted seven scenario analyses: 1) using alternative curve fitting, that is, statistical extrapolations for the curves representing overall survival and progression-free survival and 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; 2) 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; 3) an alternative utility decrement of 0.085 instead of 0.07 in the base case for progressive disease, which led to an ICER of £76,171 per QALY gained; 4) 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; 5) equivalent costs for progressive disease in both arms, which led to an ICER of £68,210 per QALY gained; 6) assuming that patients share vials of cabazitaxel, which lead to an ICER of

£60,928 per QALY gained; and 7) assuming post second-line treatment cost in accordance with an audit from the UK instead of from TROPIC data, which led to an ICER or £75,972 per QALY gained

3.19 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.

3.20 In addition to the population (subgroup) chosen for the base case, the manufacturer also calculated an ICER for the whole population enrolled in TROPIC (£87,684 per QALY gained), for European patients in TROPIC (£84,540 per QALY gained) and for all TROPIC patients with an ECOG performance score of 0 or 1 who received ≥ 225 mg/m^2 of docetaxel (£82,538 per QALY gained).

3.21 The ERG was content with the methodological quality of TROPIC but noted that it was not powered to detect differences in the incidence of specific adverse events. The ERG noted that because of the stringent management of adverse events in the trial, the incidence of adverse events associated with cabazitaxel is likely to be higher in clinical practice in the UK. The ERG stated that the trial provided insufficient information on the cardiac and renal complications associated with cabazitaxel. The ERG considered the manufacturer's model to be robust and transparent, allowing variables to be altered and the variability and uncertainty in the model to be assessed.

3.22 The ERG's view was that the population used by the manufacturer in the base case was inappropriate because there was no a-priori 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 ≥ 225 mg/m^2 docetaxel (p = 0.4098). The ERG therefore suggested the population most clinically relevant to the UK to be all patients in TROPIC who received ≥ 225 mg/m^2 of first-line docetaxel and who had an ECOG performance score of 0 or 1.

3.23 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 arbitrary. 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 were likely to have overfit the data and were less generalisable to other populations. The ERG stated that therefore the use of parametric curves throughout would be more appropriate.

3.24 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 from the analysis. The ERG believed that these deaths in TROPIC 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%) had died within the first month after 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 after 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.

3.25 The ERG also 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 utility values observed in the general population for that age group, which the ERG thought to be implausible. The ERG also noted that the utility values for stable disease and progressive disease were sampled independently, 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 also identified a minor error in the way in which the model implemented the discount rate, but this had minimal impact on the ICER.

3.26 The ERG performed an exploratory analysis using the manufacturer's model on the 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/m^2 of first-line docetaxel and who had an ECOG performance score of 0 or 1. The ICER for this population was £82,538 per QALY gained. The ERG amended the manufacturer's model by using parametric curves for the entire duration of 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, and correcting the error in the discount rate. The combined impact of all these amendments was to increase the ICER to £89,476 per QALY gained.

3.27 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 95% CI 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 (also reported in the literature) increased the ERG's base-case ICER from £89,476 to £90,865 per QALY gained.

3.28 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. 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 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 for a short time, and the hope that this offers. The Committee further heard that patient experts are aware that cabazitaxel is associated with serious adverse events and that it would not be suitable for some patients who are not fit for chemotherapy. The Committee agreed with the patient experts that clinicians should inform patients about the potential serious toxicity of cabazitaxel and the lack of evidence showing that cabazitaxel improves health-related quality of life before taking the decision to start cabazitaxel therapy. 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 manufacturer on the clinical effectiveness of cabazitaxel. The

Committee noted that the evidence was based on a large, multinational, phase III, randomised trial (TROPIC) 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. The Committee 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 level and in pain. The Committee heard from the clinical specialists that in clinical practice a rise in PSA level 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, although on average younger (median age 68 years). 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 clinical specialists that the choice of ten cycles was arbitrary, and from the manufacturer that ten cycles was chosen because mitoxantrone is limited to ten cycles owing to 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 events, or would have died. The Committee also noted that clinicians commonly discuss with patients their response to cabazitaxel treatment after six cycles and on this basis decide whether to continue treatment. 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. However, the Committee also noted that there is uncertainty about the effect of cabazitaxel relative to mitoxantrone on overall survival in the long term, that is, beyond the period of the trial.

4.6 The Committee considered the appropriateness of the manufacturer's base-case population based on the subgroup defined post hoc from TROPIC that comprised European patients with an ECOG performance score of 0 or 1 who had received ≥ 225 mg/m^2 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 different subgroups, an a-priori clinical rationale justifying this would be needed and statistical tests for interaction between patients with or without the characteristics that define the different subgroups would be necessary.

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 events similarly to clinicians in the UK. The Committee also noted the ERG's comments that survival in European patients was not significantly different from that in non-European patients. The Committee concluded that it is not appropriate to restrict the base-case population to patients recruited at European centres.

