Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer: A single technology appraisal

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Matt Stevenson and Ben Kearns critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Myfanwy Lloyd Jones and Chris Littlewood critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Ruth Wong commented on the searches included in the manufacturer's submission and contributed to the writing of the report. Matt Stevenson acted as project lead.

TABLE OF CONTENTS

List of Tables and Figures

List of abbreviations

ADT	Androgen-Deprivation Therapy
AE	Adverse Event
AIC	Akaike Information Criterion
AS	Analgesic Score
ASCO	American Society of Clinical Oncology
BAUS	British Association of Urological Surgeons
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSA	Body Surface Area
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence interval
CR	Complete Response
EAP	Early Access Programme
ECOG	European Cooperative Oncology Group
EQ-5D	EuroQol 5-Dimension
ERG	Evidence Review Group
FDA	Food and Drug Administration
G-CSF	Granulocyte-Colony Stimulating Factors
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IQR	Interquartile Range
ITT	Intention To Treat
KM	Kaplan-Meier
LHRH	Luteinising Hormone-Releasing Hormone
mCRPC	Metastatic Castration-Resistant Prostate Cancer
mHRPC	Metastatic Hormone Refractory Prostate Cancer
MS	Manufacturer's Submission
NCDB	National Cancer Data Base
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PPI	Present Pain Intensity

PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RD&TC	Regional Drug and Therapeutics Centre
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SD	Stable Disease
SRE	Skeletal-Related Event
VAS	Visual analogue scale

Glossary

Analgesic score	Mean daily patient-recorded analgesic use expressed in morphine equivalents.
European Cooperative Oncology Group (ECOG) performance status (PS)	Criteria used to assess a patient to determine appropriate treatment and prognosis. Performance is graded from 0 to 5, where: 0 = fully active, able to carry on all predisease performance without restriction 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work 2 = ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours 4 = completely disabled. Cannot carry on any self-care. Totally confined to bed or chair 5 = dead.
Hazard ratio	A measure of relative risk used in survival studies.
Karnofsky performance status score	A performance measure used to rate a person's ability to perform normal activities. It can be used to determine a patient's suitability for therapy, or to evaluate the impact of a therapeutic procedure. It is commonly used in patients with cancer. The health care professional assesses the patient's ability to perform certain ordinary tasks on a scale of 0-100%, where: 100% is normal; 90% is able to carry on normal activity but with minor signs or symptoms of disease; 80 is able to carry on normal activity with effort and with some signs or symptoms of disease; 70% cares for self but unable to carry on normal activity or to do active work; 60% requires occasional assistance but is able to care for most needs; 50% requires considerable assistance and frequent medical care; 40% is disabled and requires special care and assistance; 30% is severely disabled and hospitalisation is indicated although death not imminent; 20% hospitalisation is necessary, very sick, active supportive treatment necessary; 10% moribund, fatal processes progressing rapidly; 0% dead.
Neutropenia	An abnormally low level in the blood of neutrophils, cells which are important in fighting infections within the body.
Prostate-specific antigen	A protein produced by the prostate gland. It is found in small quantities in the serum of men with healthy prostates, but is often elevated in men with prostate cancer or other prostate disorders. The PSA level should fall following curative therapy for prostate cancer; a subsequent rise is likely to indicate cancer recurrence.
Skeletal-related event	Adverse events associated with bone metastases, and including pathological fractures, spinal cord compression, hypercalcaemia, and severe pain requiring bone surgery, radiation therapy or opioid analgesics
Visual analogue scale (VAS)	A simple measurement scale frequently used for the assessment of an attitude or characteristic, e.g. pain.

1. SUMMARY

1.1 Scope of the manufacturer's submission

The manufacturer's submission (MS) to NICE sought to provide evidence relating to the clinical and cost effectiveness of cabazitaxel used within its licensed indication in combination with prednisolone for the second-line treatment of metastatic hormone refractory prostate cancer (mHRPC) which has progressed following or during docetaxel therapy.

The NICE final scope identified two relevant comparators - mitoxantrone plus prednisolone, and chemotherapy without cabazitaxel (e.g. 5-fluorouracil, cyclophosphamide and carboplatin/etoposide). However, the MS limited the comparator to mitoxantrone plus prednisolone on the basis that mitoxantrone plus prednisolone is the active treatment most commonly used in the UK as second-line treatment in patients with mHRPC, and that other chemotherapy agents were not relevant to the decision problem because they are seldom used for this purpose and therefore cannot be considered part of standard UK clinical practice. The ERG's clinical advisors concurred with this view.

The MS addressed the outcomes specified within the NICE final scope.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS included a systematic review of all randomised controlled trials (RCTs) of cabazitaxel versus any comparator. This identified only one relevant study: the TROPIC study, a multinational open-label active-controlled randomised trial designed to compare the efficacy and safety of cabazitaxel plus prednisone or prednisolone against mitoxantrone plus prednisone or prednisolone in patients with mHRPC which has progressed following or during docetaxel therapy. (Prednisone, which is widely used outside the UK, appears to be functionally interchangeable with prednisolone.)

Efficacy

The TROPIC study found that, relative to mitoxantrone plus prednisone/prednisolone, cabazitaxel plus prednisone/prednisolone was associated with a median overall survival (OS) gain of 2.4 months (15.1 vs. 12.7 months; hazard ratio (HR) 0.70, 95% CI 0.59-0.83, $p<0.0001$). An updated analysis found that the median values were unchanged, but the HR was 0.72 (95% CI 0.61-0.84, $p<0.0001$). Cabazitaxel was associated with statistically significant improvements in median progression-free survival (PFS) (2.8 vs 1.4 months; HR 0.74, 95% CI 0.64-0.86, $p<0.0001$), and in Prostate-Specific Antigen (PSA) response, time to PSA progression, objective tumour response, and time to tumour progression, but was not associated with statistically significant differences in pain response or pain progression. Quality of life data comparing cabazitaxel with mitoxantrone were not available.

Safety

In the TROPIC study, the most common adverse events (AEs) associated with cabazitaxel were haematological: the incidence of grade $\geq$ 3 neutropenia and leukopenia were both noticeably higher with cabazitaxel than with mitoxantrone (82% vs 58%, and 68% vs 42%, respectively). The incidence of diarrhoea of any grade, and of grade $\geq$ 3 gastrointestinal disorders of all types, were also substantially higher with cabazitaxel (47% vs 11%, and 12.4% vs 1.6%, respectively). The risk of most AEs was substantially increased in patients aged 65 and over.

Deaths within 30 days of the last dose of study drug were more common with cabazitaxel (5% vs 2%). The most common causes of such deaths were neutropenia in patients receiving cabazitaxel, and disease progression in patients receiving mitoxantrone. Cardiac and renal complications other than deaths appear to be poorly reported.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The MS appears to be complete in that it includes the only RCT of cabazitaxel plus prednisone/prednisolone which is known to have been undertaken in the relevant population. This study, the TROPIC study, is an open-label study and is therefore susceptible to bias in the assessment of subjective outcomes such as pain and symptomatic disease progression; PFS, a composite endpoint which incorporates pain progression, is also susceptible to bias, although OS (the primary outcome), and tumour response, both of which are objective measures, are unlikely to have been affected. Pain outcomes may also have been affected by the lower prevalence of bone metastases in patients randomised to cabazitaxel than in those randomised to mitoxantrone (80% vs 87%).

The assessment of clinical AEs is also susceptible to bias because of lack of blinding, although the assessment of laboratory AEs is unlikely to have been affected. Despite this, concern has been expressed about the raised incidence of neutropenic complications (febrile neutropenia and infection), renal failure, haematuria, and cardiac toxicity associated with cabazitaxel. There is particular concern that deaths were attributed to cardiac and renal failure even though the TROPIC study's inclusion criteria included adequate cardiac and renal function.

Because the TROPIC study used more stringent criteria relating to dose modifications and discontinuations of cabazitaxel therapy than are included in the product specification, the incidence of AEs associated with cabazitaxel may be higher in clinical practice than observed in TROPIC.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer supplied a *de novo* cohort Markov model constructed in Microsoft Excel©. Three states are modelled: stable disease; progressive disease and death. All patients begin in the stable disease state, from which transitions to progressive disease or death are possible. Following progression the only transition possible is to death, which is an absorbing state.

In the manufacturer's base case analysis, costs and transition probabilities are based on a subgroup of the TROPIC study, namely 'European patients who received ≥225mg/m2 of first-line docetaxel and with European Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1'. Transition probabilities are time-varying and based on Kaplan-Meier data, until the point when they are judged (by the manufacturer) to be too unreliable and are then replaced with transition rates calculated from parametric curves. In the absence of data relating to health-related quality of life from controlled trials of cabazitaxel, the manufacturer utilised interim results from the early access programme (EAP) for cabazitaxel, which allow comparison with baseline but not with mitoxantrone or any other comparator therapy. Data from the EAP was only available for a relatively small number of patients with stable disease; an estimation of the decreased utility for patients with progressive disease was taken from published literature.

In their base case the manufacturer estimated a deterministic cost per quality adjusted life year (QALY) gained of £74,938. Probabilistic sensitivity analysis (2,000 simulations) indicated that this value ranged from £45,760 to £890,372. Univariate sensitivity analyses showed that the main drivers for this variation are changes in utility estimates for both disease states and the time point from which the parametric curve were used. If the parametric curves were used for the entire modelling period the incremental cost-effectiveness ratio (ICER) became £82,950.

There is uncertainty regarding whether the deaths observed within 30 days of randomisation in TROPIC could be preventable with more vigilant treatment of neutropenia. The occurrence of these deaths prompted advice to the TROPIC investigators to manage neutropenia by strictly following the protocol regarding dose modification and delay and treating neutropenia as per ASCO guidelines. Following this, no new neutropenic deaths were reported. Accordingly the manufacturer conducted an exploratory analysis evaluating the change in the ICER were the deaths associated in the first 30 days not considered. This increased the ICER to £78,319 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG did not concur with the manufacturer in the choice of patient population and regarding the use of the Kaplan-Meier data that constitute the base case. These are discussed in turn.

Compared with the full TROPIC trial population, the patient population used within the economic model is filtered in three ways: it is restricted to European patients; patients who did not receive at least 225mg/m^2 of first-line docetaxel were excluded; and patients with an ECOG PS of 2 were excluded. Whilst the ERG (following discussions with its clinical advisors) believes that the last two filters have clinical validity, the restriction to just European patients is less justified. Given that there were no *a priori* reasons for considering just this population, and that a statistical test of treatment interaction by region gave a non-significant result, the ERG feels that the arguments for making this geographic restriction are not sufficiently compelling, and that all regions should be included.

The ERG feels that the use of parametric curves throughout is preferable compared with directly using the Kaplan-Meier curves followed by the transition proportions from the curves. This is primarily for two reasons: firstly the Kaplan-Meier curves are likely to overfit the data and be less generalisable; secondly the choice of time point at which the data from the Kaplan-Meier curves are considered unreliable has a marked effect on the ICER, which ranged from £72,184 to £90,786 dependent on when the Kaplan-Meier data were considered unreliable.

It is additionally noted that the ICER is sensitive to the choice of utility values and fuller data from the EAP are required before a robust ICER can be provided.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The manufacturer undertook a systematic review of the evidence for cabazitaxel as second-line treatment of mHRPC. The one study which was identified and included in this review used cabazitaxel within its licensed indication in the relevant population, and measured outcomes which were appropriate and clinically relevant. The study's methodological quality appeared to be generally good. However, because of lack of blinding, it incorporated some risk of bias.

The conceptual model used appears robust and transparent, allowing both variability and uncertainty in the model inputs to be altered and assessed. The model contained the functionality to assess the impact of changing parameters and structural uncertainties on the ICER, and included a number of built-in alternative scenarios.

1.6.2 Weaknesses and areas of uncertainty

The adverse event data observed within the TROPIC RCT was of concern, the Food and Drug Administration recommended a review of renal toxicity and a submission of updates from active RCTs for three years after the US approval date (2010); data are currently not available. Therefore, caution may be prudent until these data emerge.

There is dispute (and hence corresponding uncertainty in the ICER) regarding the correct population from which to estimate transition probabilities, and whether parametric curves should be used throughout the modelling horizon. The ERG has a different view on these issues than the manufacturer.

A key uncertainty relates to the utility values that should be assigned to stable and progressive disease, as the available data is not sufficiently robust. The importance of this is highlighted by the sensitivity of the results to the utility values used. It is noted that more data should soon be made available from the EAP.

Updated data from the TROPIC study (based on 585 deaths rather than 513) is available that were not used in the submission. During the clarification process the manufacturer indicated that this has little impact on the ICER (using the population in the manufacturer's base case and when the parametric curves are used throughout the modelling horizon) although it is unclear what effect would be observed using the population constituting the ERG base case.

There is also uncertainty in whether the deaths observed within 30 days of randomisation in TROPIC could be prevented with more vigilant treatment of neutropenia. If so, exploratory analyses indicate that the ICER may increase.

1.7 Summary of additional work undertaken by the ERG

The ERG made 3 amendments to the manufacturer's base case.

- Estimating the transition probabilities from all patients who received ≥225mg/m2 of first-line docetaxel and with ECOG PS 0 or 1, rather than just European patients
- Using the parametric curves throughout the modelling horizon
- Making a small change to the discount rate used

This increased the ICER to £89,684, which was calculated from probabilistic sensitivity analyses. It was seen that the choice of utility values had a marked impact on the ICER and these are currently

highly uncertain. There is also residual uncertainty regarding whether the deaths observed within 30 days of randomisation in TROPIC may be preventable.

2. BACKGROUND

This report provides a review of the evidence submitted by sanofi-aventis in support of cabazitaxel for the second-line treatment of metastatic hormone refractory prostate cancer (mHRPC) which has progressed following or during docetaxel therapy. It considers both the original manufacturer's submission (MS) received on 10th June 2011[1] and subsequent addenda supplied on 13th July 2011.[2]

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of mHRPC which has progressed following or during docetaxel therapy is appropriate and relevant to the decision problem under consideration. It defines metastatic prostate cancer as stage IV cancer. Prostate cancer may be classified either by the tumour-node-metastasis (TNM) system or by numbered Stages I-IV; the latter defines Stage IV cancer as cancer which has either invaded local adjacent structures (the bladder or rectum) or has spread to the lymph nodes or other parts of the body such as the bones, liver, or lungs.[3] The MS then follows the NICE guideline[4] in stating that, while there is no universally accepted definition of hormone refractory prostate cancer, prostate cancer may be considered to be hormone refractory when androgen withdrawal therapy or combined androgen blockade no longer controls the prostate-specific antigen (PSA) or the symptoms of the disease, or when there is radiological evidence of progression. However, the guideline notes that such cancer may still respond to agents such as oestrogens or corticosteroids which probably work via the androgen receptor, and that luteinising hormone-releasing hormone (LHRH) therapy is usually continued even when the disease becomes hormone refractory.

The MS states in section 6.4.1 that metastatic prostate cancer is associated with a range of symptoms which substantially affect quality of life: these symptoms are said to include lymphoedema, weight loss, pain, and skeletal-related events (SREs) associated with bone metastases. It also states, in section 2.1, that bone metastasis is a common form of metastatic disease in prostate cancer; that bone metastases often lead to SREs including fractures, spinal cord compression, and severe pain; and that bone metastases, and the associated pain, contribute substantially to the burden of disease in patients with metastatic prostate cancer.[1] However, it should be noted that lymphoedema is not common in prostate cancer. Furthermore, although Cancer Research UK states that bone pain is the biggest problem associated with mHRPC,[5] the Prostate Cancer Charity notes that not all men with metastatic prostate cancer will have pain.[6] Moreover, the pathological fracture rate associated with bone metastases in prostate cancer is low relative to that associated with other metastatic cancers, and the rate of healing approaches that of normal bone, with surgical stabilisation required in only about a quarter of cases.[7]

Prostate cancer is common in England and Wales. There were 33,373 new cases in 2008, the most recent year for which data are available;[8] in that year, 9,150 deaths were attributed to prostate cancer.[9] Five-year survival with metastatic cancer is poor: although the overall five-year survival rate for patients diagnosed with prostate cancer in England and Wales in 2001-2006 was 77%, five-year survival in patients in England who presented with metastatic cancer in 1999-2002 was only around 30%.[10]

There are no published data for the incidence of mHRPC. The MS[1] estimates that 7,047 patients in England and Wales have mHRPC. This estimate is derived from an epidemiological model developed by sanofi-aventis which was not made available to the Evidence Review Group (ERG), but which was said to incorporate the following data:

- An estimated incidence of prostate cancer in England and Wales in 2011 of 36,105. This is based on the Cancer Research UK figure, noted above, of 33,373 new cases of prostate cancer in England and Wales in 2008,[8] uplifted for 2011 using an observed annual rate of increase of 2.6% which the MS claims to be based on Cancer Research UK data. However, the ERG has failed to find evidence within Cancer Research UK data to indicate that the incidence of prostate cancer has been rising at a rate of 2.6% per annum in recent years; rather, those data indicate that, in Great Britain as a whole, the age-standardised prostate cancer incidence rate fell from a peak of 103 per 100,000 males in 2004 to 97.7 in 2008. During the period from 2001-2010, the annual average population increase for England and Wales was only 0.6%.[11] Using this figure, and conservatively assuming the incidence rate of prostate cancer to be stable, the ERG suggests that the absolute incidence of prostate cancer in England and Wales in 2011 would be more appropriately estimated at 33,977 than at 36,105.
- Data from the British Association of Urological Surgeons (BAUS) indicating that, in 2009, 9.3% of patients with prostate cancer had metastatic disease at diagnosis
- Data from studies by Cooperberg *et al.*,[12] and Stephenson and Eastham[13] relating to the number of patients who progress to metastatic disease from earlier stages.
- An assumption that patients with metastatic disease would become hormone-refractory within 3 years, whatever primary therapy was used. Progression rates were assumed to be 80% at year 1 and 20% in following years, adjusted for patients dying before developing hormone-refractory disease according to US National Cancer Data Base (NCDB) survival reports.[1]

The MS notes that its estimate of 7,047 patients with mHRPC is supported by Cancer Research UK data that, in 2008, 9,150 men in England and Wales died from prostate cancer,[9] since most but not all deaths from prostate cancer will occur in patients with mHRPC.[1] However, the ERG suggests that, for the reasons indicated above, the number of patients in England and Wales with mHRPC might more appropriately be estimated at 6,632 than 7,047.

The MS then calculated that 1,938 patients with mHRPC would be eligible for cabazitaxel per annum on the basis that their disease had progressed following or during docetaxel therapy, and that they were fit to receive further chemotherapy.[1] This figure is calculated by applying to the estimate of 7,047 the following factors based on market research commissioned by sanofi-aventis:

- 50% of patients referred to an oncologist with mHRPC are eligible to receive first-line therapy with docetaxel
- 55% of these patients are fit to receive further chemotherapy following docetaxel.[1]

Application of these factors to the ERG's estimate of 6,632 patients with mHRPC results in a lower figure of 1,823 patients per annum who might be eligible for cabazitaxel (for details, see Table 1).

Table 1: Manufacturer's and ERG's estimates of the number of patients with mHRPC who might be eligible for second-line therapy with cabazitaxel

Step		Estimate contained in MS	ERG estimate
1	Incidence of prostate cancer in England and Wales, 2008	33,373	33,373
2	Estimated 2011 incidence calculated by application of annual rate of increase by manufacturer of 2.6% and by ERG of 0.6%	36,105	33,977
3	BAUS figure of 9.3% for metastatic disease at diagnosis, plus data indicating numbers who progress from earlier stages	Not stated*	*
4	Assumption that metastatic disease will become hormone-refractory within 3 years, with progression rates of 80% at year 1 and 20% in years 2 and 3	7047	6632**
5	50% eligible to receive first-line docetaxel	3524	3316
6	55% fit to receive second-line chemotherapy	1938	1823

* In the absence of the manufacturer's epidemiological model, these figures could not be calculated.

** Because it was not possible to calculate the figure for the preceding step in the calculation, this figure was derived by applying the same percentage change to the figure of 33,977 as is seen between steps 2 and 4 in the manufacturer's estimate.

2.2 Critique of manufacturer's overview of current service provision

The MS states that the initial approach to metastatic prostate cancer is generally medical castration using hormonal therapy to reduce levels of circulating testosterone and thus inhibit cancer growth; infrequently, surgical castration is used. In time, all patients become refractory to first-line hormonal

agents (LHRH agonists or antagonists). Second- and third-line hormonal approaches using anti-androgens followed by anti-androgen withdrawal are effective for only a minority of patients in the short-term only, estimated to be around four months.[1] This description of treatment options in metastatic prostate cancer is congruent with that presented by Khan and Partin.[14]

The MS correctly states that docetaxel in combination with prednisolone is the only chemotherapy regimen licensed in the UK for the first-line treatment of mHRPC. NICE recommends a maximum of ten cycles of docetaxel in patients with a Karnofsky performance-status score of 60% or more.[4] The aim of this chemotherapy is to slow disease progression and prolong survival.

There is currently no NICE-approved second-line chemotherapy for use in patients whose mHRPC has progressed on or after docetaxel. The MS states that such patients are frequently offered palliative therapy with mitoxantrone plus prednisolone,[1] although mitoxantrone is not licensed in the UK for use in this application; alternatively, they may receive best supportive care (BSC) which may involve corticosteroids, palliative radiotherapy, analgesics, and bisphosphonates.[4] However, section 5.10.4 of the MS states that, in an audit of five UK centres, [redacted] of patients with mHRPC which had progressed on or after docetaxel therapy received second-line treatment with cytotoxic chemotherapy; the manufacturer therefore anticipates that clinicians would consider these patients to be potentially eligible for second-line therapy with cabazitaxel.[1]

The MS notes that BSC is costly in patients with mHRPC, not least because of the need for surgery to treat medullar compression or fractures resulting from bone metastases.[1] However, as noted in section 2.1, the pathological fracture rate is relatively low in metastatic prostate cancer, healing is relatively good, and surgical stabilisation is required in only about a quarter of cases.[7]

3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem as issued by NICE and addressed by the MS is shown in Table 2.

Table 2: Decision problem as issued by NICE and addressed by the MS

	Final scope issued by NICE[15]	**Decision problem addressed in the MS[1]**	**Rationale if different from the scope**
Population	Men who have hormone refractory metastatic prostate cancer which has progressed following or during docetaxel-based treatment	As in final scope	Not applicable
Intervention	Cabazitaxel in combination with prednisolone	As in final scope	Not applicable
Comparator(s)	• Mitoxantrone in combination with prednisolone • Chemotherapy without cabazitaxel (e.g. 5-fluorouracil, cyclophosphamide and carboplatin/etoposide)	Mitoxantrone in combination with prednisone or prednisolone	• Prednisone is used in many countries in preference to prednisolone, which is used in the UK; the two may be regarded as equivalent • The MS excluded the second comparator, citing as reasons the lack of clinical consensus on the choice of second-line cytotoxic agent; the absence of RCT evidence for any individual agent other than mitoxantrone; and the low frequency of use of such agents.
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rate • PSA level • Adverse effects of treatment • Health-related quality of life (HRQoL)	• Overall survival • Progression-free survival • Time to progression • Response rate PSA response or progression • Pain response or progression • Grade 3/4 adverse events • Cost-effectiveness • HRQoL	The MS included pain outcomes on the basis that pain is an important outcome in mHRPC.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost-effectiveness of cabazitaxel is expressed as a cost per QALY. The base case time horizon is 747 weeks, which was assumed to be equivalent to the patient's lifetime. Costs are considered from an NHS and Personal Social Services perspective.	Not applicable
Other considerations	If evidence allows, consideration will be given to subgroups defined by: • baseline performance status • duration of prior docetaxel exposure • time since docetaxel treatment. Guidance will only be issued in accordance with the marketing authorisation.	The TROPIC trial included pre-planned analyses of the primary outcome (OS) for subgroups defined by: • baseline performance status • total docetaxel dose • time since docetaxel treatment	The MS includes subgroup analyses of OS by baseline performance status, by total docetaxel dose (which broadly equates to, and is proxy for, the duration of prior docetaxel exposure), and by time from last docetaxel treatment to randomisation. Further sub-grouping by geographical region has also been conducted.