4.8 The Committee considered limiting the subgroups to those who had received at least 225 mg/m^2 docetaxel as first-line therapy. The Committee heard from the manufacturer that best practice guidelines recommend receiving this dose. 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 insufficient docetaxel therapy. The Committee also heard from the clinical specialists that it is appropriate for patients to receive at least three cycles 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/m^2 of docetaxel was appropriate.

4.9 The Committee considered limiting the subgroups to those with an ECOG performance score of 0 or 1. The Committee heard from the

clinical specialists that in patients with hormone-refractory metastatic prostate cancer ECOG is routinely used to assess performance and this 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 three cycles of docetaxel and had an ECOG performance score of 0 or 1.

4.10 The Committee considered the evidence on adverse effects associated with cabazitaxel. It noted that haematological adverse events and diarrhoea were major concerns. The Committee heard from the clinical specialists that the majority of 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 the management of neutropenia and, as a result, few patients in the UK develop febrile neutropenia or neutropenic sepsis. 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 heard from the manufacturer about an ongoing phase I study evaluating renal toxicity in patients receiving cabazitaxel. The Committee concluded that there remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events.

4.11 The Committee noted that TROPIC did not collect data on health-related quality of life and that the manufacturer obtained data on utility in patients with stable disease from a programme in the UK that permits early access (before marketing authorisation) to cabazitaxel. The Committee heard from the manufacturer that the data were based on a small number of patients in nine UK centres. The Committee concluded that because the utility data were based on such a small number of patients from a potentially select population, there is considerable uncertainty as to the validity of these data.

Cost effectiveness

4.12 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 considered the structure of the submitted Markov model to be acceptable.

4.13 The Committee considered the transition probabilities that reflected moving between different states in the model. The Committee noted that in the manufacturer's model, the calculated transition probability from either the stable disease or progressive disease state to the death state was based on Kaplan-Meier data from TROPIC for overall survival until completion of 37 cycles of treatment, after which the model used parametric curves. The Committee noted the ICER was very 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 the most favourable ICER. The Committee considered the ERG's concerns that Kaplan-Meier curves could overfit the data and that parametric curves are more likely to lead to 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 £82,950 per QALY gained. The Committee concluded that the parametric fitted curves more closely fit data from TROPIC and are more generalisable to the population outside the trial.

4.14 The Committee noted that the ERG had carried out an analysis for the Committee's preferred patient population (all patients in TROPIC who received at least three cycles of docetaxel and had an ECOG performance score of 0 or 1; see sections 4.7–4.9) which included, in addition to the parametric curve fitting, a correction of an error in the discount rate. This analysis produced an ICER of £89,500 per QALY gained for cabazitaxel compared with mitoxantrone. The Committee concluded that this ICER would be an appropriate starting point for its decision making.

4.15 The Committee considered hat removing data from patients who died within 30 days of randomisation from the analysis increased the ICER. 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, which resulted in a difference between the mean survival within the cabazitaxel and the mitoxantrone arms. The Committee concluded that with better management of neutropenia these early deaths could be avoided and it is plausible that the ICER would be slightly higher than estimated.

4.16 The Committee noted that the manufacturer based the utility value for the stable disease state on a small selected sample of patients and that therefore the value had wide confidence intervals, and may have been biased. The Committee understood that the utility

value for stable disease incorporated in the model was similar to the utility value observed in the age-matched general population and concluded that the manufacturer had likely overestimated the utility of the stable disease state. 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 considered that both the absolute values of, and difference in, utilities between stable and progressive disease were likely to be underestimated. The Committee was aware that the choice of utility value in progressive disease had an impact on the ICER, and that changing this parameter by 20% either way resulted in ICERs of £65,000 to £89,000 per QALY gained. The Committee heard from the clinical specialists that it is difficult to determine the difference in quality of life between the two health states because symptoms vary across patients (for example, some patients sustain fractures arising from bone metastases that cause considerable pain and loss of independence, whereas in other patients with bone metastases such fractures do not occur). 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 considered that a decrement of only 0.07 between the stable and the progressive disease state underestimates the difference in quality of life between the two health states. The Committee also noted that using a slightly larger utility decrement of 0.085 for progressive disease raised the ICER from the ERG's base case of £89,500 to £90,900 per QALY gained, and that using the lower limit of the 95% CI for the utility value for stable disease increased the ICER from £89,500 to £111,700 per QALY gained. The Committee concluded that there is uncertainty over the utility values used in the model, that it is likely that the manufacturer had

overestimated the utility values and that the use of more realistic utility values would increase the ICER.

4.17 The Committee considered the assumptions related to resource use in the manufacturer's model. The Committee heard from the clinical specialists that the manufacturer had assumed that an improbably high proportion of patients received post second-line chemotherapy (designated as academic in confidence in the manufacturer's submission and therefore not shown) 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 UK values for post second-line chemotherapy from the audit would increase the ICER. 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 model. The Committee concluded that this would further increase the ICER.