3.1 Population

The relevant patient population is patients with mHRPC which has progressed following or during docetaxel therapy. This population is appropriately defined in the MS.

3.2 Intervention

Cabazitaxel is a semi-synthetic taxane created by modifying 10-deacetylbaccatin III, a substance extracted from the European yew tree.[16] It binds to tubulin, inhibiting the disassembly of microtubules and thus inhibiting mitotic and interphase cellular functions, leading to tumour cell cytotoxicity.[17]

Cabazitaxel is licensed within the EU for use in combination with prednisone or prednisolone for the treatment of patients with mHRPC previously treated with a docetaxel-containing regimen.[17] It

received this marketing authorisation on 17th March 2011.[18] It is marketed in the UK by Aventis Pharma under the trade name Jevtana and supplied as a pack containing one 1.5 ml vial of liquid cabazitaxel concentrate (60 mg of cabazitaxel diluted in polysorbate 80 and citric acid), and one vial containing 4.5 ml of solvent (15% v/v ethanol 96% in water). Dosing is by body surface area (BSA) calculated in square metres; the recommended dose is 25 mg/m^2. The concentrate should first be mixed with the supplied solvent; the appropriate volume of concentrate-solvent mixture to produce the required dose for the patient should then be diluted to a concentration between 0.10 and 0.26 mg/ml in either 0.9% sodium chloride solution or 5% glucose solution. The dilution process must take place in controlled and aseptic conditions.[17] The list price of cabazitaxel is £3,696 per pack.[1] Because dosing is by BSA, some patients will require more than one pack per cycle. Unopened vials of cabazitaxel have a shelf-life of two years but, after opening, the concentrate and solvent should be used immediately.[17]

Cabazitaxel is administered as a 60-minute intravenous infusion every three weeks for a maximum of 10 cycles. Only one course of 10 cycles should be given. Patients should be observed closely for infusion-related hypersensitivity reactions, especially during the first and second infusions. Dose modifications should be made if patients experience specified adverse reactions, and treatment should be discontinued if the patient continues to experience any of those reactions at a dose of 20 mg/m^2 [2 17] (for details, see Table 3).

Table 3: Recommended dose modifications for adverse reactions in patients treated with cabazitaxel[17]

Adverse reaction	**Dose modification**
Prolonged (longer than 1 week) grade ≥3 neutropenia despite appropriate treatment including Granulocyte-Colony Stimulating Factors (G-CSF)	Delay treatment until neutrophil count is >1,500 cells/mm^3, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm^3, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2
Grade ≥3 diarrhoea or persisting diarrhoea despite appropriate treatment, including fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2
Grade ≥2 peripheral neuropathy	Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2

To minimise the risk and severity of infusion-related hypersensitivity reactions, the following premedication regimen should be administered at least 30 minutes prior to each dose of cabazitaxel:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent)
- corticosteroid (dexamethasone 8 mg or equivalent)
- H_2 antagonist (ranitidine or equivalent).[17]

To minimise the risk of neutropenia and its complications, complete blood counts should be monitored on a weekly basis during the first cycle of cabazitaxel, and before each subsequent cycle, so that if necessary the dose can be adjusted.[17]

Anti-emetic prophylaxis is recommended and can be given orally or intravenously as needed. Primary prophylaxis with G-CSF should be considered in patients with clinical features which put them at high risk of increased complications from prolonged neutropenia (i.e. age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities).[17] The MS suggests that G-CSF may also be used as secondary prophylaxis to prevent recurrent neutropenic complications.[1]

Cabazitaxel should not be given to patients with hepatic impairment. Patients with moderate or severe renal impairment, or end stage renal disease, should be treated with caution and monitored carefully during treatment. Co-administration with strong CYP3A inhibitors or strong CYP3A inducers should be avoided.[17]

Oral prednisone or prednisolone, at a dose of 10 mg/day, should be taken throughout the course of treatment with cabazitaxel.[17] Prednisone is a synthetic corticosteroid which is converted in the liver into the corticosteroid prednisolone. In the UK, prednisone is only licensed for use in moderate to severe rheumatoid arthritis, whereas prednisolone is licensed for use in a range of conditions.[19] The MS notes that, in the UK, the majority of patients are medically rather than surgically castrated; when receiving cabazitaxel, medically castrated patients would also require ongoing therapy with luteinising hormone-releasing hormone (LHRH) agonists.[1]

The licensed indication states that the use of cabazitaxel should be limited to units specialised in the administration of cytotoxic drugs, and that it should only be administered under the supervision of a qualified physician experienced in the use of anti-cancer chemotherapy and with facilities and equipment available to treat serious hypersensitivity reactions such as hypotension and bronchospasm.[17]

3.3 Comparators

The NICE final scope stated that cabazitaxel in combination with prednisolone should be compared with:

- Mitoxantrone in combination with prednisolone
- Chemotherapy without cabazitaxel (e.g. 5-fluorouracil, cyclophosphamide and carboplatin/ etoposide).[15]

The MS is limited to one comparator: mitoxantrone in combination with prednisone or prednisolone. Mitoxantrone is an anthracycline derivative licensed for the treatment of metastatic breast cancer and other cancers.[19] Although it is not licensed in the EU for use in patients with mHRPC, the MS states that mitoxantrone plus prednisolone is the active treatment most commonly used in the UK in patients with mHRPC which has progressed after docetaxel. It states that it is used mainly for its palliative benefits on pain, and has not been shown to improve survival compared with corticosteroids alone in any indication.[1] This is consistent with its selection for use as the comparator in the TROPIC study because it "improves response but not OS and because of its beneficial effects on quality of life, including pain palliation".[16]

In section 2.5, the MS justifies its failure to include the second comparator specified in the NICE scope, chemotherapy without cabazitaxel, claiming its lack of relevance to the decision problem on the basis that chemotherapy agents other than mitoxantrone plus prednisolone are seldom used in the UK as second-line treatment for patients with docetaxel-resistant mHRPC, and therefore cannot be considered part of standard UK clinical practice.[1] The ERG's clinical advisors concurred with this view.

The MS further states that the manufacturer found no RCT evidence relating to the use of chemotherapy agents other than mitoxantrone plus prednisolone in second-line mHRPC, and that therefore the validity of comparisons against these agents would be limited.[1] The ERG agrees that there are no RCTs which compare cabazitaxel with chemotherapy agents other than mitoxantrone plus prednisolone although, as noted in section 5.10.3 of the MS, there are RCTs of other agents in the relevant population. In particular, there is a large RCT showing that abiraterone acetate, an androgen biosynthesis inhibitor not currently licensed for use in the UK, is effective in this group of patients.[20] The manufacturer claimed that, owing to the limited availability of abiraterone data at this time, further discussion was beyond the scope of the MS;[1] the ERG accepts that full publication of the abiraterone study postdated the manufacturer's searches, whilst considering it to be a relevant intervention in this population, however the ERG notes that abiraterone would not be considered a

comparator within this single technology appraisal as it is neither licensed nor in routine use within the UK.

3.4 Outcomes

As noted in Table 1, the outcomes reported in the MS are largely the same as those listed in the final scope.[15] They are discussed in more detail below.

Overall survival (OS)

The primary outcome measure, overall survival, is the gold standard efficacy outcome measure in this patient population.[21] The TROPIC study defined OS as the time from the date of randomisation to death. OS data were censored at the last date the patient was known to be alive, or at the data cut-off date, whichever was earlier.[22]

Progression-free survival (PFS)

PFS is a composite endpoint which has no standard definition. The TROPIC study defined it as the time from randomisation to tumour progression, PSA progression, pain progression, or death due to any cause, whichever occurred first.[22] The MS states that this is a conservative definition of PFS because it includes biochemical (PSA) progression, which frequently precedes symptomatic or radiological progression.[1] Consequently, it is likely to underestimate the clinical PFS experienced by patients with mHRPC who receive cabazitaxel therapy in clinical practice. The ERG notes that the TROPIC study's definition of PFS includes a subjective outcome, pain progression, which is susceptible to bias given the unblinded nature of the study. Treatment was discontinued following the identification of disease progression.[23]

Tumour response rate (assessed only in patients with measurable disease at baseline)

In patients with measurable disease at baseline, tumour response rate was assessed according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria.[22,24] These criteria define measurable disease as the presence of at least one lesion which can be accurately measured and whose longest dimension is $\geq$20 mm using conventional techniques or $\geq$10 mm using spiral CT scan. Smaller lesions are considered to be nonmeasurable, and a range of lesions including bone lesions are considered to be truly nonmeasurable. The RECIST criteria stipulate that all measurable lesions up to a maximum of 5 per organ and 10 in total, representative of all involved organs, should be regarded as target lesions and measured at baseline; if a patient has only one measurable lesion, it should be confirmed as neoplastic by cytology or histology.[24] The RECIST criteria define tumour responses as follows:

- Complete response (CR): disappearance of all target lesions
- Partial response (PR): decrease of at least 30% in the sum of the longest diameter of target lesions

- Progressive disease (PD): increase of at least 20% in the sum of the longest diameter of target lesions
- Stable disease (SD): neither sufficient decrease to qualify as partial response nor sufficient increase to qualify as progressive disease.[24]

In the TROPIC study, objective responses (CR and PR) had to be confirmed by repeat tumour imaging.[1] Although only 405 out of 755 patients (54%) in the TROPIC study had measurable disease,[22] this seems to be inconsequential in terms of the interpretation of the outcomes.

Time to tumour progression

Time to tumour progression was defined as the number of months from the date of randomisation to evidence of PD using the RECIST criteria.[22] Patients without PD were censored at their last tumour assessment.[1]

PSA response (assessed only in patients with baseline PSA ≥ 20 ng/ml)

PSA response was defined as a reduction in serum PSA concentration of ≥ 50% in patients with a baseline value of ≥20 ng/ml confirmed by a second PSA value at least three weeks later. The duration of PSA response was measured from baseline to the last assessment at which the above criteria were satisfied.[1,22]

PSA progression (assessed in all patients):

- In PSA non-responders, progression was defined as a ≥ 25% increase over nadir provided that the increase in the absolute value PSA level was at least 5 ng/ml.[22]
- In PSA responders and in patients not evaluable for PSA response at baseline, progression was defined as a ≥ 50% increase over the nadir, provided that the increase in the absolute value PSA level was at least 5 ng/ml).[1,22]

Pain

Pain is an important outcome in mHRPC because of the prevalence of considerable pain, mainly from bone metastases. In the TROPIC study, it was assessed using the present pain intensity (PPI) scale on the McGill-Melzack pain questionnaire.[25] Patients were asked to complete the PPI every day for the week prior to evaluation.[21] The use of the PPI aspect of the Short-Form McGill-Melzack pain questionnaire as a stand-alone tool has precedent in previous prostate cancer trials.

Pain was also assessed using an analgesic score (AS) defined as the mean daily patient-recorded analgesic use for the one-week period prior to each evaluation, expressed in morphine equivalents.[23]

As a subjective outcome measure, pain is susceptible to assessment bias in unblinded studies.

Pain response (assessed only in patients with a median baseline PPI score of ≥ 2 and/or a mean baseline AS of ≥ 10 points)

Pain response was defined as a two-point or greater reduction from baseline in median PPI with no concomitant increase in AS, or a reduction of more than 50% in analgesic use with no concomitant increase in PPI score. Either criterion had to be maintained for three or more weeks.[22]

Pain progression (assessed in all patients)

Pain progression was defined as any of the following:

- an increase of ≥ 1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits
- an increase of ≥ 25% in the mean AS compared with the baseline score and noted on two consecutive three-week-apart visits
- a requirement for local palliative radiotherapy.[1,22]

In addition to the risk of assessment bias noted above, the Food and Drug Administration (FDA) reviewers observed that, in the TROPIC study, outcomes relating to pain were also susceptible to bias resulting from missing data: pain response was not evaluable if more than two PPI and/or AS values were missing for the week in question, while pain progression was not evaluable if more than two PPI and/or AS values were missing for that week unless a complete evaluation (i.e. at least five values) of PPI or AS showed a pain progression.[21] The TROPIC investigators stated that pain response was evaluable only in 174/378 patients randomised to cabazitaxel (46%) and 168/377 randomised to mitoxantrone (45%) who had pain at baseline;[22] there is no indication that any of these 342 patients were not evaluable because of missing data.

Health-related quality of life (HRQoL)

The TROPIC study did not collect data relating to HRQoL. For this outcome, the MS therefore utilised interim UK results from the early access programme (EAP) for cabazitaxel, a global study which includes nine active sites in the UK. In the UK sites only, EuroQol 5-Dimension (EQ-5D) questionnaires are administered to all patients at baseline, cycle 2, cycle 4, cycle 6, cycle 8, cycle 10, and 30 days after withdrawal from or completion of treatment; utility is also assessed using a visual analogue scale (VAS).[1] The use of data from the EAP is clearly potentially problematic as, while it

allows comparison with baseline, it does not allow for comparison with patients receiving mitoxantrone or any other comparator therapy.

Adverse events (AEs)

Adverse events were recorded in patients who had received at least one dose of study drug (the safety population).[22] AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 which classifies severe AEs as grade 3, and life-threatening or disabling AEs as grade 4, while grade 5 is used for deaths related to AEs.[26] The worst NCI grade was used for each AE per patient and per cycle.[1]

3.5 Other relevant factors

The MS claims that end-of-life considerations are relevant to cabazitaxel on the basis that it is indicated for patients with a life expectancy of ~12 months, and that, by their calculation, the population in England and Wales for which it is indicated would be fewer than 2000 patients.

In the UK, the risk of prostate cancer is approximately two to three times higher in black Caribbean and black African men than in white men, while the risk in Asian men is lower than the national average.[27]

Because the cabazitaxel infusion contains 15% v/v ethanol, equivalent to 14 ml of beer or 6 ml of wine, it may be harmful to patients suffering from alcoholism.[17]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

4.1.1 Objective of the systematic review, and description and critique of the manufacturer's search strategy

The manufacturer performed three systematic searches, with the following aims and objectives:

1. To identify all studies of cabazitaxel versus any comparator, in order to identify the complete evidence base for cabazitaxel
2. To identify all RCTs of second-line therapy in patients with mHRPC which had progressed after first-line docetaxel, in order to identify any RCT evidence for comparators specified in the NICE scope which had not been directly compared with cabazitaxel
3. To identify all non-randomised studies of second-line therapy in patients with mHRPC which had progressed after first-line docetaxel, in order to identify any non-randomised evidence for cabazitaxel or its comparators which might potentially be relevant to the decision problem.

The MS reports that a wide range of sources was searched. In addition to the core databases recommended by the NICE guidelines manual, there is evidence of searching for grey literature in governmental and HTA websites, gateways, conference proceedings sites, and research registers. Bibliographic reference tracking of included trials was also reported.

In relation to the manufacturer's first systematic review, of studies of cabazitaxel versus any comparator, the manufacturer's searches were comprehensive, and the ERG believes that no relevant studies which were available at the time of the manufacturer's review were missed. The ERG reproduced all of the manufacturer's database searches on 23rd June 2011. As expected, because these searches were undertaken at a later date, a higher number of unique records was retrieved (148, compared with the 52 identified by the manufacturer's searches, of which 68 were published in 2011). The ERG also ran slightly modified versions of the manufacturer's Medline and Embase searches; these retrieved 20 additional records in Embase (for details, see Table 4). One minor comment regarding the manufacturer's Embase search strategy is that the field limits applied could be broadened to "af" rather than "ti,ab,rn". When this was done by the ERG, it increased the sensitivity of the search, resulting in the retrieval of 18 (out of 20) more unique records. The ERG also conducted searches in the Web of Science, BIOSIS Preview, and TOXNET (a specialist adverse events database), none of which were included in the manufacturer's searches; an additional 8 unique records were identified. The ERG agrees with the manufacturer that the cabazitaxel searches are sufficiently comprehensive to retrieve all relevant studies pertaining to the intervention's adverse

events. The ERG also performed a citation search relating to the TROPIC study in Google Scholar; this identified 29 unique records.

Table 4: Repeat database searches for the manufacturer's first systematic search, relating to cabazitaxel

Database	Search strategy	MS/ERG strategy	Comments
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>	1 cabazitaxel.ti,ab,rn. (42) 2 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).ti,ab,rn. (6) 3 jevtana.ti,ab,rn. (1) 4 1 or 2 or 3 (47)	MS strategy	47 records in June 2011 compared to 14 in Sept 2010
	1 cabazitaxel.af. (42) 2 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).af. (6) 3 jevtana.af. (1) 4 5 or 6 or 7 (47)	ERG strategy (all field search)	No difference in no of records retrieved
Embase <1980 to 2011 Week 24>	1 cabazitaxel/ (94) 2 cabazitaxel.ti,ab,rn. (88) 3 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).ti,ab,rn. (8) 4 jevtana.ti,ab,rn. (1) 5 1 or 2 or 3 or 4 (110)	MS strategy	110 records in June 2011 compared to 15 in Sept 2010
	1 cabazitaxel.af. (106) 2 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).af. (39) 3 jevtana.af. (25) 4 1 or 6 or 7 or 8 (130)	ERG strategy (all field search)	An extra 20 records retrieved
Cochrane Library	#1 (cabazitaxel) #2 "XRP 6258" or XRP6258 or "RPR 116258A" or rpr116258A #3 (jevtana) #4 (#1 OR #2 OR #3)	MS strategy	CDSR = 0 CENTRAL = 1 DARE = 0 HTA = 2 records
Conference Proceedings Index (CPCI-S) <1990 to present>	TS=cabazitaxel TS= ("XRP 6258" or XRP6258 or "RPR 116258A" or rpr116258A) TS= jevtana #1 or #2 or #3	MS strategy	Statement 2 is not valid. 2 records

Science Citation Index Expanded (SCI-EXPANDED) <1899-present>	#1 Topic=(cabazitaxel) #2 Topic=(jevtana) #3 #2 OR #1	ERG strategy	42 records retrieved (only 5 unique)
BIOSIS Previews <1969 to present>	Topic=(cabazitaxel)	ERG strategy	23 records retrieved (only 3 unique)
TOXNET (National Library of Medicine)	Cabazitaxel	ERG strategy	13 results (already retrieved in previous searches)
HEED	AX=cabazitaxel AX=("XRP 6258) or XRP6258 or (RPR 116258A) or rpr116258A AX=jevtana CS=1 OR 2 OR 3	MS strategy	No records retrieved
EconLit	cabazitaxel.mp. (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).mp. jevtana.mp. or/1-3	MS strategy	No records retrieved
Citation search in Google Scholar	de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; **376:** 1147–1154	ERG approach	48 records (only 29 unique)
ClinicalTrials.gov	Cabazitaxel OR "XRP 6258" OR XRP6258 OR "RPR 116258A" OR rpr116258A OR jevtana	MS strategy	11 records retrieved (for details, see Appendix 1)

With respect to the manufacturer's second set of searches, for RCTs of second-line therapy in mHRPC, the manufacturer applied a sensitive RCT filter to the four core databases searched. The ERG could only use the Ovid platform instead of Embase.com for Medline and Embase. The ERG considers that it was unnecessary to apply an RCT filter to searches in Cochrane since the CENTRAL database consists entirely of clinical trial records. A number of criticisms could be made of the manufacturer's search strategies. It is not clear why duplicate EMTREE terms such as 'clinical trial'/exp or 'randomized controlled trials'/exp (statements 3, 6 & 7) appeared in several statements in the Embase and Medline strategy. Given the small number of records retrieved in statements 37-44, the proximity terms (NEAR/3 or NEAR/4) could be broadened by using 'NEAR/10' or even 'NEAR/20'. There was evidence of incorrect nesting of search terms within statement 22 in the CENTRAL searches (perhaps the Boolean operator 'AND' should read 'OR'). Translation of the strategy across databases from Medline was inconsistent: the first-line treatment term ('Taxotere') which was present in Medline was absent in Medline in Process and CENTRAL (if this term had been included, the searches would have retrieved 140 rather than 8 records); 'OR' was used to combine 'second line' with 'docetaxel' in Medline and Embase strategies, whereas 'AND' was used in Medline in Process and CENTRAL; and some word variants for disease terms (i.e. 'tumour' and 'oncolog*') were missing from the Medline in Process searches. However, the database searches were reproducible, and the ERG obtained a similar number of records.

The manufacturer's third set of systematic searches, intended to identify all non-randomised studies of second-line therapy in mHRPC, included duplication of search terms present in the non-RCT studies filter and the mHRPC RCT strategies. However, additional population terms were introduced which were not present in the RCT searches: these included 'hrpc', 'crpc', 'docetaxel-refractory' and 'taxane refractory'. The database searches in Medline and Embase were reproducible, but the ERG recommends that the manufacturer use a published observational studies filter for retrieval of non-RCT evidence.

For a quality assessment of the manufacturer's search strategies, see Appendix 2.

The MS states that study selection was performed independently by two reviewers as a two-step process, in accordance with the PRISMA guidelines. It presents, for each of the three reviews, a PRISMA flow diagram (http://www.prisma-statement.org/statement.htm) showing the number of studies included and excluded at each stage.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection, and whether they were appropriate

Details of the inclusion criteria used for study selection were presented in Table 5-1 of the MS; for convenience, this is reproduced here as Table 5. It was not clear why the inclusion criteria for the

second and third systematic reviews were limited to studies published in the English language, while no language restrictions were applied to the first systematic review: logically, the approach taken should have been consistent throughout and, if non-English language studies were to be excluded, this decision should have been justified. The manufacturer subsequently provided clarification indicating that the inclusion criteria differed in this respect because the three systematic reviews were conducted at different times with slightly different objectives, and also supplied details of all records excluded from the systematic review of RCTs in second-line chemotherapy as a result of the limitation of the search to studies published in the English language.[2] With the possible exception of two short papers for which abstracts were not available,[28,29] none of these studies would have met the inclusion criteria for that review.

The second and third systematic reviews were restricted to literature published in and after 2000, in order to focus on the most relevant, up-to-date, literature. This restriction seems appropriate in the relatively fast-moving field of cancer research.

Thus, with the exception of the inconsistent application of language restrictions, for which the manufacturer's clarification provided an explanation rather than a theoretical justification, the specified inclusion criteria appear to be appropriate.

Table 5: Inclusion criteria used in study selection, as presented in the MS[1]

Review	1. Systematic review of RCTs of cabazitaxel	2. Systematic review of all RCTs in second-line mHRPC	3. Systematic review of non-randomised studies in second-line mHRPC
Population	Men with mHRPC or mCRPC who had progressed following or during docetaxel-based treatment		
Intervention(s)	Cabazitaxel with prednisone or prednisolone	Any active intervention (not best supportive care)	Any active intervention (not best supportive care)
Comparator(s):	Any	Any	Any or none
Outcome(s) of interest:	OS, PFS, time to progression, overall response rate, PSA response or progression, pain response or progression, Grade 3 or 4 AEs		
Study design:	Phase II or III RCT or systematic review of Phase II or III RCTs; extension studies and cohort studies reporting AEs were also eligible for inclusion		Non-randomised controlled studies, single-arm studies, case-control, cohort, cross-sectional studies
Language restrictions	There was no language restriction	English language only	
Publication timeframe:	Any date	2000 – present (as the aim of these reviews was to provide a context for the cabazitaxel studies identified by the targeted systematic review, the date restriction was imposed for reasons of pragmatism, to focus on the most relevant, up-to-date literature)	
Publication status	Published, unpublished and grey literature (for example, conference abstracts) were eligible for inclusion		
Exclusion criteria	Dosing studies were excluded, on the basis that they do not provide evidence of the effectiveness of cabazitaxel relative to relevant comparators	N/A	N/A

Key: AE = adverse event; mCRPC = metastatic castration-resistant prostate cancer; mHRPC = metastatic hormone-resistant prostate cancer; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RCT = randomised controlled trial

4.1.3 Studies included in the clinical effectiveness review, with a table of identified studies

The manufacturer's systematic review of RCTs of cabazitaxel identified and included only one relevant study. This was the TROPIC study, which compared cabazitaxel plus prednisone or prednisolone with mitoxantrone plus prednisone or prednisolone in patients with mHRPC which had progressed during or after previous treatment with docetaxel (for details, see Table 6).

Table 6: Characteristics of the TROPIC study[1,22]

Design and clinical trial identification codes	Randomised, open-label, active-controlled, multicentre study Protocol number: EFC6193 Clinicaltrials.gov identifier: NCT00417079
Participants	*Inclusion criteria:* • Pathologically proven prostate cancer • Documented disease progression during or after completion of docetaxel treatment (for patients with measurable disease, documented disease progression by RECIST with at least one visceral or soft-tissue metastatic lesion; for patients with non-measurable disease, rising serum PSA concentrations (at least 2 consecutive increases relative to a reference value measured at least a week apart) or the appearance of at least 1 new demonstrable radiographic lesion) • Age >18 years • ECOG performance status 0-2 • Previous and ongoing castration by orchiectomy or LHRH agonists, or both • Antiandrogen withdrawal followed by progression taken place at least 4 weeks (6 weeks for bicalutamide) before enrolment • Adequate haematological, hepatic, renal, and cardiac function • Left-ventricular ejection fraction of more than 50% assessed by multigated radionuclide angiography or echocardiogram • Life expectancy >2 months *Exclusion criteria*: • Previous mitoxantrone therapy • Radiotherapy to 40% or more of the bone marrow • Cancer therapy (other than LHRH analogues) within 4 weeks before enrolment • Active grade 2 or higher peripheral neuropathy or stomatitis • Other serious illness • History of hypersensitivity to polysorbate 80-containing drugs or prednisone • Participation in another clinical trial with any investigational drug within 30 days prior to study enrolment • For patients enrolled in the UK: patient with reproductive potential not implementing accepted and effective method of contraception
Intervention	Cabazitaxel 25 mg/m^2 intravenously over 1 hour on day 1 of each 21-day cycle plus oral prednisone 10 mg/d (or similar doses of prednisolone in countries in which prednisone was unavailable) Premedication (single intravenous doses of an antihistamine, corticosteroid (dexamethasone 8 mg or equivalent), and histamine H_2-antagonist (except cimetidine)) administered 30 min or more before cabazitaxel.
Comparator	Mitoxantrone 12 mg/m^2 intravenously over 15-30 minutes on day 1 of each 21-day cycle plus oral prednisone 10 mg/d (or similar doses of prednisolone where prednisone was unavailable).
Concomitant therapy	Antiemetic prophylaxis given at the physician's discretion
Outcomes	*Primary outcome measure:* Overall survival *Secondary outcome measures:* • Progression-free survival • PSA response

	• PSA progression • Objective tumour response (in patients with measurable disease) • Time to tumour progression • Pain response (in patients with a median PPI score of >2 or a mean AS of >10 points at baseline, or both) • Pain progression • Adverse events
Follow-up	Until death or the cut-off date for analysis (25.9.2009), whichever happened first. Overall median follow-up was 12.8 months (IQR 7.8-16.9)

The manufacturer's broader systematic review of RCTs of all second-line agents in mHRPC identified six studies in addition to the TROPIC study which were carried out in the relevant population of men with mHRPC which had progressed after docetaxel therapy (for details, see Table 7). The manufacturer considered that these studies did not provide data relevant to the decision problem for the following reasons:

- Studies which compared mitoxantrone (the first comparator specified in the final scope) with other interventions were felt to be unnecessary given the existence of a head-to-head comparison of mitoxantrone with cabazitaxel (the TROPIC study)
- Studies of other forms of chemotherapy without cabazitaxel (the second comparator specified in the final scope) were not considered relevant on the basis that such agents cannot be considered part of standard UK clinical practice as they are seldom used in the UK as second-line treatment for patients with docetaxel-resistant mHRPC. The MS further claimed, in section 5.10.3, that the limited evidence available for such agents would limit the validity of any comparisons.[1] However, the latter argument is weak since the evidence for cabazitaxel itself rests on only one RCT, while two of the potentially relevant agents (abiraterone and satraplatin) are each supported by an RCT which included more patients than the TROPIC study (see Table 7); however, as noted earlier, the ERG recognises that full publication of the abiraterone study[20] post-dated the manufacturer's searches, which only found a conference abstract.

Reproduction of the searches related to the manufacturer's second systematic review did not yield any relevant studies other than the full publication of the abiraterone study.[20] For clarity, Table 7 has included the full publication rather than the conference abstract.

Table 7: Intervention identified by the manufacturer's systematic review of all RCTs in second-line mHRPC which had progressed over docetaxel therapy (excluding the TROPIC study)

Trial name or identifier	Intervention	Comparator	Study references	Study design and number randomised	Study conclusion
COU-AA-301	Abiraterone acetate plus prednisone	Placebo plus prednisone	de Bono 2011[20]	Phase III randomised double-blind placebo-controlled study 1195	Abiraterone was associated with a significant improvement in OS and PFS
The SPARC trial	Satraplatin + prednisone	Placebo plus prednisone	Sternberg 2009,[30] Witjes 2009,[31] Sartor 2008,[32] Sartor 2009[33] Petrylak 2009*	Phase III randomised double-blind placebo-controlled study 950	Satraplatin did not improve OS, but did improve PFS
Saad 2009	Docetaxel + prednisone + custirsen	Mitoxantrone + prednisone + custirsen	Saad 2009*, Saad 2008[34]	Phase II randomised study; level of blinding not specified 42	MS states that no statistical comparisons were reported, but that both regimens were well tolerated and associated with better-than-expected survival. Saad 2008[34] indicates that, while OS was the same in both groups, PSA response and pain response were better with docetaxel, which was also better tolerated than mitoxantrone.
de Bono 2010	CNTO 328 + mitoxantrone	Mitoxantrone	de Bono 2010[35]	Phase II randomised open-label study 97 in efficacy study	CNTO 328 did not improve OS; PFS was better in the control group, but this may be misleading as enrolment was terminated after an interim analysis showed an imbalance in baseline patient characteristics which favoured the control group.
Fleming 2010	Cetuximab + mitoxantrone	Mitoxantrone + prednisone	Fleming 2010[36]	Phase II randomised	Cetuximab did not improve PFS or OS

	+ prednisone			study; level of blinding not specified 115	and was not recommended for further study
Rosenberg 2007	Ixabepilone	Mitoxantrone + prednisone	Rosenberg 2007[37]	Phase II randomised open-label study 82	No difference was identified in OS

* The MS did not include details of these publications, nor were they identified by the ERG's rerun searches

The objective of the manufacturer's third systematic review, of non-RCT studies of second-line therapy in patients with mHRPC which had progressed after first-line docetaxel, was to identify any non-randomised evidence for cabazitaxel or its comparators which might potentially be relevant to the decision problem. The searches identified 40 potentially relevant studies. None investigated cabazitaxel. Nine studies investigated mitoxantrone alone,[38,39] with prednisone,[40-43] or in combination with ixabepilone and prednisone[44,45] or GM-CSF and ketoconazole.[46] The manufacturer considered that, given the existence of a head-to-head comparison of mitoxantrone with cabazitaxel, these uncontrolled studies did not provide useful information. Thirteen studies investigated rechallenge with docetaxel, either alone[47-51] or in combination with other agents.[52-59] Finally, 19 studies investigated other drugs (pemetrexed,[60,61] vorinostat,[62] sunitinib,[63,64] sorafenib,[65,66] carboplatin plus etoposide,[67] carboplatin plus 5-fluorouracil plus epirubicin,[68] paclitaxel plus carboplatin plus estramustine,[69] ketoconazole plus doxorubicin,[70] cyclophosphamide plus dexamethasone,[71] bevacizumab plus satraplatin plus prednisone,[72] oxaliplatin plus capecitabine,[73,74] cisplatin plus prednisone,[75] paclitaxel poliglumex plus estradiol,[76] and TPI 287[77]). The MS considered these studies to be the only published evidence which could be used to address the second comparator specified in the final scope, namely 'chemotherapy without cabazitaxel'. However, it did not undertake any such comparisons because all the studies were small (<50 patients) and uncontrolled, and it was therefore felt that any comparisons would be associated with a high degree of uncertainty. The ERG agrees that, given their size and nature, these studies are unlikely to provide any useful data relating to either efficacy or safety. However, reproduction of the searches related to the manufacturer's third systematic review identified a conference abstract which provided some additional data relating to the TROPIC study.[78]

The MS did not identify any observational studies or publications of post-marketing surveillance data relating to the use of cabazitaxel in mHRPC. Given this paucity of safety data, the ERG felt that it would arguably have been appropriate to include safety data relating to the use of cabazitaxel in women with breast cancer - for example, the unreferenced phase II trial which the MS stated was not relevant to the systematic review or the decision problem because of the nature of its population. In

clarification, the manufacturer claimed that differences would be expected between the safety profile of cabazitaxel in the TROPIC study and in the breast cancer study because the populations differed not only in gender but also in age (the median age in the breast cancer study being 53, compared with 67-68 in TROPIC), prior therapy, and intended cabazitaxel dose.[2] The ERG comment that two deaths in the breast cancer study (one from cyanosis and one from dyspnoea) were deemed probably or possibly related to cabazitaxel; these represent 3% of the study population.[2] It is unclear whether this information can inform the evidence regarding use of cabazitaxel in mHRPC.

4.1.4 Details of relevant studies not discussed in the MS

The ERG is not aware of any relevant studies of cabazitaxel in mHRPC which were not discussed in the MS.

4.2 Summary and critique of submitted clinical effectiveness evidence

4.2.1 Summary of submitted clinical evidence for each relevant trial

The MS stated that the TROPIC study of cabazitaxel vs. mitoxantrone had been reported in the following journal article and conference abstracts or posters:

- de Bono JS *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010; 376: 1147–1154[22]
- Sartor AO *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational Phase III trial (TROPIC). Conference abstract, American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium 2010 (San Francisco, CA)[79]
- de Bono JS *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational Phase III trial (TROPIC). Conference abstract, American Society of Clinical Oncology (ASCO) 2010 (Chicago, IL)[80]
- Oudard S *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: estimating mean overall survival (OS) for health economics analyses from a phase III trial (TROPIC). Poster presentation at ASCO-GU 2011 (Orlando, FL).[81]

The MS also drew on an unpublished clinical study report which was made available to the ERG.[23]

The ERG identified the following publications in the public domain which contain additional data from the TROPIC study:

- the web appendix (http://www.sciencedirect.com/science/article/pii/S014067361061389X) to the article by de Bono *et al*;[22] this was not mentioned in the MS

- the FDA medical review[21]
- an article by Oudard[16] which included an updated efficacy analysis whose full results were not included in the MS
- a conference abstract presenting data relating to clinical benefit and symptom control[78]
- a conference abstract presenting a subgroup analysis of survival by time from first docetaxel treatment in both arms of the study[82]
- a conference abstract presenting a subgroup analysis of survival by reason for discontinuation of docetaxel therapy[83]
- an analysis of the impact of G-CSF prophylaxis on the occurrence of neutropenia.[84]

4.2.2 Description and critique of the manufacturer's approach to validity assessment for each relevant trial

The manufacturer's quality assessment of the TROPIC study (presented in Appendix 3 section 9.3.1 of the MS included criteria relating to both internal and external validity. The following internal validity criteria were used:

- Appropriateness of method of randomisation
- Adequate concealment of treatment allocation
- Baseline similarity of treatment groups in terms of prognostic factors
- Blinding of patients, care providers, and outcome assessors to treatment allocation
- Unexpected imbalances in dropouts between treatment groups
- Whether the authors appeared to have measured more outcomes than they reported
- Adequateness of follow-up
- Use of ITT analysis, and appropriate methods to account for missing data.

The manufacturer considered the TROPIC study to be adequate in relation to all of these criteria with the exception of the criterion relating to the blinding of patients, care providers, and outcome assessors. The manufacturer considered that the fact that the trial was unblinded was unlikely to have introduced bias into the assessment of the primary outcome (OS), or into objective assessments of tumour response or biochemical measurements such as PSA, but recognised that it might have introduced bias into the subjective assessment of pain and symptom deterioration (both of which were included in the definition of PFS) and of clinical AEs.[1] The MS did not provide adequate justification for the study being open label rather than blinding participants and care providers using double dummy procedures. The ERG's clinical advisors indicated that the use of such double dummy procedures would have been complicated by differences in the nature of the treatments, and by the requirement for premedication of patients receiving cabazitaxel; moreover, the use of such procedures might have been considered to cause unnecessary discomfort or inconvenience to study participants.

However, the ERG notes that there appears to be no reason why outcome assessors should not have been blinded to treatment allocation.

The MS states that the investigators used appropriate methods to generate the random allocation sequence and ensure allocation concealment, using a dynamic allocation method – a form of minimisation – to avoid extreme imbalance of treatment allocation within each study centre.[1] However, it should be noted that such allocation is not truly random, and can potentially be subverted because of difficulties in concealing the allocation sequence. It is therefore theoretically possible that some patients may have been deliberately allocated to one or other treatment group on the basis of prognostic factors; however, the ERG has no reason to believe that this was the case.

The external validity criteria used by the manufacturer were:

- Whether the RCT was conducted in the UK, or was a multinational RCT with one or more centres in the UK
- How participants included in the RCT compare with patients who are likely to receive the intervention in the UK
- Whether the dosage regimens used in the study were within those detailed in the summary of product characteristics.

The manufacturer considered all the external validity criteria to be adequately met. However, the ERG notes that, whilst the first criterion was met, [redacted] of participants were recruited in the UK. In relation to the second criterion, the NHS Regional Drug and Therapeutics Centre notes that participants in the TROPIC study may have been younger is typical of patients with docetaxel-resistant mHRPC who are generally seen in the UK, and may have fewer co-morbidities than would be expected in clinical practice.[85]

4.2.3 Description and critique of the statistical approach used within each relevant trial

The statistical analyses used in the TROPIC trial are summarised in Table 8. The ERG did not believe that the statistical tests undertaken were inappropriate.

Table 8: Summary of statistical analyses used in the TROPIC trial[1,22]

Objective	The study objective was to evaluate whether cabazitaxel plus prednisone improved overall survival compared with mitoxantrone plus prednisone in patients with mHRPC which had progressed during or after docetaxel treatment
Statistical analysis	• Analysis of OS and PFS was by ITT (i.e. all patients randomly allocated to treatment groups) • The final analysis was planned to take place when 511 deaths had occurred • The safety analyses included all patients who had received at least one dose of study medication • The Kaplan-Meier method was used to analyse OS, with log-rank comparisons stratified according to disease measurability (measurable vs. non-measurable) and ECOG status (0-1 vs. 2). • OS data were censored at the last date the patient was known to be alive or at the analysis cut-off date (25.9.2009), whichever was the earliest. • PFS, tumour progression, PSA, and pain were compared between treatments using log-rank comparisons stratified according to disease measurability (measurable vs. non-measurable) and ECOG status (0-1 vs. 2). • Hazard ratios and 95% CIs were calculated using a Cox proportional hazards model • Proportions were compared using the χ^2 test or Fischer's exact test. • SAS version 9.1.3 was used for all analyses.
Sample size, power calculation	Assuming a median overall survival in the mitoxantrone group of 8 months, it was calculated that a total of at least 511 deaths in the 2 groups would be needed to detect a 25% reduction in the hazard ratio for death in the cabazitaxel group relative to the mitoxantrone group with 90% power, using a 2-sided log-rank test at a significance level of 0.05. To achieve the target of 511 deaths within 30 months of the first patient enrolment, approximately 720 patients (360 per group) had to be randomised.
Data management, patient withdrawals	• For time to event analyses, missing data were handled based on censoring rules. • For categorical data, missing data were reported as missing. • Patients in the mitoxantrone group were not allowed to cross over to cabazitaxel following progression; however, 44 (12%) received treatment with tubulin-binding drugs at progression

	• Patients in the cabazitaxel group were allowed to cross over to mitoxantrone at progression; it was assumed that this would not affect the survival curves as mitoxantrone has not been associated with an effect on survival.

Subgroup analyses

The MS states that pre-specified subgroup analyses of OS were performed in the ITT population. The prognostic factors which were considered were:

- ECOG performance status
- Disease measurability
- Number of prior chemotherapy regimens
- Age
- Geographical region
- Pain at baseline
- PSA status
- Time from last docetaxel to randomisation
- Total docetaxel dose received
- Time of progression from last docetaxel.[1]

The MS also states that post-hoc subgroup analyses were performed using combinations of these factors. The three key subgroups presented in the economic evaluation section included one which was based on a pre-specified factor, namely region (i.e. the subgroup of European patients who formed [redacted] of the study population), and two subgroups which used post-hoc combinations of factors:

- All patients with an ECOG performance status of 0-1 who received $\geq$ 225 mg/m^2 docetaxel
- European patients with an ECOG performance status of 0-1 who received $\geq$ 225 mg/m^2 docetaxel.

The MS states that the last of these three subgroups was presented as the base-case because it was considered the most representative of patients who will receive cabazitaxel in UK practice. This subgroup was justified as follows:

- The restriction to European patients is justified on the basis that the benefits demonstrated in the European region were considered most likely to represent those which might be expected in UK practice. The TROPIC trial recruited from a number of countries where the manufacturer felt that treatment patterns differed from UK clinical practice in ways which might be expected to affect treatment outcomes with cabazitaxel, and differences in the point estimates were identified by geographic region both in the hazard ratio for overall survival and in rates of AEs.

- The restriction to patients with an ECOG performance status of 0-1 reflects clinical opinion that it is extremely unlikely that, in the UK, patients with an ECOG status of 2 would be considered for cabazitaxel treatment
- The restriction to patients who had received ≥ 225 mg/m^2 docetaxel is justified on the basis that NICE guidance recommends docetaxel as first-line chemotherapy for mHRPC, and therefore it is unlikely that UK patients would be considered for second-line chemotherapy before receiving sufficient exposure to docetaxel.

The base case subgroup is said to form [redacted] of the total population of the TROPIC study.[1]

The ERG has concerns as to whether the manufacturer's selected base case is the most appropriate population. In order to avoid repetition, this discussion is contained only in section 5.2.12; the text is placed in that section as the choice of base case population impacts on the cost-effectiveness ratios.

4.2.4 Description and critique of the manufacturer's approach to outcome selection within each relevant trial

The MS listed the following clinical outcomes observed within TROPIC which were perceived to be relevant to the decision problem:

- Overall survival
- Progression-free survival
- Tumour response rate
- Time to tumour progression
- PSA response
- PSA progression
- Pain response
- Pain progression
- Adverse events.

These differ from the outcomes listed in the final scope by the inclusion of pain response or progression, and the exclusion of health-related quality of life.

4.2.5 Discussion of the extent to which relevant trial includes the patient population(s), intervention(s), comparator(s) and outcomes as defined in the final scope

The TROPIC study is substantially similar to the final scope in terms of its patient population, intervention, and outcomes (see Table 9).

Although the population of the TROPIC study is defined as men with castration-resistant rather than hormone-refractory prostate cancer, it should be noted that the terms 'castration-resistant' and 'hormone refractory' have been used interchangeably in the literature to describe prostate cancer which no longer responds to androgen withdrawal therapy or combined androgen blockade, whether

caused by medical or surgical castration. However, it has been suggested that the term 'endocrine-resistant' is more accurate than either 'castration-resistant' or 'hormone-refractory'.[86] The MS anticipates that cabazitaxel would not be used in all patients whose cancer had progressed during or following docetaxel therapy, but only in the subset with good performance status that were able and willing to tolerate further chemotherapy. The population of the TROPIC study was considered representative of that subset since over 91% in each arm had an ECOG performance status of 0-1. The MS also anticipates that, in line with NICE guidance, UK patients would receive at least 3 cycles (equating to 225 mg/m^2) of docetaxel before being considered for second-line chemotherapy; again, the TROPIC population reflects this, since over 92% of participants had received at least 225 mg/m^2 of docetaxel.

The population was further defined in the final scope as having mHRPC which has progressed following or during docetaxel-based treatment. The MS notes that, in the absence of a clear definition of disease progression in patients with mHRPC, such progression often incorporates a number of measures including rising serum PSA concentrations, new or enlarging radiological lesions, or the appearance of symptoms.[1] In the TROPIC study, disease progression was defined as follows:

- In patients with measurable disease: documented disease progression by RECIST criteria with at least one visceral or soft-tissue metastatic lesion
- In patients with non-measurable disease, either rising serum PSA concentrations (at least two consecutive increases relative to a reference value, measured at least one week apart) or the appearance of at least one new demonstrable radiographic lesion.[22]

The intervention evaluated in the TROPIC study is essentially that defined in the final scope. The cabazitaxel dosing schedule is the same as that in the licensed indication. Patients received the study treatment until disease progression, death, unacceptable toxicity, or for a maximum of 10 cycles.[23] The scope stipulates the use of cabazitaxel plus prednisolone, which is licensed in the UK, whereas the TROPIC study used prednisone rather than prednisolone in countries where the former was available. However, the two drugs appear to be functionally interchangeable, and the HTA report by Collins *et al.,* sets a precedent for treating them as such in a systematic review.[87] However, the TROPIC study only includes one of the comparators specified in the final scope (mitoxantrone plus prednisone/prednisolone).

The TROPIC study includes all the outcomes specified in the final scope with the exception of health-related quality of life. It includes additional pain-related outcomes which the MS considers to be to some extent surrogates for HRQoL.

Table 9: Comparison of key aspects of the final scope and the TROPIC study

	Final scope issued by NICE[15]	**TROPIC study[22]**
Population	Men with metastatic hormone refractory prostate cancer which has progressed following or during docetaxel-based treatment	Men with metastatic castration-resistant prostate cancer which had progressed following or during docetaxel-based treatment
Intervention	Cabazitaxel in combination with prednisolone	Cabazitaxel in combination with prednisone (prednisolone in countries where prednisone was unavailable)
Comparator(s)	• Mitoxantrone in combination with prednisolone • Chemotherapy without cabazitaxel (e.g. 5-flourouracil, cyclophosphamide and carboplatin/etoposide)	Mitoxantrone in combination with prednisone (prednisolone in countries where prednisone was unavailable)
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rate • PSA level • Adverse effects of treatment • Health-related quality of life	• Overall survival (OS) • Progression-free survival (PFS) • PSA response rate • PSA progression • Objective tumour response • Time to tumour progression • Pain response • Pain progression • Adverse effects of treatment

4.2.6 Description and critique of any meta-analysis, indirect comparisons and/ or mixed treatment analysis carried out by the manufacturer

The manufacturer could not undertake a meta-analysis because only one RCT of cabazitaxel was identified.