4.18 The Committee considered the sensitivity analysis related to vial sharing of cabazitaxel and noted that if patients shared vials, the ICER would decrease. 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.

4.19 In summary, the Committee considered the most appropriate base-case population to be all patients in TROPIC with ECOG performance scores of 0 or 1 who had received at least three cycles of prior docetaxel. The Committee therefore considered the ICER of £89,000 per QALY gained 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, the costs of post second-line chemotherapy were not appropriately estimated, and the costs associated with the management of adverse events were underestimated. The Committee therefore concluded that the most plausible ICER would be above £89,000 per QALY gained and that therefore cabazitaxel could not be recommended as a cost effective use of NHS resources.

4.20 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.

4.21 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 holds a marketing authorisation can be considered to be small. The Committee considered the degree to which cabazitaxel extended life. It noted that 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 agreed that further exploration and validation of the modelled mean survival benefit using updated trial-based or observational data would be necessary before the mean extension to life of 4.2 months could be considered sufficiently robust for the end of life criteria to be met.

4.22 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 was 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.

4.23 The Committee considered whether cabazitaxel can be considered innovative. 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: Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen**	**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. The Committee considered the incremental cost-effectiveness ratio (ICER) of £89,000 per quality-adjusted life year (QALY) gained 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, the costs of post second-line chemotherapy were not appropriately estimated, and the costs associated with the management of adverse events were underestimated. The Committee therefore concluded that the most plausible ICER would be above £89,000 per QALY gained and that therefore cabazitaxel could not be recommended as a cost effective use of NHS resources.		1.1 4.19
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	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.	4.3
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	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.	4.23

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' 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.	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 concluded that there remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events.	4.10
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Evidence of clinical effectiveness comes from an open-labelled randomised controlled trial (TROPIC) in men aged over 18 years with hormone-refractory metastatic prostate cancer and an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, with evidence of disease progression during or after completion of docetaxel-containing treatment 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
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. There were also uncertainties related to the effect of cabazitaxel on long term overall survival.	4.4, 4.7
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 three cycles of docetaxel and had an ECOG performance score of 0 or 1.	4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that the evidence demonstrated that cabazitaxel is an effective second-line treatment for hormone-refractory metastatic prostate cancer. However, the Committee also noted that there is uncertainty about the effect of cabazitaxel relative to mitoxantrone on overall survival and progression-free survival in the long term, that is, beyond the period of the trial.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	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 (15 years) with a 3-week cycle length. The model included three health states: stable disease, progressive disease and death. The Committee considered the structure of the submitted Markov model to be acceptable.	3.12 4.12

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that there remains considerable uncertainty in the robustness of manufacturer's base case ICER because effectiveness data used from a post hoc subgroup from TROPIC without any plausible clinical or statistical rationale, model used data from Kaplan Meier curves to calculated transition probabilities (until the small number of patients made the curve erratic after which parametric curves were used) making its result less generalisable to the population outside the trial, 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 resulted in imprecise and overestimated values , the costs of post second-line chemotherapy were not appropriately estimated, and the costs associated with the management of adverse events were underestimated.	4.9, 4.13, 4.16, 4.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that the ICERs were sensitive to the absolute and relative difference in the utility for stable disease and progressive disease. None identified	4.11, 4.16
Are there specific groups of people for whom the technology is particularly cost effective?	n/a	n/a
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, utility value assigned to stable and progressive disease state and the cost of post second-line chemotherapies.	4.13, 4.16, 4.17

Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered the most plausible ICER to be £89,000 per 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, the costs of post second-line chemotherapy were not appropriately estimated, and the costs of associated with the management of adverse events were underestimated. The Committee therefore concluded that the most plausible ICER would be above £89,000 per QALY gained and that therefore cabazitaxel could not be recommended as a cost effective use of NHS resources.	4.19
Additional factors taken into account		
Patient access schemes (PPRS)	n/a	n/a
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 further exploration of the modelled mean survival gain using updated trial-based or observational data on mean overall survival would be necessary before the mean extension to life of 4.2 months could be considered sufficiently robust for the end of life criteria to be met.	4.21
Equalities considerations and social value judgements	The Committee concluded that this appraisal's recommendations should refer to people rather than men to include people who have proposed, started or completed gender reassignment.	4.22

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 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 guidance (publication expected May 2012). Available from www.nice.org.uk/guidance/TA/Wave26/4

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in February 2015. 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
September 2011

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. Its 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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 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, Littlewood C, Wong R. Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer: a single technology appraisal. ScHARR, The University of Sheffield, (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 and II 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 for the second-line treatment of hormone refractory metastatic prostate cancer by attending the initial Committee discussion and providing written evidence to the Committee. They are 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 is invited to comment on the ACD.

- Suzanne Heafield, selected by NHS Warwickshire – NHS Commissioning expert

E Representatives from the following manufacturer attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Sanofi