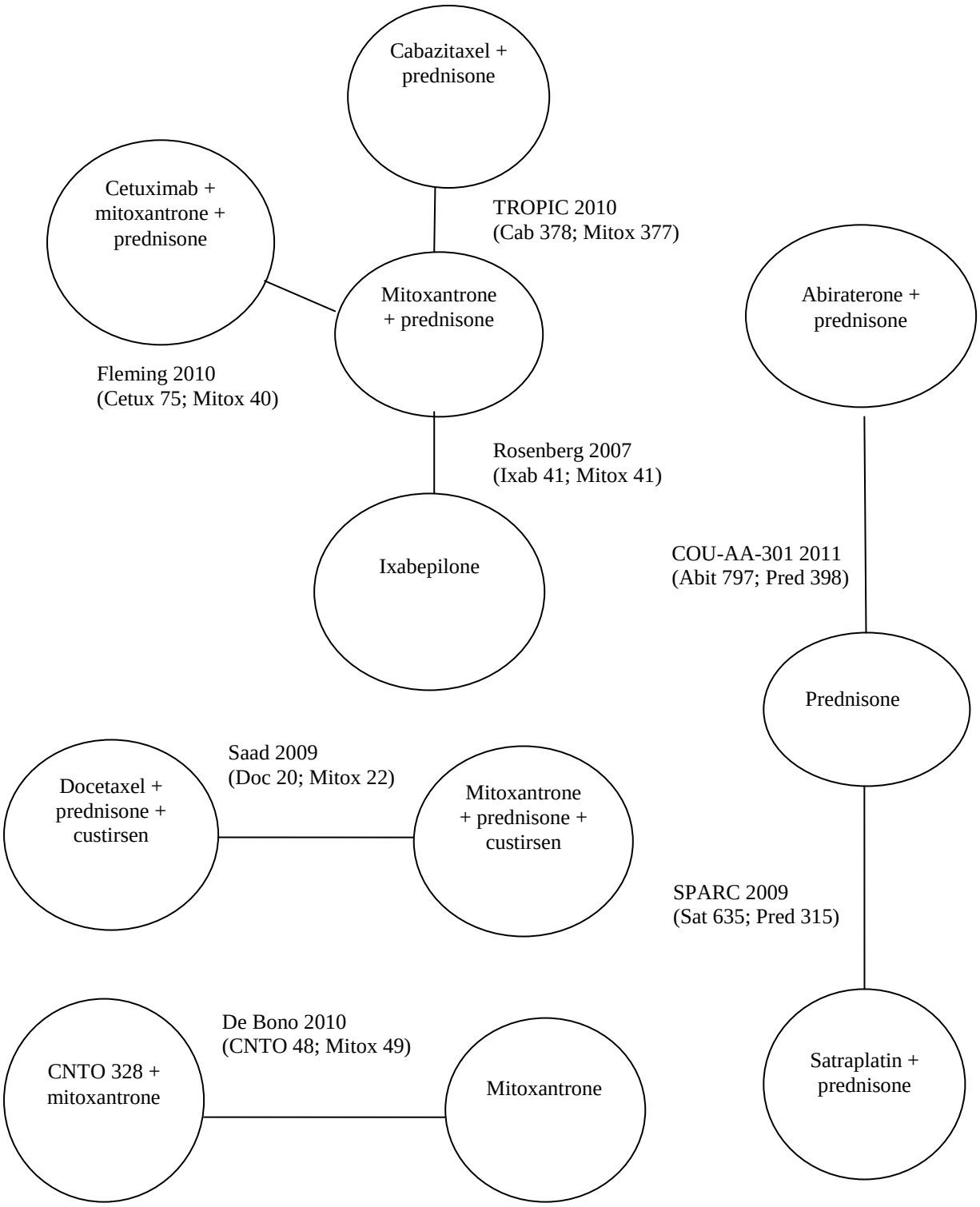
The MS states that indirect comparisons were not performed for the following reasons:

- indirect comparison was not necessary in relation to mitoxantrone, the first comparator identified in the final scope, because the one RCT of cabazitaxel took the form of a head-to-head comparison with mitoxantrone
- indirect comparisons were not considered relevant in relation to the second comparator identified in the final scope, chemotherapy without cabazitaxel. This was because, although RCTs were identified which investigated the use of docetaxel,[34] ixabepilone[37], and satraplatin[30] in the specified patient group, they were considered to be irrelevant to the decision problem for the following reasons:
    - Docetaxel rechallenge was not considered to be a suitable comparator for an agent designed to overcome docetaxel resistance
    - Ixabepilone was not reported to be used in the UK
    - Satraplatin failed to improve survival.[1]

However, in section 5.2.4, the MS indicates that the manufacturer's searches also identified RCTs of a further three agents: abiraterone, cetuximab, and CNTO 328. It is understood that none of these three agents are chemotherapy agents according to the usual interpretation of the term in oncology. The ERG believes that it is possible to conduct an indirect comparison of cabazitaxel against ixabepilone and cetuximab, but that such a comparison would be of limited value; this is discussed in more detail below. In section 5.10.3, the MS acknowledges that abiraterone has been shown to be effective in second-line therapy of patients with mHRPC, but claims that, as it has a different mechanism of action from cabazitaxel, in future the two drugs will probably be used to complement each other rather than as alternatives. As previously noted, it states that further discussion is beyond the scope of the MS because of the limited availability of data relating to abiraterone; full publication of the abiraterone study post-dated the manufacturer's searches. The MS also notes that abiraterone is not yet licensed in the UK for use as second-line therapy in patients with mHRPC.

The ERG has produced a schematic of the RCTs identified by the manufacturer (see Figure 1).

Figure 1: Evidence networks for RCTs of second-line therapy in mHRPC



Furthermore, the manufacturer did not undertake a mixed treatment comparison on the basis that:

- An MTC comparing cabazitaxel with mitoxantrone would not be helpful.[1] The reasons given were the small size of the two studies other than TROPIC which had mitoxantrone plus prednisolone as their comparator (Fleming's study of cetuximab plus mitoxantrone and prednisolone[36] and Rosenberg's study of ixabepilone,[37] which had total populations of 115 and 82 respectively), and the fact that the cetuximab trial did not report OS.
- An MTC comparing cabazitaxel with 'chemotherapy without cabazitaxel' was rejected by the manufacturer on the grounds that their searches only identified RCTs of three chemotherapy agents other than cabazitaxel or mitoxantrone (docetaxel,[34] ixabepilone[37], and satraplatin[30]). These studies were considered to be irrelevant to the decision problem for the reasons noted above. However, as also noted above, the manufacturer's searches also identified RCTs of abiraterone, cetuximab, and CNTO 328.

Figure 1 demonstrates that there are no closed networks which would allow a mixed treatment comparison to be conducted. However, as noted above, the manufacturer's review of all RCTs in second-line mHRPC identified two studies in addition to the TROPIC study which were carried out in the relevant patient group and which used mitoxantrone plus prednisolone as the comparator: Fleming's study of cetuximab plus mitoxantrone and prednisolone[36] and Rosenberg's study of ixabepilone[37] (for details, see Table 10, and Figure 2). Thus an indirect comparison with cetuximab in addition to mitoxantrone and with ixabepilone appeared possible. However, the cetuximab RCT concluded that further study was not recommended, and the ixabepilone RCT was relatively small; furthermore, the manufacturer reported that this intervention is not used in the UK. The clinical advisors to the ERG concurred with the manufacturer that comparisons with treatments other than mitoxantrone were not appropriate.

4.2.7 Additional clinical work conducted by the ERG

No additional clinical work was conducted by the ERG.

4.3 Conclusions

4.3.1 Summary and critique of submitted clinical effectiveness evidence

The manufacturer's systematic review identified one relevant RCT. This was the TROPIC study, a multinational open-label active-controlled randomised trial designed to compare the efficacy and safety of cabazitaxel plus prednisone/prednisolone with mitoxantrone plus prednisone/prednisolone in patients with mHRPC which has progressed following or during docetaxel therapy. Its primary outcome measure was overall survival.[22] For details of study design, see Table 6. The baseline characteristics of patients in the intervention and control groups are presented in Table 10. The NHS Regional Drug and Therapeutics Centre (RD&TC) report draws attention to the notable difference

between treatment groups in baseline median PSA serum concentration (143.9 μg/L in the cabazitaxel group vs 127.5 μg/L in the mitoxantrone group) but adds that, as both levels are hugely elevated from the reference range of 2-5 μg/L, the difference may not be clinically important. However, the RD&TC report also notes that fewer patients randomised to cabazitaxel had bone metastases (80% vs 87%), and that this may have implications for the pain scores.[85]

Table 10: Baseline characteristics of patients in the TROPIC study[22]

	Cabazitaxel + prednisone (n=378)	Mitoxantrone + prednisone (n=377)
Age (years)		
Median (IQR)	68 (62-73)	67 (61-73)
75 and above	69 (18%)	70 (19%)
Ethnic origin		
White	317 (84%)	314 (83%)
Asian	26 (7%)	32 (8%)
Black	20 (5%)	20 (5%)
Other	15 (4%)	11 (3%)
ECOG performance status 0 or 1	350 (93%)	344 (91%)
Extent of disease		
Metastatic	364 (96%)	356 (94%)
Bone metastases	303 (80%)	328 (87%)
Visceral metastases	94 (25%)	94 (25%)
Loco-regional recurrence	14 (4%)	20 (5%)
Unknown	0	1 (<1%)
PSA		
Number of patients	371	370
Median (IQR) serum PSA (ng/l)	143.9 (51.1–416.0)	127.5 (44.0–419.0)
Serum PSA concentration $\geq$ 20 ng/l	329 (87%)	325 (86%)
Measurable disease	201 (53%)	204 (54%)
Pain at baseline[†]	174 (46%)	168 (45%)
Previous therapy:		
Hormonal	375 (99%)	375 (99%)
1 chemotherapy regimen	260 (69%)	268 (71%)
2 chemotherapy regimens	94 (25%)	79 (21%)
>2 chemotherapy regimens	24 (6%)	30 (8%)
Radiation	232 (61%)	222 (59%)
Surgery	198 (52%)	205 (54%)
Biological agent	26 (7%)	36 (10%)
Number of previous docetaxel regimens		
1	316 (84%)	327 (87%)
2	53 (14%)	43 (11%)
>2	9 (2%)	7 (2%)
Median (IQR) total previous docetaxel dose (mg/m^2)	576.6 (408.4-761.2)	529.2 (380.9-787.2)
Disease progression relative to docetaxel administration		
During	115 (30%)	104 (28%
< 3 months from last dose	158 (42%)	181 (48%)
$\geq$ 3 months from last dose	102 (27%)	90 (24%)
Unknown	3 (1%)	2 (1%)
Median time in months from last docetaxel dose to disease progression (IQR)	0.7 (0.0-2.9)	0.8 (0.0-3.1)

4.3.2 Summary of results

This section summarises the main clinical efficacy evidence from the TROPIC study.

Overall survival

At 25th September 2009, the cut-off date stipulated for analysis, 513 deaths had occurred, 234 in patients randomised to cabazitaxel and 279 in patients randomised to mitoxantrone.[1] Median overall survival was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group; the hazard ratio (HR) was 0.70 (95% CI 0.59-0.83, p<0.0001)[22] (for details, see Table 11). Thus, cabazitaxel plus prednisone/prednisolone was associated with a median survival gain of 2.4 months relative to mitoxantrone plus prednisone/prednisolone. The mean survival gain, reported only in the MS, was 4.2 months.[1]

The MS states that an updated analysis was presented at ASCO in 2010, after 585 deaths had occurred. This analysis found that, while the median survival values were unchanged, the HR was 0.72.[1] The reference which is supplied in the MS, to an abstract by de Bono *et al*,[80] does not relate to these data. However, they are presented in an article by Oudard,[16] who states that this updated analysis was performed on 10th March 2010, and gives confidence intervals (CI) for the HR (for details, see Table 11).

Table 11: The TROPIC study: overall survival[1,22]

	Cabazitaxel	Mitoxantrone	HR (95% CI)	P value
Analysis at 25.9.2009 ('final' analysis) [1,22]				
Total deaths, safety population	227/371 (61%)	275/371 (74%)	NR	NR
Total deaths, ITT population	234/377 (61.9%)	279/378 (74.0%)	NR	NR
No of patients censored[1,2]	144, including 7 lost to follow-up before cut-off	98, including 3 lost to follow-up before cut-off		
Median overall survival (months)	15.1 (95% CI 14.1-16.3)	12.7 (95% CI 11.6-13.7)	0.70 (0.59-0.83)	<0.0001
Analysis at 10.3.10 (updated efficacy analysis)[16]				
Median overall survival (months)	15.1	12.7	0.72 (0.61-0.84)	<0.0001
Data from MS[1]				
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR

[redacted]				

OS is the only outcome for which subgroup data are available. The final scope stated that, if the data permitted, three subgroup analyses should be considered: by baseline performance status, duration of prior docetaxel exposure, and time since docetaxel treatment. If total docetaxel dose may be assumed to be equivalent to duration of prior docetaxel exposure, then De Bono *et al.*,[22] published data relating to the first two of these subgroups; updated analyses were later published by Oudard.[16] Data relating to time from last docetaxel treatment to randomisation are available only in the MS.[1] These subgroup analyses are summarised in Table 12. Data contained in this table have been obtained from the following sources:

- The 2010 Lancet paper by de Bono *et al*.[22] (the 'final' analysis)
- A 2011 article by Oudard[16] (the updated analysis)
- The MS[1]
- A 2011 conference abstract by de Bono *et* al. which presented a subgroup analysis of survival by reason for discontinuation of docetaxel therapy.[83]

Table 12: The TROPIC study: overall survival by subgroup

	Cabazitaxel No (%)	Mitoxantrone No (%)	HR (95% CI)
ECOG status 0-1 'Final' analysis (n=694)[22] Updated analysis (n=694)[16]	NR	NR	0.68 (0.57-0.82) 0.71 (0.60-0.84)
ECOG status 2 'Final' analysis (n=61)[22] Updated analysis (n=61)[16]	NR	NR	0.81 (0.48-1.38) 0.78 (0.46-1.33)
Total docetaxel dose <225 mg/m^2 'Final' analysis (n=59)[22] Updated analysis (n=59)[16]	NR	NR	0.96 (0.49-1.86) 1.02 (0.55-1.87)
Total docetaxel dose 225-450 mg/m^2 'Final' analysis (n=206)[22] Updated analysis (n=206)[16]	NR	NR	0.60 (0.43-0.84) 0.61 (0.44-0.84)
Total docetaxel dose 450-675 mg/m^2 'Final' analysis (n=217)[22] Updated analysis (n=217)[16]	NR	NR	0.83 (0.60-1.16) 0.81 (0.59-1.10)
Total docetaxel dose 675-900 mg/m^2 'Final' analysis (n=131)[22] Updated analysis (n=131)[16]	NR	NR	0.73 (0.48-1.10) 0.77 (0.52-1.12)
Total docetaxel dose >900 mg/m^2 'Final' analysis (n=134)[22] Updated analysis (n=134)[16]	NR	NR	0.51(0.33-0.79) 0.57 (0.39-0.84)
Time from last docetaxel to randomisation <6 months (n=504)[1]	NR	NR	0.77 (0.63-0.94)
Time from last docetaxel to randomisation >6 months (n=250)[1]	NR	NR	0.64 (0.46-0.89)
Discontinued docetaxel due to disease progression[83]	NR	NR	0.70 (0.57-0.87)
Discontinued docetaxel for reasons other than disease progression (n=286)[83]	NR	NR	0.63 (0.46-0.85)
Discontinued docetaxel due to an adverse event (n=26)[83]	NR	NR	0.63 (0.30-1.33)

With the exception of patients who received a total docetaxel dose less than 225 mg/m^2, these analyses consistently favour cabazitaxel, suggesting that there were generally no significant interactions between the prognostic factors of interest and treatment response. Moreover, a post-hoc

subgroup analysis relating OS to the reason for discontinuation of prior docetaxel therapy suggested that the survival benefit associated with cabazitaxel was maintained irrespective of whether prior docetaxel therapy was discontinued due to disease progression (see Table 12).[83]

Progression-free survival

Cabazitaxel was associated with a statistically significant improvement in median PFS, a composite endpoint including tumour, PSA, or pain progression, or death. Further data available in the FDA reviewers' report[21] indicate that the majority (43-49%) of progression events related to PSA progression (for details, see Table 13).

Table 13: Progression-free survival

	Cabazitaxel (n=378)	**Mitoxantrone (n=377)**	**HR (95% CI)**	**P value**
Median progression-free survival (months)[22]	2.8 (2.4-3.0)	1.4 (1.4-1.7)	0.74 (0.64-0.86)	<0.0001
No of patients with PFS events (%)[21]	364 (96.3%)	367 (97.3%)	NR	NR
Death	38 (10.1%)	29 (7.7%)	NR	NR
Tumour progression	67 (17.7%)	68 (18.0%)	NR	NR
PSA progression	163 (43.1%)	186 (49.3%)	NR	NR
Pain progression	86 (22.8%)	70 (18.6%)	NR	NR
Symptom deterioration	10 (2.6%)	14 (3.7%)	NR	NR
No of patients censored (data censored at last available assessment)	14 (3.7%)	10 (2.7%)	NR	NR

PSA response

Cabazitaxel was associated with a statistically significant improvement in PSA response rate, relative to mitoxantrone (for details, see Table 14).

Table 14: PSA response rate[22]

	Cabazitaxel	**Mitoxantrone**	**HR (95% CI)**	**P value**
No of evaluable patients	329	325		
Response rate (%)	39.2% (33.9-44.5)	17.8% (13.7-22.0)	NR	0.0002

PSA progression

In an ITT analysis, cabazitaxel was associated with a statistically significant improvement in time to PSA progression, relative to mitoxantrone (for details, see Table 15).

Table 15: Time to PSA progression[22]

	Cabazitaxel (n=378)	Mitoxantrone (n=377)	HR (95% CI)	P value
Median time to PSA progression (months)	6.4 (2.2-10.1)	3.1 (0.9-9.1)	0.75 (0.63-0.90)	0.001

Objective tumour response

In patients with measurable disease, cabazitaxel was associated with a statistically significant improvement in objective tumour response, relative to mitoxantrone.[22] The MS notes that all responses were partial rather than complete. However, the FDA reviewers consider that the fact that 65 of the 405 potentially evaluable patients were actually not evaluable because of missing data could potentially affect this result because the number of patients with missing data exceeds the number of patients who displayed a response.[21] Consequently, this result may not be robust. An additional analysis which combined complete response, partial response, and stable disease to form a measure of disease control found that disease control was significantly better in the cabazitaxel group,[78] (for details, see Table 16) but the robustness of this result is presumably also open to some doubt.

Table 16: Objective tumour response[22,78]

	Cabazitaxel (n=378)	Mitoxantrone (n=377)	HR (95% CI)	P value
No of evaluable patients	201	204		
Response rate[22]	14.4% (9.6-19.3)	4.4% (1.6-7.2)	NR	0.0005
Disease control[78]	61.7%	47.5%	NR	0.004

Time to tumour progression

An ITT analysis indicated that cabazitaxel was associated with a statistically significant improvement in time to tumour progression, relative to mitoxantrone (for details, see Table 17).

Table 17: Time to tumour progression[22]

	Cabazitaxel (n=378)	Mitoxantrone (n=377)	HR (95% CI)	P value
Median time to tumour progression (months)	8.8 (3.9-12.0)	5.4 (2.3-10.0)	0.61 (0.49-0.76)	<0.0001

Pain response (measured in patients with a median PPI score of ≥2 points and/or a mean AS of ≥10 points at baseline)

Pain response (defined as a ≥ 2-point reduction from baseline in median PPI with no increase in AS, or a ≥50% reduction in analgesic use with no increase in PPI score) could only be evaluated in the 342/755 patients (45%) whose baseline PPI or AS scores enabled this outcome to be measured. There was no significant difference in pain response rate between treatment groups. However, on the basis of a comparison of the mean cumulative area under the curve of the PPI curves over the treatment period, Oudard suggested that there was a trend towards a reduction in pain in the cabazitaxel group[16] (for details, see Table 18). As noted earlier, the RD&TC report[85] drew attention to the higher baseline prevalence of bone metastases in the mitoxantrone group than in the cabazitaxel group, and suggested that this might have an impact on pain outcomes. Such an imbalance would presumably favour cabazitaxel.

Table 18: Pain response rate

	Cabazitaxel	**Mitoxantrone**	**P value**
No of evaluable patients[22]	174	168	
Pain response rate (95% CI)[22]	9.2% (4.9-13.5)	7.7% (3.7-11.8)	0.63
Patients with improvement in pain from baseline[16]	21.3%	18.2%	NR
Patients with deterioration in pain from baseline[78]	32%	32%	NR

Pain progression

An ITT analysis found no significant difference between treatment groups in relation to median time to pain progression (for details, see Table 19). Data for 265 patients in the cabazitaxel group and 279 in the mitoxantrone group were censored because of missed assessments.[22]

Table 19: Pain progression[22]

	Cabazitaxel (n=378)	**Mitoxantrone (n=377)**	**HR (95% CI)**	**P value**
Median time to pain progression (months)	11.1 (2.9-not reached)	Not reached	0.91 (0.69-1.19)	0.52

Quality of life

As noted earlier, the TROPIC study did not collect quality of life data. The MS therefore uses pain as a partial surrogate for HRQoL, and suggests that, as the TROPIC study showed no significant difference between cabazitaxel and mitoxantrone in terms of pain response and time to pain progression, cabazitaxel may be similar to mitoxantrone at least in relation to this aspect of quality of life.[1] However, as noted above, the pain results may have been affected by the imbalance in baseline prevalence of bone metastases. The MS also refers to interim UK results from the early access

programme (EAP) for cabazitaxel. An analysis performed in May 2011 using a cut-off date of 29th April 2011 included EQ-5D data from [redacted] patients who had received at least one dose of cabazitaxel, and [redacted] indicated [redacted]. The MS suggests that this result indicates that cabazitaxel therapy is not associated with a significant negative effect on utility, and may even improve it.[1] Unfortunately, however, no EQ-5D data were identified relating to patients with mHRPC receiving mitoxantrone.

4.3.3 Critique of reported efficacy data

The MS appears to be complete in that it includes the only RCT of cabazitaxel plus prednisone/prednisolone which has been undertaken in the relevant population.

The reported efficacy data indicate that, relative to mitoxantrone plus prednisone/prednisolone, the use of cabazitaxel plus prednisone/prednisolone is associated with improved overall survival, progression-free survival, PSA response, time to PSA progression, objective tumour response, and time to tumour progression. It is not associated with improved pain outcomes. Comparative data are not available in relation to quality of life.

However, as the MS recognises, as an open label study, the TROPIC study is susceptible to ascertainment bias in the assessment of pain and symptomatic progression, both of which are subjective outcomes. PFS, a composite endpoint which incorporates pain progression, is therefore also susceptible to bias. However, as the MS also notes, the lack of blinding is unlikely to have biased the assessment of OS (the primary outcome), or tumour response.[1]

4.3.4 Safety and tolerability

Evidence for the safety and tolerability of cabazitaxel in patients with mHRPC appears to be limited to the data on adverse events, discontinuations, dose reductions, and treatment delays available from the TROPIC study. This study was not said to be powered to detect differences between treatment arms in relation to the incidence of specific adverse events. Moreover, even if that study had sufficient power to detect significant differences in common adverse events, it should be noted than an RCT cannot form the best source of evidence for rarer adverse events.

Data relating to selected adverse events reported from the TROPIC study are summarised in Table 20. As may be seen, the most common AEs were haematological, and the incidence of grade $\geq$ 3 neutropenia and leukopenia were both noticeably higher in the cabazitaxel group than in the mitoxantrone group. The incidence of diarrhoea was also very substantially higher in the cabazitaxel group. The MS notes that the incidence of grade $\geq$ 3 gastrointestinal disorders of all types was

substantially higher in patients receiving cabazitaxel than in those receiving mitoxantrone (12.4% vs 1.6%).[1]

Table 20: The TROPIC trial: numbers of patients suffering selected adverse events[22]

	Cabazitaxel (n=371)		Mitoxantrone (n=371)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Haematological AEs				
Neutropenia	347 (94%)	303 (82%)	325 (88%)	215 (58%)
Febrile neutropenia	-	28 (8%)	-	5 (1%)
Leukopenia	355 (96%)	253 (68%)	343 (92%)	157 (42%)
Anaemia	361 (97%)	39 (11%)	302 (81%)	18 (5%)
Thrombocytopenia	176 (47%)	15 (4%)	160 (43%)	6 (2%)
Selected non-haematological AEs				
Diarrhoea	173 (47%)	23 (6%)	39 (11%)	1 (<1%)
Fatigue	136 (37%)	18 (5%)	102 (27%)	11 (3%)
Asthenia	76 (20%)	17 (5%)	46 (12%)	9 (2%)
Back pain	60 (16%)	14 (4%)	45 (12%)	11 (3%)
Nausea	127 (34%)	7 (2%)	85 (23%)	1 (<1%)
Vomiting	84 (23%)	7 (2%)	38 (10%)	0
Haematuria	62 (17%)	7 (2%)	14 (4%)	2 (1%)
Abdominal pain	43 (12%)	7 (2%)	13 (4%)	0

In the web appendix to their article (http://www.sciencedirect.com/science/article/pii/S014067361061389X), de Bono *et al.*,[22] present data suggesting that the incidence of neutropenia and diarrhoea may vary by age, previous radiotherapy, and geographical region (for details, see Table 21). These subgroup analyses suggest that the incidence of diarrhoea and neutropenia is significantly higher in older patients; the incidence of diarrhoea also appears to be significantly higher in patients who have undergone previous radiotherapy. Regional differences were also identified in the incidence of neutropenia, and these may reflect differences in patterns of care. No differences in the incidence of neutropenia and diarrhoea were found in subgroups defined by race, baseline liver function, baseline renal function, ECOG performance status, or prior chemotherapy.

However, as may be seen from Table 21, de Bono *et al.*, used different age-related subgroups for diarrhoea and neutropenia. No justification was provided for this, prompting the suspicion that the use of the same age bands for both AEs would have made one or other result non-significant. This is supported by the statement in the MS[1] that, in patients treated with cabazitaxel, the following AEs occurred at rates ≥ 5% higher in patients aged 65 and over than in those aged under 65:

- fatigue (40.4% versus 29.8%)

- neutropenia (24.2% versus 17.6%)
- asthenia (23.8% versus 14.5%)
- pyrexia (14.6% versus 7.6%)
- dizziness (10.0% versus 4.6%)
- urinary tract infection (9.6% versus 3.1%)
- dehydration (6.7% versus 1.5%).

It is noticeable that, while this list includes neutropenia, it does not include diarrhoea. The MS also states that the incidence of Grade ≥ 3 neutropenia based on laboratory abnormalities (86.3% versus 73.3%), clinically complicated neutropenia (23.8% versus 16.8%), and febrile neutropenia (8.3% versus 6.1%) were all higher in patients aged ≥ 65 years than in younger patients.[1]

Table 21: Incidence of neutropenia and diarrhoea (all grades) in subgroups of patients treated with cabazitaxel in the TROPIC study

	AE rate (all grades) % of patients	P value (by logistic regression)
Diarrhoea by age (years)		<0.1
<75 (N=301)	44.5%	
≥75 (N=70)	55.7%	
Diarrhoea by prior radiotherapy		<0.1
Yes (N=226)	50.0%	
No (N=145)	41.4%	
Neutropenia by age		<0.1
<65 (N=131)	17.6%	
≥65 (N=240)	24.2%	
Neutropenia by region		<0.1
North America (N=109)	25.7%	
Europe (N=205)	16.1%	
Other* (N=57)	35.1%	

* Argentina, Brazil, Chile, India, republic of Korea, South Africa, Taiwan, Turkey

27 deaths were reported within 30 days of the last dose of study drug. Such deaths were more common with cabazitaxel than with mitoxantrone. Neutropenia was the most common cause of such death in patients receiving cabazitaxel, compared with disease progression in those receiving mitoxantrone[22] (for details, see Table 22). The FDA reviewers considered 5 of the 18 deaths in the cabazitaxel group to be due to infections; 80% of these deaths occurred after a single dose of cabazitaxel, and none of the five patients had been given prophylactic G-CSF. A further death occurred in a patient who did not have documented infection at the time of death, and who had

developed febrile neutropenia despite the use of prophylactic G-CSF. The FDA reviewers also attributed 4 deaths to renal failure,[21] rather than the three reported by de Bono *et al*.[22]

Table 22: Deaths occurring within 30 days of last dose of study drug[22]

	Cabazitaxel (n=371)	**Mitoxantrone (n=371)**
Deaths within 30 days of last dose of study drug	18 (5%)	9 (2%)
Causes of deaths within 30 days of last dose of study drug		
Disease progression	0	6 (2%)
Neutropenia & clinical consequences/sepsis	7 (2%)	1 (<1%)
Cardiac	5 (1%)	0
Dyspnoea (apparently related to disease progression)	0	1 (<1%)
Dehydration/electrolyte imbalance	1 (<1%)	0
Renal failure	3 (1%)	0
Cerebral haemorrhage	1 (<1%)	0
Unknown cause	1 (<1%)	0
Motor accident	0	1 (<1%)

Some indication of relative toxicity may also be gained from data relating to discontinuation of treatment. The median number of treatment cycles administered, and the number of patients completing the planned 10 cycles of treatment, were both higher in the cabazitaxel group than in the mitoxantrone group. Disease progression was the most common reason for discontinuation of study treatment, and was more common in the mitoxantrone group than in patients receiving cabazitaxel, whereas discontinuations because of unacceptable adverse effects or patient request were both more common in the cabazitaxel group. In addition, more patients in the cabazitaxel group than in the mitoxantrone group required dose reductions and treatment delays, suggesting that cabazitaxel was less well tolerated than mitoxantrone (for details, see Table 23).

Table 23: Treatment received and reasons for discontinuation in the TROPIC study[22]

	Cabazitaxel (n=378)	Mitoxantrone (n=377)
Median number of treatment cycles (assessed in patients who received study treatment, i.e. 371 in each arm)	6 (3-10)	4 (2-7)
No of patients completing planned 10 cycles of study treatment	105 (28%)	46 (12%)
Discontinuation of study treatment	266 (70%)	325 (86%)
Reasons for discontinuation of study treatment		
Disease progression	180 (48%)	267 (71%)
Adverse event	67 (18%)	32 (8%)
Non-compliance with protocol	1 (<1%)	0
Lost to follow-up	0	2 (1%)
Patient request	8 (2%)	17 (5%)
Other	10 (3%)	7 (2%)
Dose reductions, number of patients*	45 (12%)	15 (4%)
Treatment delays, no of patients*	104 (28%)	56 (15%)

* Data from MS[1]

4.3.5 Critique of reported safety data

The lack of blinding in the TROPIC study may have biased the assessment of clinical AEs. However, as the MS notes, it is unlikely to have biased the assessment of laboratory AEs.[1]

In the TROPIC study, new cycles of therapy started when absolute neutrophil counts were $\geq$1500/mm^3, the platelet count was $\geq$75,000/mm^3, and non-haematological toxicities (except alopecia) had recovered to baseline levels. A maximum of two weeks' delay was allowed between two treatment cycles, and patients were removed from the study treatment if treatment was delayed for more than two weeks.[21] As these criteria appear more stringent than the EMEA recommendations for dose modifications,[17] the number of AEs reported in the TROPIC study may be lower than that which might be expected in clinical practice.

Despite the use of these stringent criteria, the TROPIC study found that cabazitaxel was associated with a higher incidence of AEs than was mitoxantrone. The FDA reviewers considered that the AEs of interest in cabazitaxel-treated patients included neutropenic complications (febrile neutropenia and infection), renal failure, haematuria, and cardiac toxicity.[21] The MS recognises that, since 8% of patients treated with cabazitaxel had febrile neutropenia, cabazitaxel treatment requires careful monitoring and management of emerging symptoms.[1] The TROPIC study reported haematuria as an AE, but did not report renal failure or cardiac toxicity other than as causes of deaths within 30 days of treatment.[22] The RD&TC report considers the deaths attributed to cardiac and renal failure to be of

particular concern given that the inclusion criteria for the TROPIC study included adequate cardiac and renal function.[85]

Because of its concerns about serious toxicity in general, and renal toxicity in particular, associated with the use of cabazitaxel at a dose of 25 mg/m^2, the FDA recommended four post-marketing requirements:

- A phase III RCT in patients with mHRPC to compare first-line docetaxel/prednisone with cabazitaxel 20 mg/m^2/prednisone and cabazitaxel 25 mg/m^2/prednisone, with overall survival as the primary endpoint, powered to detect a realistic difference in primary endpoint
- A phase III RCT in patients with HRPC previously treated with docetaxel to compare cabazitaxel 20 mg/m^2/prednisone with cabazitaxel 25 mg/m^2/prednisone, with overall survival as the primary endpoint, powered to preserve 50% of the treatment effect of cabazitaxel 25 mg/m^2
- A review and analysis by a group of renal experts of renal toxicity from all currently available cabazitaxel trials to identify aetiologies and provide recommendations for toxicity mitigation by patient selection or other measures; the group's recommendations and findings should be submitted within 9 months of the US cabazitaxel approval date of 17th June 2010
- The submission of updates on renal toxicity from all active randomised trials every 6 months for 3 years after the US cabazitaxel approval date.[21]

The ERG notes that 9 months have now passed since the FDA approved cabazitaxel, but that no publications have been identified which report the results of the expert review of renal toxicity. During the fact check process, the manufacturer indicated that they had information from the renal safety report, and also from a trial evaluating the effect of cabazitaxel on the QTc interval, which has relevance for cardiac toxicity, which could be provided. However, these data were not offered within the timescale of the ERG report.

The NHS RD&TC considers that further safety data are required before cabazitaxel can be recommended as it feels that a median gain of 2.4 months in overall survival may not be acceptable given cabazitaxel's AE profile.[85]

Non-RCT evidence

No non-RCT evidence has been identified relating to the adverse events of cabazitaxel.

4.3.6 Critique of submitted evidence analyses

No evidence analyses were submitted.

4.3.7 Conclusions

The clinical effectiveness evidence submitted by the manufacturer indicated that, relative to mitoxantrone plus prednisone/prednisolone, cabazitaxel at a dose of 25 mg/m^2 plus

prednisone/prednisolone is associated with improved overall survival, progression-free survival, PSA response, time to PSA response, objective tumour response, and time to tumour progression. However it is not associated with improvements in pain response or time to pain progression, and it is associated with an increased risk of adverse events such as neutropenia. Patients aged over 65 years appear to be at increased risk of many adverse events, and this is a matter for concern given that, in the UK, approximately 75% of new cases of prostate cancer occur in men aged over 65.[8]

5 ECONOMIC EVALUATION

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

In the economic evaluation searches, the intervention terms for cabazitaxel were searched alone without the disease terms for mHRPC. Specialist databases such as NHS EED and HEED were searched by the manufacturer for economic evaluations. Note that any potentially relevant economic evaluations are likely to have been retrieved in the earlier clinical effectiveness review searches. The ERG believes that these searches were sensitive and reproducible.

The search strategy for HRQoL studies of prostate cancer consisted of the disease terms combined with a sensitive quality of life filter. By comparison to the disease terms used in the RCT and non-RCT search strategies in the clinical effectiveness review, fewer mHRPC terms were used and, unless tested by the manufacturer, this might affect the sensitivity of the searches for quality of life studies.

The manufacturer was unable to identify any previous economic evaluations of cabazitaxel. The ERG believes it unlikely that any studies have been overlooked. Therefore, the manufacturer developed a *de novo* model that is described in the MS.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 Adherence to the NICE reference case

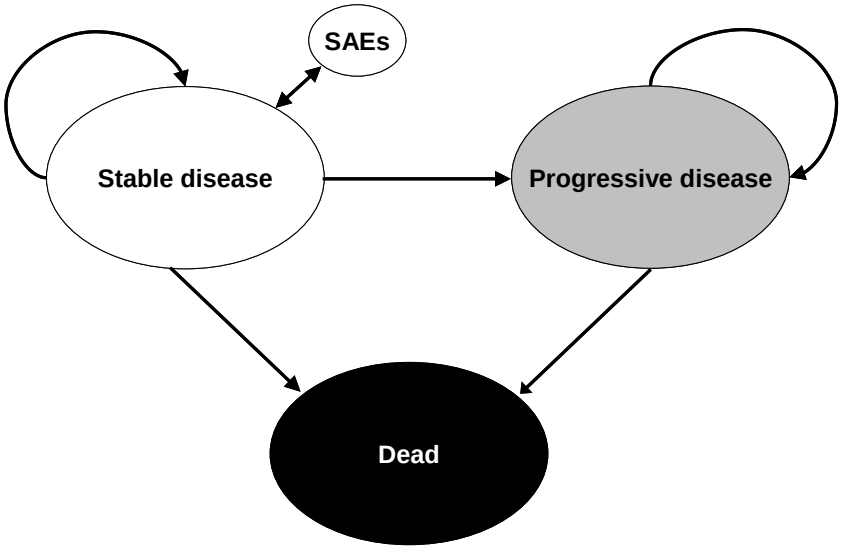
The MS is consistent with the principles of the NICE reference case.[88] The cost-effectiveness ratio is expressed in terms of cost per quality adjusted life year (QALY), the time horizon is that of assumed patient lifetime, utility has been estimated using the EuroQol 5-Dimension (EQ-5D), costs and benefits are discounted, and costs are taken from an NHS and Personal Social Services Perspective.

5.2.2 Model Structure

The manufacturer supplied a *de novo* economic evaluation based upon a cohort Markov model constructed in Microsoft Excel©. The model includes three states: stable disease; progressive disease and death (an absorbing state). All patients begin in stable disease where transitions to progressive disease and death are possible. Following transition to progressive disease it was assumed that patients could not revert to stable disease, but would instead remain in this state until death.

In addition to these health states, the possibility of experiencing serious adverse events (SAEs), which incur costs and disutilities, whilst in the stable disease state has been modelled. A schematic of the model is shown in Figure 2 (reproduced from the MS (Figure 6-1 p 90)).

Figure 2: A schematic of the manufacturer's model



Separate transition probabilities are modelled for cabazitaxel and mitoxantrone, the sole comparator within the economic analysis. Data for these come from appropriate patients within the TROPIC trial, as described in Section 5.2.6.

The model uses a cycle length of three weeks to match the timing of treatment cycles for both drugs and an assumed lifetime horizon, set as 747 weeks (14.4 years). Half-cycle correction is employed.

Within the model clinical assumptions are based on patient experience within the TROPIC trial. The intervention and comparator being compared (cabazitaxel plus prednisolone and mitoxantrone plus prednisolone) are given only to patients with stable disease. Patients with progressive disease receive either post-second-line chemotherapy, a mix of treatments, or best supportive care, which are detailed in Section 5.2.8. It is assumed that neither post-second-line chemotherapy nor best supportive care affects either survival or utility. The utility within a given health state is assumed to be independent of time within that state. The ERG and the clinical advisors are satisfied that the model captures the main aspects of patient's clinical pathway of care.

Mitoxantrone was allowed to be provided as part of post-second-line chemotherapy. The manufacturer argues that, as mitoxantrone does not impact on survival, and as the results from TROPIC include the effects of cross-over, no adjustment is required, a logic that the ERG deems is reasonable.

One-off transition costs are applied when moving to the progressive disease state (to account for post-second-line treatment) and also when moving to the death state (to account for end of life costs). These are described in Section 5.2.8.

5.2.3 Patient population considered

The MS present results for four patient populations:

- Base case: European patients within TROPIC who received ≥ 225mg/m^2 of first-line docetaxel and with an ECOG PS of 0 or 1
- Subgroup 1: The entire TROPIC population
- Subgroup 2: European patients within TROPIC
- Subgroup 3: Patients within TROPIC who received ≥ 225mg/m^2 of first-line docetaxel and with an ECOG PS of 0 or 1

The manufacturer has selected the base case claiming that it is the group most likely to reflect current practice within the United Kingdom. The ERG comment on the appropriateness of this choice in Section 5.2.12.

Following the round of clarifications the manufacturer also undertook analyses removing those patients who had died within 30 days of randomisation for the base case and for subgroup 1.

5.2.4 Intervention and comparator

The intervention was cabazitaxel (25 mg/m^2) given every three weeks plus 10 mg per day of prednisolone. The intervention could be given for a maximum of 10 cycles. The comparator was mitoxantrone (12 mg/m^2) given every three weeks plus 10 mg per day of prednisolone. These pharmaceuticals were directly compared in the TROPIC trial.

The decision scope also included chemotherapy without cabazitaxel. These comparators were not considered within the MS based on the following rationale: that the use of chemotherapy other than mitoxantrone was rare within the UK and could not be considered standard practice and that there was lack of evidence on efficacy for any other chemotherapy. The clinical advisors to the ERG believed that these statements were correct and did not consider other treatments than mitoxantrone to be appropriate.

Intervention Costs

Both cabazitaxel and mitoxantrone are provided in vials with the dosage required being dependent on body surface area (BSA) (25 mg/m^2 for cabazitaxel and 12 mg/m^2 for mitoxantrone). The average number of vials used per patient per infusion was calculated based on the distribution of BSA observed in the TROPIC trial (assumed to be normally distributed with a mean of 2.01 and a standard deviation of 0.21) and the observed relative dose intensity (0.928 for cabazitaxel and 0.941 for mitoxantrone). The cost per vial of cabazitaxel was taken from the MS[1] whilst the cost per vial of mitoxantrone was taken from the BNF61.[19] Both cabazitaxel and mitoxantrone are taken in

conjunction with prednisolone, which based on BNF61 costs and an assumption of 10 mg taken daily were costed at £1.55 per cycle.

Table 24: Cabazitaxel and mitoxantrone costs assumed within the model

	Vial size (active ingredient)	Cost per vial	Average vials used per patient per infusion	Average cost per patient
Cabazitaxel	60 mg	£3696	1.003	£3707
Mitoxantrone	20 mg	£100	1.871	£187

5.2.5 Perspective, time horizon and discounting

The perspective of the evaluation was appropriately that of the NHS and personal social services. The time horizon, considering that there was a differential mortality rate between the intervention and the comparator, was also appropriate in approximating a patient's lifetime set as 747 weeks (14.4 years).

The manufacturer intended to use discount rates of 3.5% per year for both costs and benefits, in line with the NICE reference case [88] however a slight error (of no material significance) was made in implementation. More details are provided in section 5.2.12.

5.2.6 Treatment effectiveness

The effectiveness of the treatment and the comparator were estimated from the TROPIC RCT and converted into time varying transition probabilities. The primary outcome of overall survival was used to model transition probabilities for moving to the death state. A secondary outcome, progression-free survival, was used to model the probability of those in the stable disease state moving to the progressed disease state. The probabilities (at any given time) of mortality are assumed to be the same for both the stable and the progressive disease states, which is unlikely to be correct, but the interaction with the probabilities for transitioning from stable disease to progressed disease ensures that the numbers in each health state are as intended.

The model supplied by the manufacturer has the flexibility to simulate disease progression and death using two alternative methodologies. The first methodology, and the one denoted the base case by the manufacturer, sets all transition probabilities to those observed in TROPIC, directly using the Kaplan-Meier (KM) curves, 'until the time when the small number of patients makes the curve erratic and unreliable' (p 97 of the MS) when transition probabilities calculated from fitted parametric curves are used instead. The times at which the curves became unreliable is made on a subjective examination of the KM curves and are discussed further in Section 5.2.12. In the base case the Kaplan-Meier data are used up until week 57 for progression-free survival and week 111 for overall survival (both inclusive). The second methodology uses the parametric curves for the entire time horizon.

The manufacturer considered a wide variety of parametric curves, basing their choice on a combination of information criteria and a visual inspection of goodness of fit. A Weibull distribution

was used to estimate the overall survival rates for both treatments. For progression-free disease rates a Weibull distribution was fitted to the cabazitaxel data whilst a log-normal distribution was fitted to the mitoxantrone data. The information criteria considered were the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), and these values are reproduced in Table 25; lower values are preferred, and the ERG has underlined the lowest estimate. It is commented that these goodness of fit tests do not indicate a definite selection of a curve since information criteria cannot be formally tested for significance.

Table 25: Goodness of fit data for the parametric curve

Overall Survival	**Mitoxantrone**		**Cabazitaxel**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	379,18	382,25	421,46	424,66
Weibull	<u>343,76</u>	<u>349,90</u>	397,64	404,04
Log-normal	355,96	362,10	406,40	412,80
Log-logistic	350,50	356,64	<u>396,96</u>	<u>403,36</u>
Gompertz	351,13	357,27	406,33	412,73

Progression-Free Survival	**Mitoxantrone**		**Cabazitaxel**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	456,60	459,67	510,38	513,58
Weibull	457,08	463,22	<u>503,92</u>	<u>510,32</u>
Log-normal	<u>428,96</u>	<u>435,10</u>	504,58	510,98
Log-logistic	439,30	445,44	508,30	514,70
Gompertz	458,14	464,28	507,29	513,69

The distribution with the lowest AIC and BIC was generally used within the modelling, although one exception exists, which is discussed.

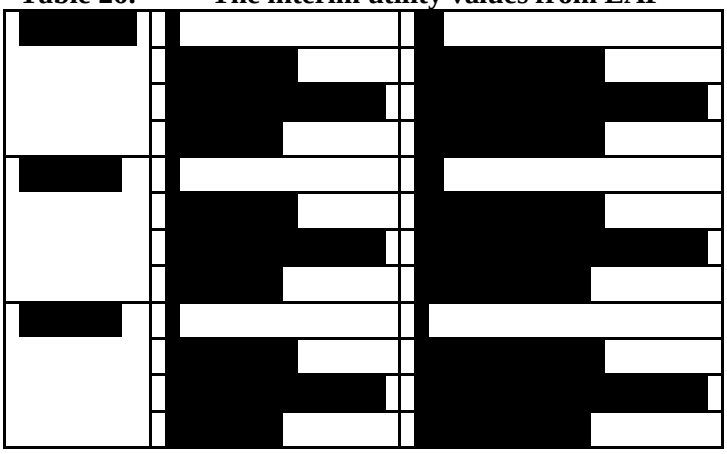
The manufacturer has assumed that the Weibull distribution is more appropriate to model OS for cabazitaxel than the Log-logistic distribution. The reasons for this choice, as explained in the clarification response A14,[2] are that 'Firstly, the Weibull is the best fit for the cabazitaxel OS in all the other patient subgroups and the whole TROPIC population, and also in the mitoxantrone arm. Given that both are a good fit, it seems reasonable to maintain consistency between analyses by using the same distribution for different patient subgroups. Secondly, graphically, the Log-logistic distribution appears to overestimate OS at the end of the curve. It was on this basis that the Weibull was chosen for the cabazitaxel arm. With the Log-logistic, the mean OS for cabazitaxel is 26.4 months, in comparison with 19.4 months with the Weibull distribution. This is much higher than that seen with the other subgroups and would be somewhat inconsistent with them. Thus the choice of Weibull distribution can be viewed as best reflecting the overall dataset.' The ERG believes this to be a reasonable approach.

The submitted model has the functionality to use the Weibull distribution for PFS for mitoxantrone in order that Weibull distributions are used throughout the modelling. The results when using the Weibull distribution are presented within the sensitivity analyses.

5.2.7 Health related quality of life

Data on quality of life were not included in the TROPIC trial. EQ-5D utilities are being collected in the United Kingdom as part of the Early Access Programme (EAP) for cabazitaxel. As of July 2011, the EAP has only provided interim utility data for the stable disease state as only two patients had entered the progressive state. The EAP is an open-label, single-arm trial of cabazitaxel and thus does not include mitoxantrone. The model assumes that within any given health state the utilities are the same for both drugs. The clinical advisors to the ERG had no reason to believe that the utility for patients would be affected by the type of second-line chemotherapy used (i.e. cabazitaxel or mitoxantrone). The values that have been estimated from the EAP are provided in Table 26, together with the number of patients from which these values have been derived. The manufacturer reports that a further interim analysis will be performed in August 2011.

Table 26: The interim utility values from EAP



The manufacturer has assumed that the values from cycle 2 represent the most plausible value for stable disease. In response to clarification question A15, the manufacturer stated that "The baseline value in the EAP comes from patients who have been selected for cabazitaxel treatment on the basis of disease progression after first-line docetaxel treatment (but they have not yet begun second-line treatment). Therefore, the baseline value represents the utility for "first-line disease progression patients". It does not represent stable disease. Further, patients are not receiving cabazitaxel at this timepoint. Therefore, it is less appropriate than the Cycle 2 value. Cycle 4 data were not used due to the small number of patients ([redacted]) for whom data were available."

This argument appears plausible, although the ERG notes both the relatively wide CIs around the means at baseline and cycle 2, and comment that the data are relatively uncertain. The exact values to

use in the evaluation, in addition to at which cycle utility should be measured, are therefore relatively uncertain

The manufacturer undertook a systematic review of health-related quality of life data to estimate the utility value within the progressed disease state. Only two studies met the manufacturer's inclusion criteria,[89,90] and of these, only one considered patients with metastatic hormone-refractory prostate cancer.[89] This study reports a similar baseline utility (0.715) to the EAP and reports a drop in utility of about 0.07 at about 3 months. This drop is maintained for the duration of the study (up to nine months). The manufacturer assumes that this drop reflects the disutility due to moving from the stable to progressive disease state and therefore have set the utility value of patients in the progressed state to be [redacted] ([redacted] minus 0.07) .

The second study[90] identified by the manufacturer reported a decline in utility between a point 16 months before death and a point eight months before death, assuming that these points approximated stable disease and progressed disease respectively. This estimated decline of 0.085 was subtracted from the estimated utility for stable disease from the EAP to produce a value of [redacted] for progressed disease. This value was used in sensitivity analyses.

5.2.8 Resources and costs

General resource use (such as inpatient visits) is based on a mixture of expert clinical opinion and a retrospective UK-based audit of five major cancer centres, with costs taken from the National Schedule of Reference Costs (2009-10).[91] These costs are detailed in Tables 6-12 and 6-13 (pages 126-128) of the MS. The ERG and clinical advisors did not identify any issues with the values used.

Post-second-line interventions

The model assumes that a proportion of patients ([redacted]) would receive post-second-line chemotherapy following progression, with the complement ([redacted]) receiving best supportive care. These percentages were assumed the same for both cabazitaxel and mitoxantrone.

Table 27 shows the breakdown of drugs used in post-second-line chemotherapy in the economic model. Note that there was a typographical error in the MS, (confirmed by the manufacturer and corrected in Table 27) in that the numbers for cabazitaxel and mitoxantrone were transposed. Table 27 additionally shows the expected costs of post-second-line chemotherapy drugs for cabazitaxel and mitoxantrone.

Table 27: Breakdown of drugs used in post-second-line chemotherapy in the economic model

Post-2nd line chemotherapy	Mean Duration		Cost (per week)	Proportions	
	Cabazitaxel	Mitoxantrone		Cabazitaxel	Mitoxantrone
Carboplatin	9.11	10.32	£118.13	2.82%	8.45%
Cyclophosphamide	20.89	9.23	£16.21	8.45%	10.56%
Docetaxel	16.14	21.37	£335.67	12.68%	19.01%
Estramustine	12.30	9.70	£47.88	9.15%	11.97%
Etoposide	10.31	15.70	£2.91	10.56%	15.49%
Mitoxantrone	12.72	12.96	£40.20	38.02%	8.45%
Paclitaxel	6.07	2.80	£261.27	3.52%	1.41%
Vinorelbine	7.58	9.49	£116.58	4.93%	11.27%
Cisplatin	18.47	5.33	£19.60	1.40%	1.41%
Gemcitabine	0	13.33	£160.80	0%	2.11%
Total Cost				£1,754	£2,422

It is noted that almost 40% of patients crossed from cabazitaxel to mitoxantrone following disease progression. Hence, if cabazitaxel is fully approved as a drug, it will not fully replace mitoxantrone.

The constituents of best supportive care (and percentage of patients assumed to require each) were taken from an audit of five major UK centres and were: analgesics ([redacted]); steroids ([redacted]); palliative radiotherapy ([redacted]) and bisphosphonates ([redacted]). These percentages were assumed to be the same for both cabazitaxel and mitoxantrone. This translated into a cost of £[redacted] per 3 week cycle. More details are provided in Table 6-12 and 6-13 (pages 126-128) of the MS.

Costs at the end-of-life

In addition, a cost associated with treatment at the end of life is incorporated. The assumptions behind this cost are provided in Table 6-12 of the MS, resulting in an estimated cost of [redacted] per patient.

5.2.9 Serious adverse events considered within the model

SAEs were defined as grade 3 or higher adverse events that either occurred during the TROPIC trial in at least 2% of patients (on either treatment) or events which are of clinical significance (which were defined as either deep vein thrombosis or neuropathy). Table 28 lists the adverse events used within the model, along with their rates per patient. As the manufacturer has appropriately used the rate per patient (allowing for multiple events), these values do not match the percentage of patients experiencing the event, which is detailed in Table 5-10 (p 77) of the MS.

Table 28: The adverse events incorporated within the manufacturer's model

Adverse Events (Grade ≥3)	Adverse Event rates		Total cost per event
	Mitoxantrone arm	Cabazitaxel arm	(£)
Neutropenia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Asthenia (weakness)	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]
Nausea / vomiting	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]
Neuropathy	[redacted]	[redacted]	[redacted]

The total cost per event has been calculated based on a number of factors: the proportion of patients hospitalised (sourced from the TROPIC trial and adjusted by expert opinion); the total inpatient days per hospitalisation (sourced from the HRG data[91]); the cost per day whilst hospitalised (sourced from the National Schedule of Reference Costs (2009-10) [91]); and the cost of pharmaceuticals to treat the SAE (sourced from the BNF).[19] These data are provided in Tables 6.14 – 6.16 (pages 128 – 130) of the MS. The manufacturer assumed 'that AEs in patients who do not require hospitalisation will be managed through the outpatient visits that occur regularly throughout the treatment period – including both visits associated with chemotherapy administration and the regular visits not directly related to chemotherapy administration. This assumption was validated by clinical expert opinion' (clarification response A24). It is unclear whether this slightly underestimates resource use.

Disutilities due to adverse events were taken from a literature review with the assumption that disutilities in patients without mHRPC would be transferable to mHRPC patients. The disutilities used within the modelling are provided in Table 29. Details regarding the sources of these values are provided in Table 6.6 of the MS (pages 111 to 112) and in Section 6.4.8 of the MS. Table 29 also reports the standard errors used within the probabilistic sensitivity analyses. The manufacturer clarified that only the value for bone pain had an associated standard error and that the remaining standard errors were estimated assuming that the ratio between the point estimate and the standard error for bone pain was applicable to all SAEs type.

Table 29: The disutilities associates with serious adverse events

SAE	Assumed Disutility	Assumed Standard Error
Neutropenia	-0.090	0.0157
Febrile neutropenia	-0.120	0.0209
Diarrhoea	-0.047	0.0082
Fatigue	-0.094	0.0163
Asthenia (weakness)	-0.094	0.0163
Leucopenia	-0.090	0.0157
Back pain	-0.069	0.0120
Anaemia	-0.125	0.0217
Thrombocytopenia	-0.090	0.0157
Pulmonary embolism	-0.145	0.0252
Dehydration	-0.151	0.0263
Nausea/vomiting	-0.076	0.0131
Bone pain	-0.069	0.0120
Deep vein thrombosis	-0.160	0.0278
Neuropathy	-0.116	0.0202

5.2.10 Deterministic cost-effectiveness results presented by the manufacturer

Following the clarification questions asked by the ERG the manufacturer altered the values of some parameters within the model: a value of 2.97 days for total inpatient days per neuropathy episode replaced the previous figure of 2.77; the value for the risk ratio for neutropenia prophylaxis, previously left blank, was updated to 0.077; the risk of AEs is now divided by 365.25 instead of 365; and the disutility for pulmonary embolism is corrected to 0.145 instead of 0.245. These changes had a marginal effect on the results, increasing the manufacturer's deterministic base case incremental cost effectiveness ratio (ICER) from £74,908 to £74,938 per QALY gained. It is commented that the change regarding the risk ratio for neutropenia prophylaxis would not affect the deterministic ICER, only the sensitivity analyses conducted.

Additionally, the manufacturer provided an updated model that allowed probabilistic sensitivity analyses to be conducted whilst using the Kaplan-Meier data. For each intervention, the methodology used the same 'random seed' to ensure coherence between PFS and OS; it is unclear what bias, if any, is introduced by this. Further details are provided in section 5.2.12.

Only the revised model will be detailed and critiqued.

Plots of the Markov trace for each intervention within the manufacturer's deterministic base case are provided in Figures 3 and 4.

Figure 3: The Markov trace for cabazitaxel in the manufacturer's deterministic base case

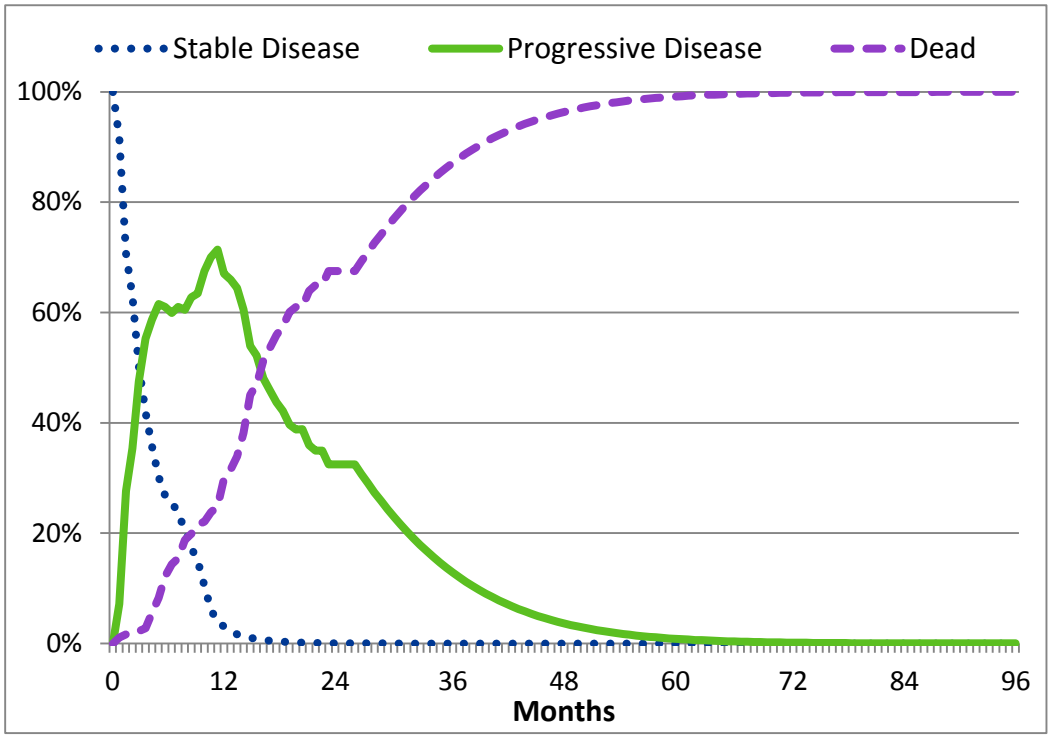
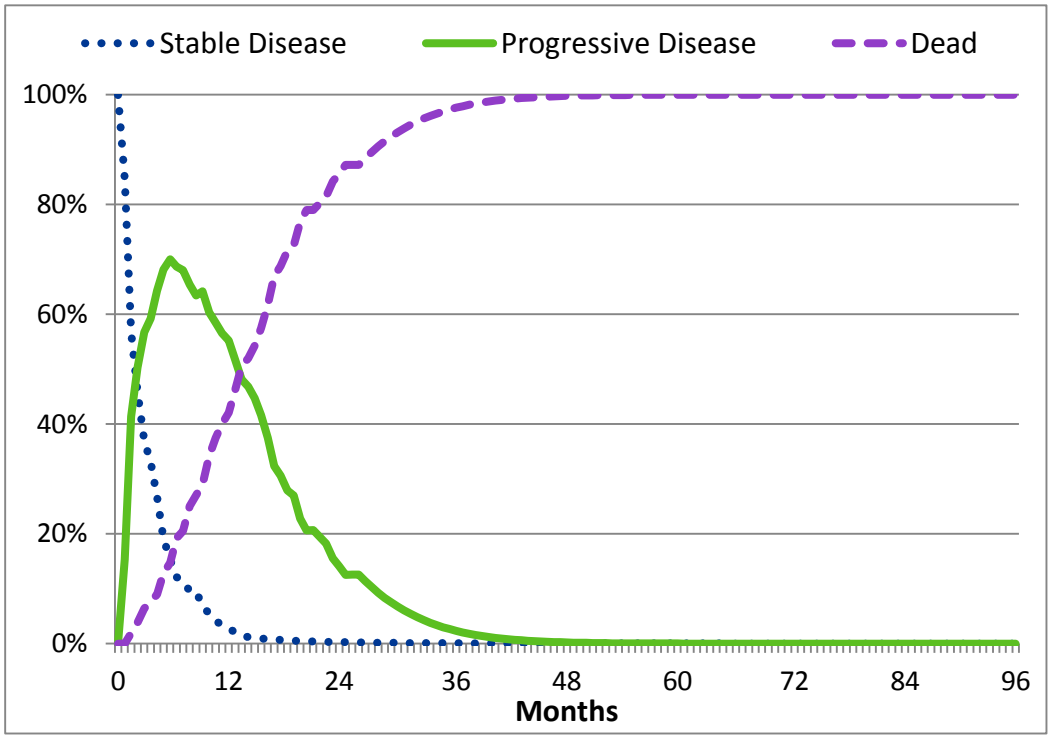


Figure 4: The Markov trace for mitoxantrone in the manufacturer's deterministic base case



The estimated costs and QALYs in the base case are provided in Table 30. Figures 5 and 6 show the constituent parts of costs and QALYs for the cabazitaxel and mitoxantrone arms in terms of SD, PD, and death.

Table 30: Deterministic base case results

	Total Costs (£)	Total QALYs	Δ Cost (£)	Δ QALY	Cost per QALY (£)
Mitoxantrone	13,047	0.849			
Cabazitaxel	35,372	1.147	22,325	0.298	74,938

Figure 5: The breakdown of costs by constituent health state

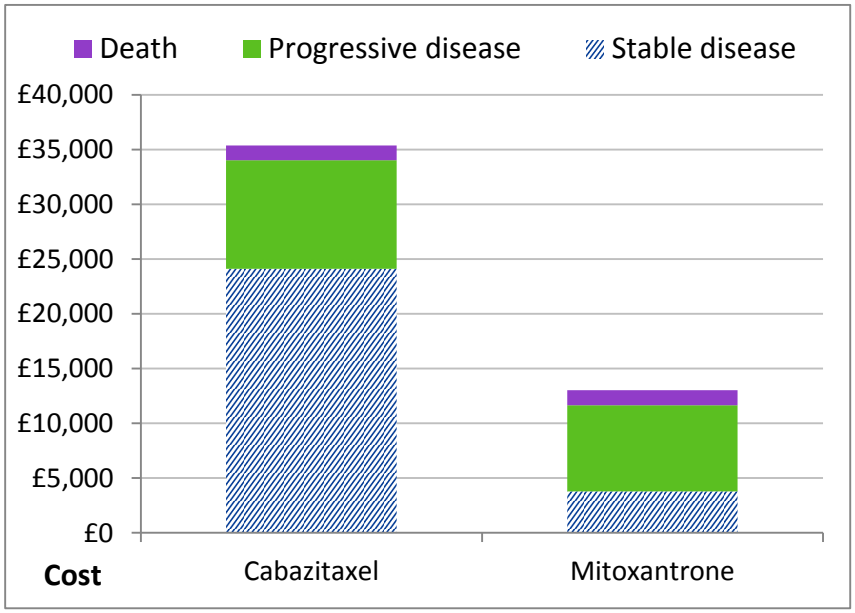
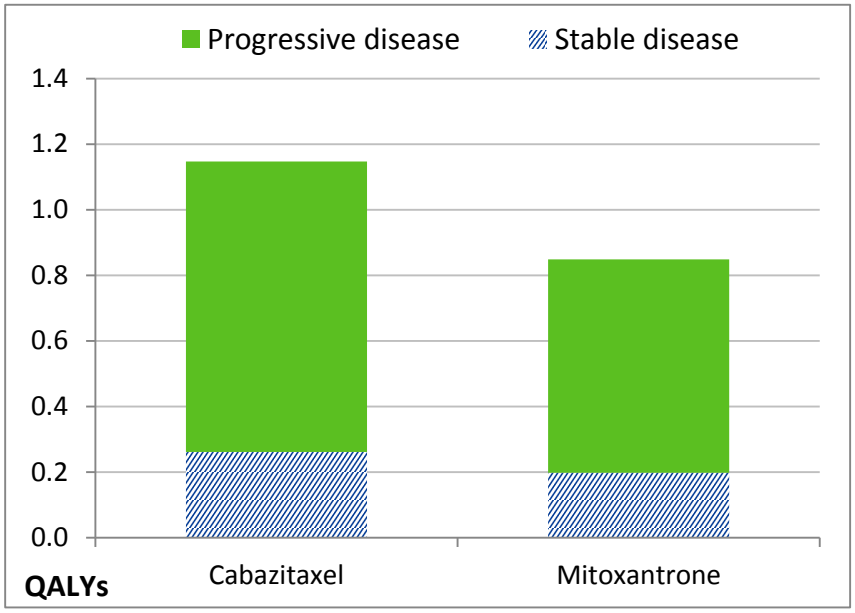


Figure 6: The breakdown of QALYs by constituent health state



5.2.10 Sensitivity analyses presented by the manufacturer

The manufacturer conducted scenario analyses (defined as using an alternative assumption for a parameter) and deterministic one-way sensitivity analyses (where the current value was subject to an increase or a decrease to assess the robustness of the ICER to changes in this parameter). A list of the alternative scenarios considered is provided on page 131 of the MS, whilst details of the one-way sensitivity analysis are on page 132. In addition, the model had the functionality to estimate the cost-effectiveness of cabazitaxel in the alternative population subgroups.

Sensitivity analyses presented by the manufacturer regarding the modelled population

The results produced from the alternative subgroups are provided in Table 31. These have been generated by the ERG using the submitted model.

Table 31: Deterministic results using the alternative subgroups

	Total Costs (£)	**Total QALYs**	**Δ Cost (£)**	**Δ QALY**	**Cost per QALY (£)**
Base case					
Mitoxantrone	13,047	0.849			
Cabazitaxel	35,372	1.147	22,325	0.298	74,938
Subgroup 1 : The entire TROPIC population					
Mitoxantrone	12,724	0.880			
Cabazitaxel	34,093	1.133	21,368	0.244	87,684
Subgroup 2 : European patients within TROPIC					
Mitoxantrone	12,736	0.875			
Cabazitaxel	34,703	1.174	21,966	0.260	84,540
Subgroup 3 : Patients within TROPIC who received ≥ 225mg/m^2 of first-line docetaxel and with ECOG 0 or 1					
Mitoxantrone	13,085	0.916			
Cabazitaxel	34,493	1.190	21,408	0.259	82,538

Sensitivity analyses presented by the manufacturer regarding an updated hazard ratio for overall survival

On page 63 of the MS the manufacturer discusses the availability of a more recent HR for death than that used. 'The HR used was 0.70 (95% CI, 0.59–0.83) in favour of cabazitaxel corresponding to a 30% reduction in risk of death.[22] An updated analysis was performed almost six months later, after 585 (rather than 513) deaths had occurred, and has been presented at ASCO, but has not yet been published in a peer-reviewed publication. The updated analysis found identical median survival values with a HR of 0.72;[80] this submission uses the HR reported in the regulatory submissions and peer-reviewed Lancet publication'. The ERG asked the manufacturer to clarify the effect of using the updated HR on the ICER (Clarification Question A1).

The manufacturer provided a comparison of the original and updated OS data for the entire TROPIC population (reproduced in Table 32) and for the base case (reproduced in Table 33). The manufacturer reports that, for the base case, the use of the updated OS data had little effect on the ICER (assuming fitted curves used throughout), increasing the cost per QALY from £82,950 to £82,963.

Table 32: Comparison of original and updated OS data for whole TROPIC population (N=755)

OS	MTX+PRED			CBZ+PRED			CBZ+PRED vs. MTX+PRED		
	Number dead / N (%)	median survival (95% C.I.)	mean survival	Number dead / N (%)	median survival (95% C.I.)	mean survival	Hazard Ratio (HR)	Median difference	Mean difference
Updated OS	308/377 (81.7%)	12.7 (11.5–13.7)	14.5	277/378 (73.3%)	15.1 (14.0–16.5)	18.5	0.72 (0.61–0.84)	2.4	4.0
Original OS	279/377 (74.0%)	12.7 (11.6–13.7)	14.0	234/378 (61.9%)	15.1 (14.1–16.3)	18.2	0.70 (0.59–0.83)	2.4	4.2

Table 33: Comparison of original and updated OS data for European patients with ECOG PS 0, 1 and with ≥ 225 mg/m² of previous docetaxel ([redacted])

	MTX+PRED			CBZ+PRED			CBZ+PRED vs. MTX+PRED		
	Number dead / N (%)	Median survival (95% C.I.)	Mean survival	Number dead / N (%)	Median survival (95% C.I.)	Mean survival	Hazard Ratio (HR)	Median difference	Mean difference
Updated data-set	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original data-set used in submission	117/159 (73.6%)	[redacted]	[redacted]	109/181 (60.2%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario analyses undertaken by the manufacturer

The scenario analyses undertaken by the manufacturer were conducted before the amendments to the model after the ERG clarification questions, and are therefore compared with a base case ICER of £74,908. The full breakdown of costs and QALYs are provided in pages 143 to 147 of the MS; for brevity, Table 34 only presents the incremental costs and QALYs, and the corresponding ICER for an evaluation of cabazitaxel and mitoxantrone.

Table 34: The results from scenario analyses

	Δ Cost (£)	**Δ QALY**	**Cost per QALY (£)**
Base case	22,325	0.298	74,908
Fitted curves used throughout	23,088	0.278	82,950
Using a Weibull distribution for PFS in the mitoxantrone arm	22,310	0.298	74,786
Post-second-line treatment set to that of a UK audit rather than Tropic	22,642	0.298	75,972
No vial wastage assumed	18,159	0.298	60,928
Using UK-estimated BSA rather than that from Tropic	22,354	0.298	75,003
Using UK-specific G-CSF use	22,146	0.278	74,387
Using the decrement in utility between SD and PD estimated from Sandblom *et al*.[90]	22,325	0.293	76,171
Excluding SAE-related disutilities	22,325	0.300	74,536
Assuming equal costs post-progression for cabazitaxel and mitoxantrone treated patients	20,329	0.298	68,210

The ERG believes that three of these scenarios (no vial wastage assumed, excluding SAE-related utilities, and assuming equal costs post-progression) are not appropriate. The clinical advisors to the ERG indicate that vial sharing would not be feasible given the proposed numbers of patients to be treated; the disutilities associated with SAE are tangible; and the prolonged survival associated with cabazitaxel will incur costs for those patients within the PD state.

For the remaining scenarios, which the ERG believes are plausible alternatives, it is seen that only the use of the fitted curve makes a marked impact on the ICER, increasing the value to £82,950 per QALY.

A scenario analysis was conducted by the manufacturer during the clarification process (A11) where patients dying within 30 days of randomisation were excluded from the analyses. This is possibly pertinent if it is believed that these deaths observed in TROPIC could be preventable with more vigilant treatment of neutropenia. The MS reports on pages 75 and 76 that 'The clinical consequences of neutropenia were the most frequent cause of death in the cabazitaxel group, with seven neutropenia-related deaths in comparison with one in the mitoxantrone group. The occurrence of these deaths prompted advice to the TROPIC investigators to manage neutropenia by strictly following the protocol regarding dose modification and delay and treating neutropenia as per ASCO guidelines. Following this, no new neutropenic deaths were reported. This shows that it is critically important that, as with other similar chemotherapies, neutropenia is appropriately managed, particularly when patients are newly started on cabazitaxel treatment.' In this analysis the manufacturer's base case ICER increased to £78,319 per QALY gained. The ERG speculates that the likely reason that the ICER increases is that the parameters for the Weibull distributions fitted to the overall survival data have altered, reducing the tail for cabazitaxel survival, which has resulted in a difference between the mean survival within the cabazitaxel and the mitoxantrone arms.

Univariate analyses undertaken by the manufacturer

Univariate sensitivity analyses were also conducted by the manufacturer. These were undertaken before the amendments to the model and are therefore compared with a base case ICER of £74,908. The results are provided on pages 141-142 of the MS. A reproduction of the incremental cost, incremental QALYs and the ICER are provided in Table 35.

Table 35: The results from univariate sensitivities

Analysis	ΔCost (£)	ΔQALY	Cost per QALY (£)
Base case	**£22,325**	**0.30**	**£74,908**
Costs			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Utilities			
AE disutilities excluded	£22,325	0.30	£74,536
SD utility +20%	£22,325	0.31	£71,764
SD utility -20%	£22,325	0.28	£78,341
PD utility +20%	£22,325	0.34	£64,733
PD utility -20%	£22,325	0.25	£88,878
Time horizon			
1 year	£19,699	0.05	£425,106
2 years	£20,418	0.12	£168,895
3 years	£21,520	0.23	£93,882
5 years	£22,279	0.29	£75,694
10 years	£22,325	0.30	£74,908
Discount rates			
Costs: 0%, Effects: 0%	£22,695	0.32	£70,705
Costs: 3.5%, Effects: 0%	£22,346	0.32	£69,618
Costs: 0%, Effects: 3.5%	£22,674	0.30	£76,078
Costs: 6%, Effects: 6%	£22,076	0.28	£78,038
State costs			
Caba & Mitox drug & adm cost -50%	£12,501	0.30	£41,945
Caba & Mitox post 2nd line (drugs & adm) cost -50%	£22,231	0.30	£74,592
Caba & Mitox other costs SD -50%	£22,150	0.30	£74,320
Caba & Mitox other costs PD -50%	£21,411	0.30	£71,840
AE costs -50%	£22,171	0.30	£74,389
Proportion with G-CSF as primary prophylaxis			
Caba & Mitox: 0%	£22,146	0.30	£74,387
Caba & Mitox: 20%	£22,128	0.30	£74,268
Caba & Mitox: 40%	£22,111	0.30	£74,150
Caba & Mitox: 60%	£22,094	0.30	£74,031
Caba & Mitox: 80%	£22,077	0.30	£73,913

Caba & Mitox: 100%	£22,060	0.30	£73,795

The ERG does not believe that the univariate analyses undertaken by the manufacturer r[redacted].

The amounts by which the utilities have been varied within the scenario analyses are arbitrary. In addition, the utilities for stable disease and progressive disease have been varied separately, leading to improbable combinations of values. Of the four utility scenarios considered, two lead to the utility for progressive disease being larger than that for stable disease (utility of SD = [redacted], utility of PD = [redacted]; utility of SD = [redacted], utility of PD = [redacted]), whilst in the other two the difference between the two utility states is greater than [redacted] (utility of SD = [redacted], utility of PD = [redacted]; utility of SD = [redacted], utility of PD = [redacted]). However, the results show that the choice of utility values, in particular that of progressive disease, can have a large impact on the ICER, placing more emphasis on obtaining robust estimates from the EAP.

Consistent with evaluations of technologies where there is a relatively large cost borne in the initial stages, with a resulting elongated survival, the ICER decreases as the time horizon lengthens. The ERG believes that the time horizon used by the manufacturer in their base case is appropriate. Discounting has some effect on the ICER but the manufacturer provides no reason as to why different rates than 3.5% for both costs and benefits should be used. It is seen that altering the costs assumed post-second-line, or other costs accrued within stable disease or progressive disease, have little effect on the ICER; as before, the ERG do not consider a sensitivity analysis on the [redacted]. The assumed proportion of patients receiving prophylactic G-CSF treatment has minimal effect on the ICER.

5.2.11 Probabilistic sensitivity analyses presented by the manufacturer

For the manufacturer's probabilistic uncertainty analyses, the assumed distributions for the parametric curves and the utilities are shown in Table 36. The assumed uncertainties in the remaining parameters incorporated into the probabilistic uncertainty analyses are provided in Appendix 3. It is noted that the utilities for stable disease and progressive disease were sampled independently, which resulted in the utility for progressive disease being assumed to be greater than the utility for stable disease on over 3% of simulations.

Table 36: The distributions for key variables within the manufacturer's probabilistic sensitivity analyses

Parametric Curves	Distribution	Shape*	Scale*	Mean (months)	95% CI
OS: Cabazitaxel	Weibull	1.587	0.0076	[redacted]	See text
OS: Mitoxantrone	Weibull	1.693	0.0089	[redacted]	
PFS: Cabazitaxel	Weibull	1.195	0.170	[redacted]	
PFS: Mitoxantrone	Log-normal	0.693	0.937	[redacted]	
Utilities	**Distribution**	**Alpha**	**Beta**	**Mean**	**95% CI**
Stable Disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Note that the values for the lognormal distribution represent mean and standard deviation

Where possible, standard errors for the variables are derived from the TROPIC trial. Simulated values for the parametric curves are taken from a Cholesky decomposition in order to maintain correlations. For proportions included in the TROPIC trial their standard error is calculated as:

$$SE = \sqrt{\frac{p(1-p)}{n}}$$

Proportions estimated using expert opinion have their standard error estimated by the Beta-Pert method; SE = (Maximum value – minimum value) / 6. The manufacturer assumed that these maximums and minimums were equal to the point estimate plus or minus 25%. This is the same as assuming that the standard error is equal to the expected value divided by twelve. The Beta-Pert methodology is also applied to average length of stay data.

Uncertainty in the Kaplan-Meier curves was not included in the initial model. However, in response to the ERG's clarification letter, it was incorporated in the manufacturer's revised model. To achieve this, the manufacturer used the observed data to model beta distributions at each time point (for a probability 'p', the alpha parameter is equal to p times the sample size, and the beta parameter is equal to 'one minus p' times the sample size). For each simulation of the probabilistic sensitivity analyses, a random percentile is simulated from these beta distributions. To account for the fact that the survival percentages at different time points are not independent, the same random percentile – which the manufacturer refers to as a 'random seed' – is simulated at all time points and for both OS and PFS (within a given probabilistic sensitivity analyses simulation and for a given drug). This methodology is likely to overestimate the uncertainty in the decision as extreme values for the random seed would be applied throughout the modelling horizon.

Whilst the manufacturer provided a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC), the actual ICER was not reported (Clarification Response A13). The ERG ran 2,000 simulations to provide an estimate of the ICER. The mean ICER was £75,682, range (£45,760 - £890,372); 95% of all the ICERs fell into the range £54,749 to £148,647.

A cost-effectiveness plane and cost-effectiveness acceptability curve for the manufacturer's base case are shown in Figures 7 and 8.

Figure 7: The cost-effectiveness plane comparing cabazitaxel with mitoxantrone

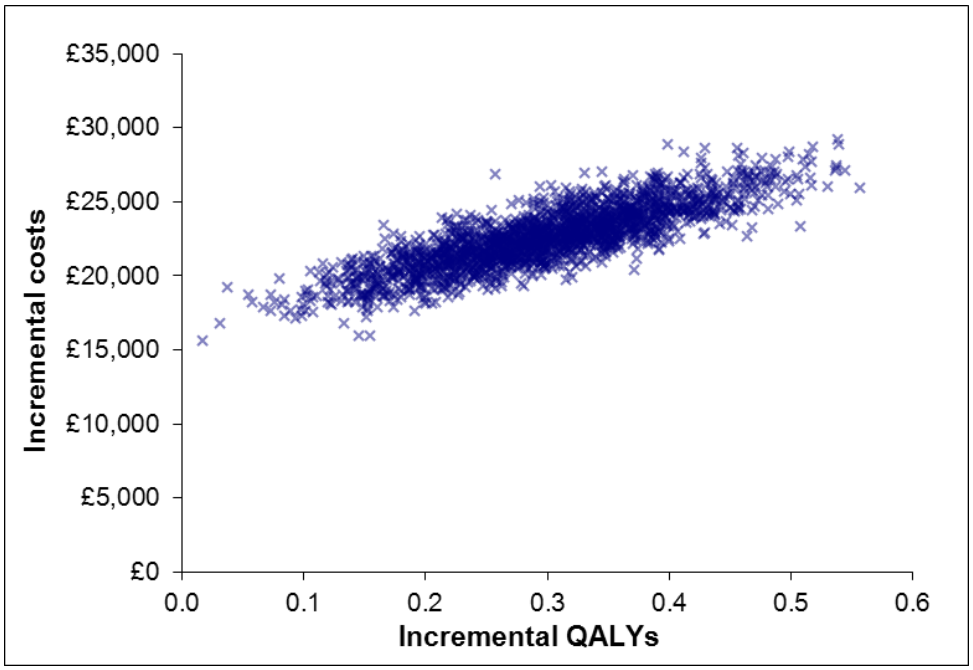
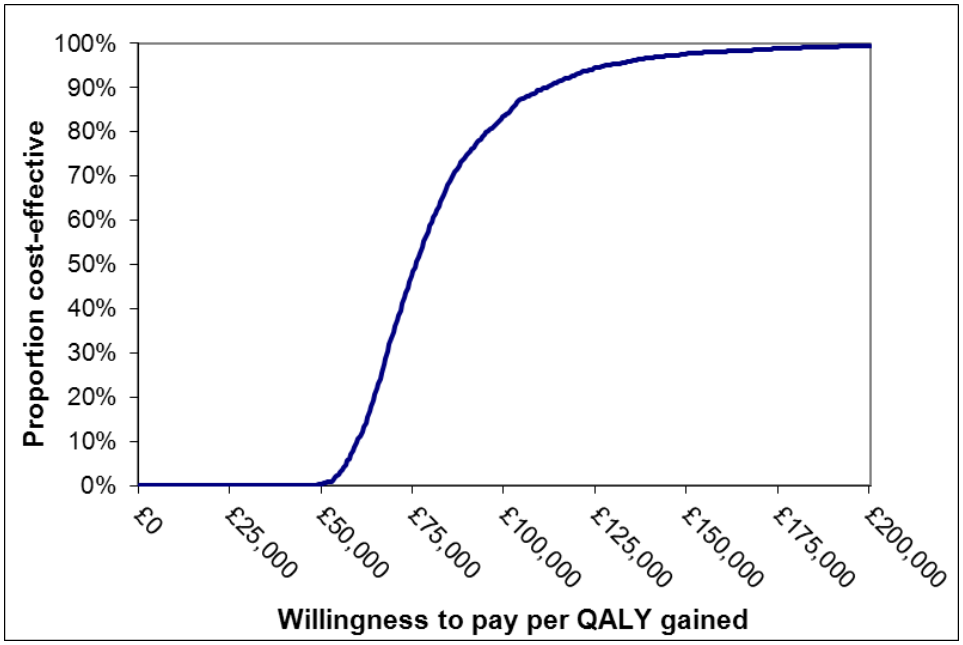


Figure 8: The CEAC comparing cabazitaxel with mitoxantrone



5.2.12 ERG critique of the submitted model

Generally, the ERG is satisfied with the model structure presented by the manufacturer. The use of a relatively simple model (employing only three states) enhances its transparency whilst the inclusion of additional costs (for example due to adverse events) reflects the clinical pathway likely to be encountered by patients on the drug.

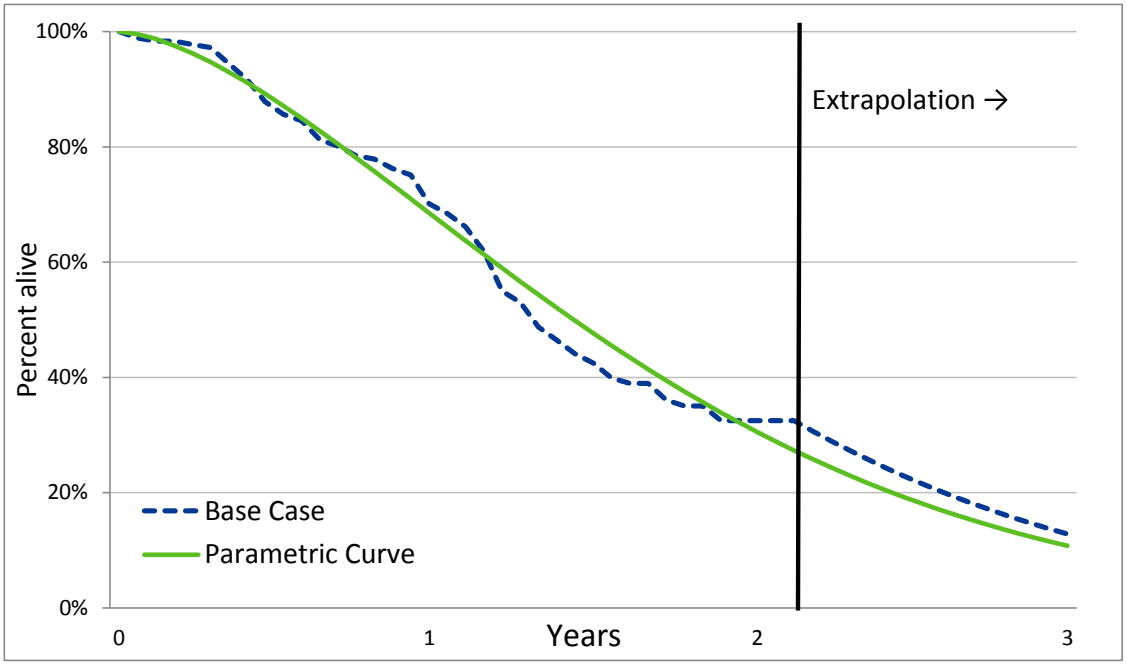
However, the ERG identified a number of concerns, of varying severity. These are discussed below.

Discussion of the use of parametric curves versus the use of the Kaplan-Meier data

The main source of data for the *de novo* model is the TROPIC trial, which only includes a small number of patients from England and Wales. The ERG recommends that parametric curves be used throughout instead of Kaplan-Meier curves for two reasons. First the Kaplan-Meier curves may over-fit the data, and thus model patterns that would not repeatedly occur whereas the use of parametric curves tries to avoid this by smoothing the data to an assumed underlying pattern, which is more likely to generalise to other populations.

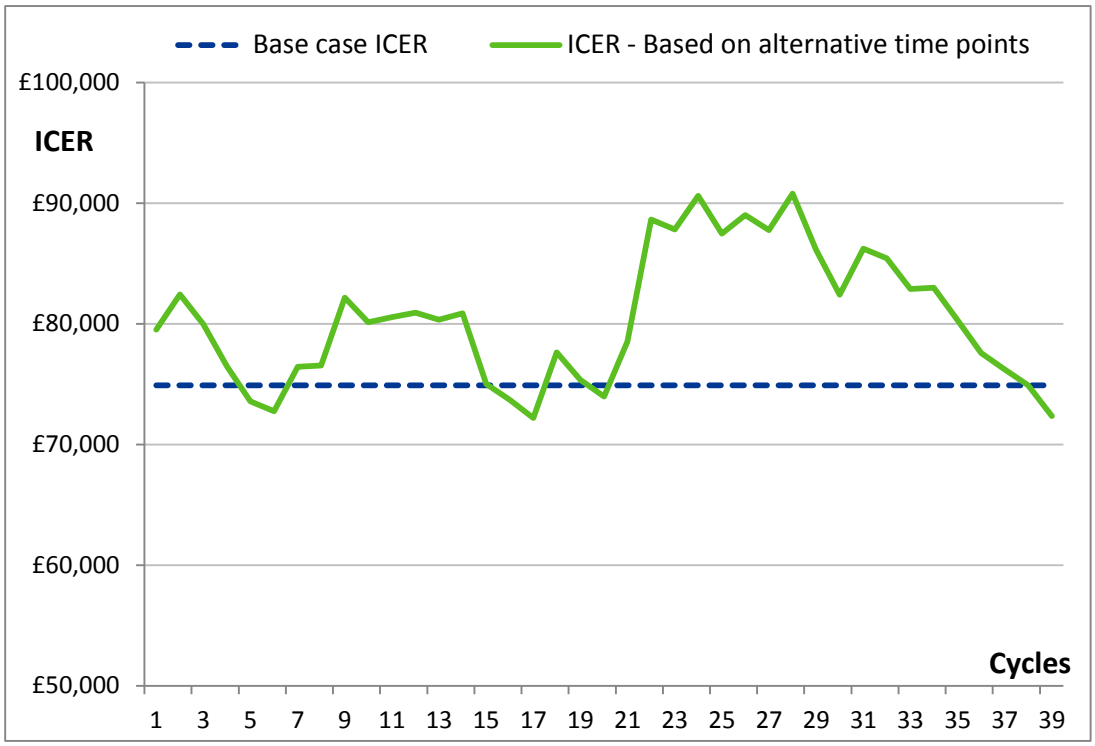
Second, the selection of the time point at which the proportions from the fitted curve is preferred to the Kaplan-Meier data is arbitrary, and can significantly affect the ICER. Figure 9 shows that, for OS in cabazitaxel, when the proportions from the parametric curve are adopted, the Kaplan-Meier data estimate that more patients are alive than would be estimated from the Weibull distribution. The discrepancy between the PFS data and the OS data for mitoxantrone is much less pronounced and has not been provided.

Figure 9: The discrepancy in the parametric curve fit and the Kaplan-Meier data for overall survival in the cabazitaxel arm in the manufacturer's base case



In response to a clarification request (A10), the manufacturer reported the change in the ICER when assuming different time points at which the parametric curve is used for overall survival. These data have been plotted in Figure 10 and show that the time point chosen has a marked effect on the ICER, with the time point chosen by the manufacturer (cycle 38) being one of the relatively lower values.

Figure 10: The sensitivity of the ICER to the point at which the Kaplan Meier curves for overall survival are replaced with parametric curves



Due to the instability of the ICER based on the time point at which the parametric curve is used and the possibility that directly using the Kaplan-Meier curves may overfit the data, the ERG believes that the use of the parametric curves throughout the model is a preferable approach, and do not concur with the manufacturer's rationale for using the Kaplan-Meier data (clarification response A9).[2]

The ERG believes, however, that, should the Kaplan-Meier data be used, the most appropriate time point in which to switch to the parametric curve would be at cycle 34 (week 102 or 1.96 years), where the Kaplan-Meier data and the Weibull data for OS in the cabazitaxel arm are approximately equal (Figure 9). In this instance, the deterministic ICER is £82,997, compared with £82,950 in the manufacturer's base case when the parametric distributions are used throughout; the ERG notes the similarity of these values.

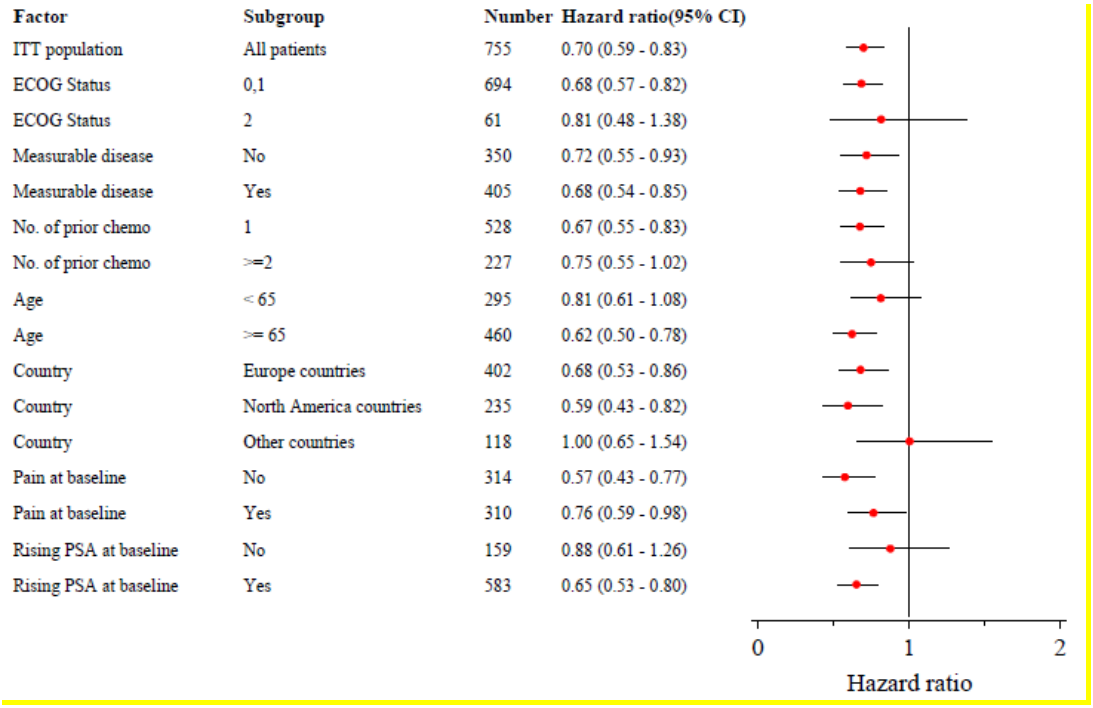
The patient population

The ERG believes that the patient population selected by the manufacturer within the base case is not the most appropriate. The entire TROPIC population was restricted by the manufacturer to patients 'with an ECOG performance status of 0 or 1, who have received at least 225 mg/m^2 docetaxel, and is based on European data from TROPIC'.

The manufacturer provided a Forest plot that detailed the hazard ratio by subgroup (replicated in Figure 11. Whilst it is seen that the midpoint value for 'other' countries is noticeably higher than

those for Europe and North America, it is conceivable that the hazard ratio may actually be lower in this region because of its wide associated CIs.

Figure 11: Hazard ratio of overall survival for baseline data (cabazitaxel and prednisone/prednisolone versus mitoxantrone and prednisone/prednisolone; ITT population)



The ERG believes that, in order to conduct sub-group analyses, there must be an *a priori* belief and rationale that the results may differ between subgroup, and that a formal statistical test of interaction between the outcome and the subgroup should be performed. In the manufacturer's response to the clarification question (A2) it was reported that 'There was no *a priori* clinical hypothesis for a difference in treatment effect by region. However, treatment practices vary between different countries and these different practices can affect treatment outcomes. The interaction of treatment by region is not statistically significant. This is true of the whole population (p value =0.1535)'. These statements combined do not convince the ERG that restricting the base case population to European patients can be justified.

The interaction test between those patients with an ECOG PS of 0 or 1 patients who received ≥ 225 mg/m^2 docetaxel was less statistically significant (p = 0.4098), although the ERG were more prepared to accept the validity of this sub-group. The advice provided by the clinical advisors to the ERG was that it was extremely unlikely those patients with an ECOG PS value of 2 would be treated. Additionally all patients should have received at least 225 mg/m^2 docetaxel prior to embarking on treatment with cabazitaxel and that it is plausible that the efficacy of cabazitaxel would be lower in patients who had received insufficient docetaxel. The *a priori* belief or this subgroup is also supported

by an amendment in the TROPIC protocol (after the recruitment of 59 patients) to exclude patients who had not received sufficient docetaxel. The ERG does not believe that restricting the population to this subgroup is inappropriate.

The ERG base case population is thus Subgroup 3 as defined by the manufacturer (patients who received ≥ 225 mg/m^2 of first-line docetaxel and with an ECOG PS 0 or 1).

Estimates of Utility

As of July 2011, only interim results from the EAP are available for patients with stable disease, which are associated with wide CIs, with no data reported for progressive disease. [redacted] In order to obtain a more robust ICER, it is imperative that more data regarding the utility in each health state is collected.

As previously reported, the utilities for stable disease and progressive disease were sampled independently, which resulted in the utility associated with the value for progressive disease being assumed to be greater than that for stable disease on over 3% of simulations. The violation of monotonicity appears implausible.

Discounting

A very minor error in the implementation of the discount rate was identified by the ERG. The manufacturer attempted to implement a continuous discounting rate (see Clarification Response A28) but used a value of 0.035. For continuous discounting, a rate of 0.0344 (calculated from ln (1.035)) should be used. This amendment made little difference to the results, reducing the manufacturer's deterministic base case from £74,938 to £74,865.

5.3 Additional work undertaken by the ERG

In order to provide an estimation of the ERG base case ICER, the ERG undertook analyses having altered the manufacturer's base case in the following manners:

- Using the parametric curves for the entire duration of the modelling horizon
- Altering the population to Subgroup 3 (patients who received ≥ 225 mg/m^2 of first-line docetaxel and with an ECOG PS 0 or 1)
- Ensuring monotonicity by calculating the utility of progressive disease from the value for stable disease, assuming a mean decrement of 0.07 as suggested by the Sullivan paper,[89] with an arbitrarily defined standard deviation of 0.02

- Correcting the discounting rate to use a continuous value of ln(1.035).

In addition, a number of sensitivity analyses have been conducted to determine the robustness of the base case ERG ICER to altering parameter values within the model.

The markov traces for the ERG base case are provided in Figure 12 for cabazitaxel and Figure 13 for mitoxantrone.

Figure 12: Markov trace for cabazitaxel in the ERG base case

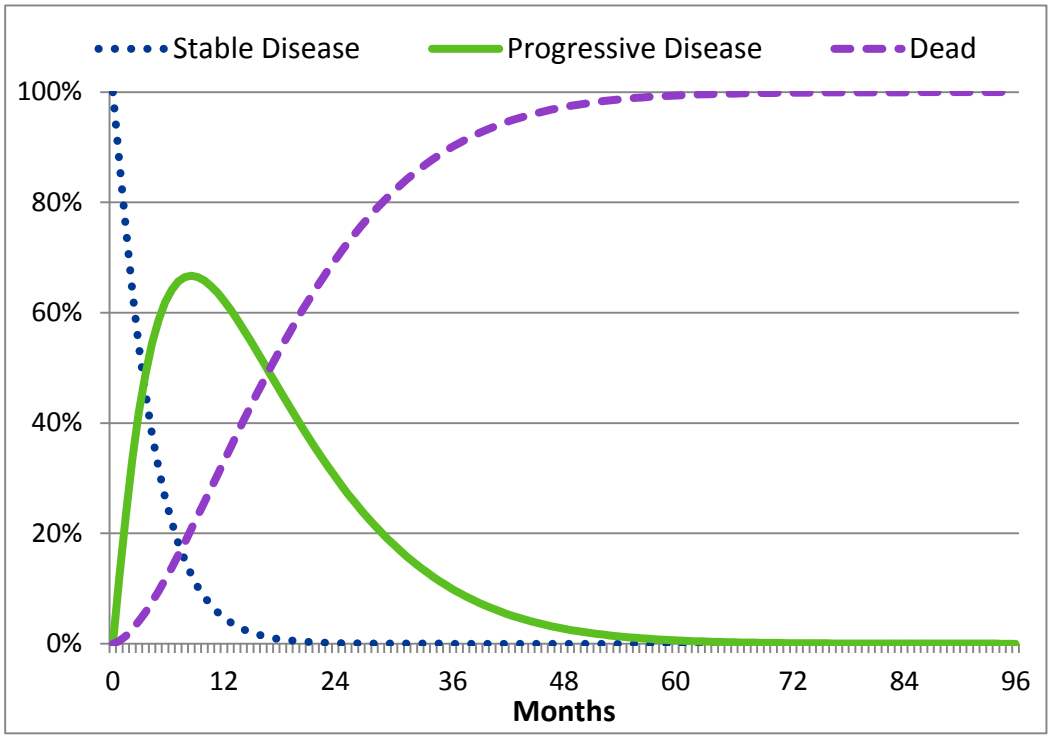
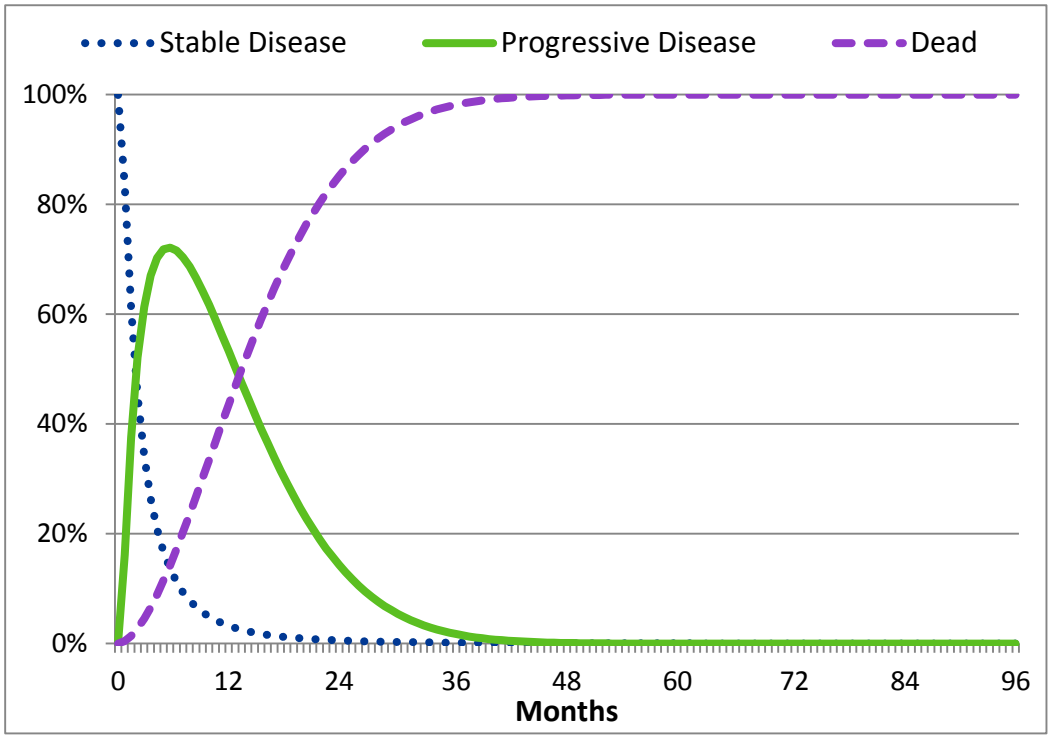


Figure 13: Markov trace for mitoxantrone in the ERG base case



5.4 Conclusions

The report was well written and the model was transparent with relatively few errors identified. The clarification process was smooth and the manufacturer responded to all the ERG's questions and amended the model accordingly.

The uncertainty in the ICER is mainly driven by choice of subgroup to use, the choice of whether to use the Kaplan-Meier data directly, and the availability of robust data regarding the utility in the stable and progressive disease states. The ERG has provided a commentary on these issues in section 5.2.12. Both the use of a parametric curve for the entire distribution and increasing the patient population by including non-European patients will increase the ICER and be less favourable to cabazitaxel. It is unclear what effect, if any, fuller data regarding the utility values associated with stable disease and progressive disease would have on the ICER.

A further uncertainty relates to the effect that the more recent OS data, which altered the HR from 0.70 to 0.72 for the entire TROPIC population, would have on the population used within the ERG base case.

An additional uncertainty is whether the deaths observed within TROPIC could be prevented if neutropenia is appropriately managed, particularly when patients are within the early stages of cabazitaxel treatment. If this is the case, then the ICER is likely to be greater than that estimated within the manufacturer's base case.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In order to provide an indication of the key drivers to the change in the ICER, three of the four amendments detailed in 5.3 were made independently to the deterministic base case, and then with all three made in combination. The amendment regarding monotonicity of utility values was not undertaken as this only affects the results from the probabilistic sensitivity analyses. Results are presented in Table 37. It is seen that the ICER is approaching £90,000.

Table 37: Changes in deterministic ICER of cabazitaxel compared with mitoxantrone based on the ERG amendments

Amendment to the base case	ΔCost (£)	ΔQALY	Cost per QALY (£)
None (base case)	22,325	0.298	74,938
Using parametric curves for the entire time horizon	23,088	0.278	82,986
Using Subgroup 3 (patients who received ≥225 mg/m^2 of 1st line docetaxel and with ECOG PS 0 or 1)	21,408	0.259	82,538
Amending discount rate	22,331	0.298	74,865
All 3 amendments	22,233	0.248	89,476

Probabilistic sensitivity analyses undertaken by the ERG.

The incremental cost of cabazitaxel was £22,439 with an incremental 0.250 QALYs accrued, resulting in an ICER of £89,684 per QALY gained. This ICER is similar to the deterministic result (£89,476). Note that the model supplied by the manufacturer only saves the incremental values. The cost-effectiveness plane and the CEAC are provided in Figures 14 and 15 respectively.

Figure 14: The cost-effectiveness plane from the ERG probabilistic sensitivity analyses

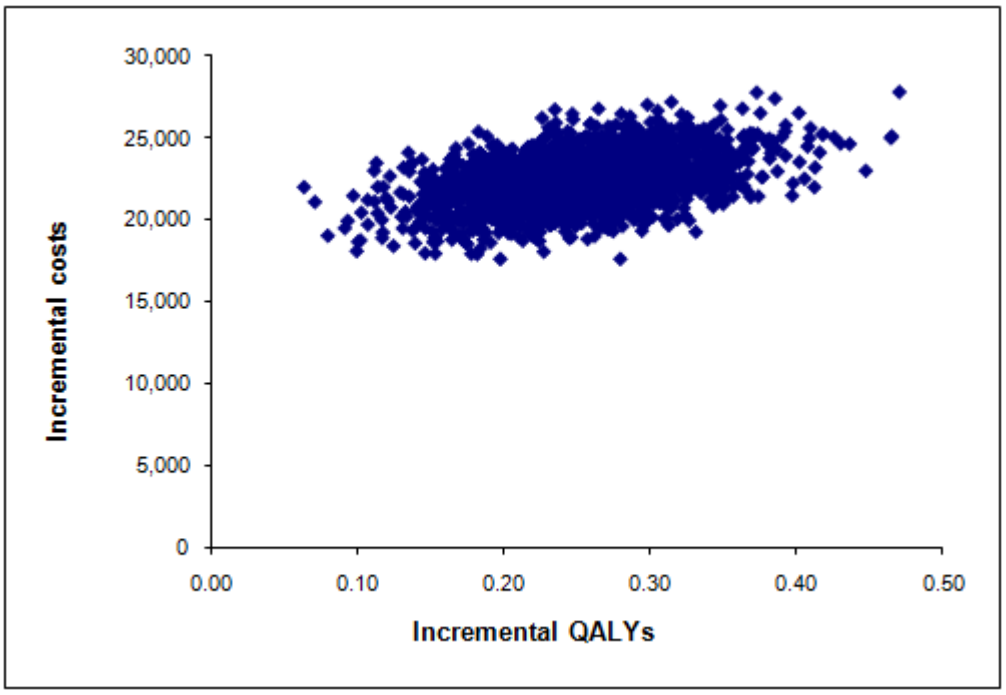
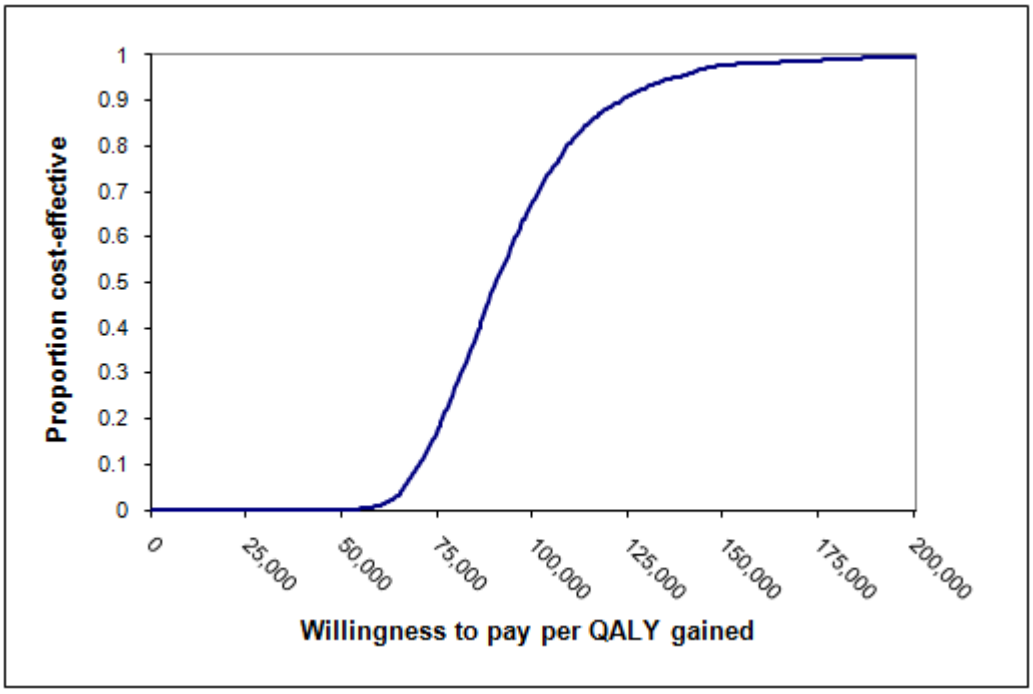


Figure 15: The CEAC from the ERG probabilistic sensitivity analyses



Sensitivity analyses undertaken by the ERG

The ERG undertook a number of sensitivity analyses to assess the robustness of the ERG-base case ICER to plausible changes. These sensitivities analyses were: using the entire TROPIC population; using the upper and lower 95% CIs for the utility of stable disease estimated from EAP at cycle 2; and using the utility decrement (0.085) taken from Sandblom[90] rather than the 0.070 estimated from Sullivan *et al*.[89] As the results from the deterministic and the probabilistic analyses were similar (£89,476 and £89,684 respectively), the impact of each change has, for computational time reasons, been undertaken only deterministically. It is seen that ICER can be changed markedly by the utility values assumed for PD and SD.

Table 38: Sensitivity analyses undertaken by the ERG

Sensitivity analyses	ΔCost (£)	ΔQALY	Cost per QALY (£)
None (ERG base case)	22,233	0.248	89,476
Using Subgroup 1 (entire TROPIC population)	22,283	0.239	93,177
Upper 95% of SD from the EAP at cycle 2 ([redacted])	22,233	0.298	74,620
Lower 95% of SD from the EAP at cycle 2 ([redacted])	22,233	0.199	111,719
Utility difference between SD and PD estimated from Sandblom[90]	22,233	0.245	90,865

The ERG note the sensitivity analyses undertaken by the manufacturer when patients dying within 30 days of randomisation were removed from the analysis which may be relevant if these deaths could be prevented by strictly following the protocol regarding dose modification and delay and treating neutropenia as per ASCO guidelines. This increased the manufacturer's base case ICER by approximately £3500 per QALY; the ICER increased by £8000 for the entire TROPIC population. Similar analyses conducted for the ERG base case led to a £2000 increase in the ICER, from £89,476 to £91,465.

The manufacturer has reported more recent OS data. The effect of this on the manufacturer's base case was limited, increasing the ICER from £82,950 to £82,963 when assuming fitted curves throughout. The effect of utilising the more recent data on the ERG's base case is unknown.

7. END OF LIFE

Within this section, the ERG provide relevant information regarding whether cabazitaxel is likely to meet the end of life criteria published by NICE.[93] It is recognised that this will be decided by the relevant NICE appraisal committee and this section may have no bearing upon their decision.

The criteria published by NICE are (numbers retained from original document):

2.1 This supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:
2.1.1 The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
2.1.2 There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
2.1.3 The treatment is licensed or otherwise indicated, for small patient populations.

Each criterion is evaluated in turn.

Life Expectancy
In the deterministic ERG base case, patients who do not receive cabazitaxel have a mean life expectancy of 1.17 years (approximately 14 months). As such, criterion 2.1.1 is likely to be fulfilled. It is noted that the probabilistic results only saved incremental life years and thus the corresponding results from probabilistic analyses were not available.

Extension of Life
In the probabilistic ERG base case, the mean extension of life is estimated to be 0.35 years (approximately 4 months). These results were relatively robust in that cabazitaxel produced a survival advantage in each of the 2000 probabilistic analyses run by the ERG (Figure 14). The median extension of life in the ERG base case was reported by the manufacturer to be [redacted]

Licensed Indication
Cabazitaxel (in combination with prednisolone) is licensed only for the treatment of mHRPC previously treated with docetaxel. The manufacturer estimates that fewer than 2,000 patients per year would be eligible following failure of docetaxel treatment. As such, although there is no formal

definition of a small patient population, it is likely that criterion 2.1.3 is fulfilled based on previous NICE guidance.

8. CONCLUSIONS

The ERG did not identify any issues relating to the manufacturer's systematic review which appeared likely to influence the size of the ICER, with the possible exception of the subgroup analyses which are discussed below.

The manufacturer reported a deterministic base case ICER of £74,938. However, the ERG has concerns regarding two important assumptions used in formulating the manufacturer's base case:

- The use of Kaplan-Meier curves (where the data were deemed sufficiently reliable) in preference to parametric curves, and

- Restricting the economic evaluation to only European patients.

As detailed in section 5.2.12 the ERG believes that using parametric curves throughout and having a patient population of 'patients who received $\geq$ 225 mg/m^2 of first-line docetaxel and with an ECOG PS 0 or 1' represents a more accurate base-case.
Altering these two assumptions and slightly amending the discount rate (which has only a minor effect on the ICER) results in the ERG's deterministic base case ICER being £89,476; the probabilistic value was similar (£89,684). This is considerably higher than the manufacturer's base case estimate (£74,938).

An additional key source of uncertainty relates to the utilities for both progressive disease and stable disease. The ERG notes that the manufacturer has an on-going study aimed at collecting utility data, but at the present time the available evidence is weak. The choice of alternative, plausible, values was shown to have a considerable impact on the ICER.

There was additional uncertainty regarding whether the deaths observed in TROPIC within 30 days of randomisation could be preventable with more vigilant treatment of neutropenia; exploratory analyses indicate that this may slightly increase the ICER, by £2000 in the ERG base case.

Finally, the adverse event data observed within the TROPIC RCT was of concern, the FDA recommended a review of renal toxicity and a submission of updates from active RCTs for three years after the US approval date (2010); data are currently not available. Therefore, caution may be prudent until these data emerge.

8.1 Implications for research

The utility of patients with mHRPC in the stable disease and progressive disease state needs to be researched more fully. It is commented that the manufacturers are running such a study but it is unclear how many patients will ultimately be followed-up. These values have a considerable effect on the ICER.

Further research on the toxicity of cabazitaxel is required. The ERG notes that these trials have been requested by the FDA.

Further research may be required to investigate if there are any genuine variations in the treatment practices for cabazitaxel and mitoxantrone by geographical region

Additional research should be conducted (even if only through the collection of observational data) to ascertain whether more vigilant treatment of neutropenia can reduce the number of observed deaths in the period following initiation with cabazitaxel treatment.

Appendix 1: Cabazitaxel trials identified by the ERG in ClinicalTrials.gov

1 Recruiting A Study to Evaluate the Effects of Combining Cabazitaxel With Cisplatin Given Every 3 Weeks in Patients With Advanced Solid Cancer

Condition: Solid Cancer
Intervention: Drug: cabazitaxel (XRP6258)

2 Recruiting Dose-Escalation, Safety, Pharmacokinetics Study of Cabazitaxel With Gemcitabine In Patients With Solid Tumor

Condition: Neoplasms, Malignant
Interventions: Drug: cabazitaxel (XRP6258); Drug: gemcitabine; Drug: midazolam

3 Recruiting Safety and Pharmacokinetic Study of Cabazitaxel in Patients With Advanced Solid Tumors and Liver Impairment

Condition: Neoplasm Malignant
Intervention: Drug: Cabazitaxel (XRP6258)

4 Recruiting Early Access to Cabazitaxel in Patients With Metastatic Hormone Refractory Prostate Cancer Previously Treated With a Docetaxel-containing Regimen

Condition: Prostate Cancer Metastatic
Intervention: Drug: CABAZITAXEL

5 Not yet recruiting Study of Cabazitaxel Plus Bavituximab as Second-line Chemotherapy for Patients With Castration-resistant Prostate Cancer

Conditions: Prostate Cancer; Prostatic Neoplasms
Intervention: Drug: Cabazitaxel plus bavituximab

6 Active, not recruiting Effect of Cabazitaxel on the QTc Interval in Cancer Patients

Condition: Neoplasms, Malignant
Intervention: Drug: Cabazitaxel (XRP6258)

7 Completed
Has Results XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC)

Conditions: Neoplasms; Prostatic Neoplasms
Interventions: Drug: cabazitaxel (XRP6258) (RPR116258); Drug: mitoxantrone; Drug: prednisone

8 Not yet recruiting Chemotherapy for Patients With Gastroesophageal Cancers Who Have Progressed After One Prior Chemo Regimen

Conditions: Esophageal; Gastrooesophageal Cancer; Gastric Cancer
Intervention: Drug: jevtana

9 Recruiting Cabazitaxel at 20 mg/m² Compared to 25 mg/m² With Prednisone for the Treatment of Metastatic Castration Resistant Prostate Cancer

Condition: Prostate Cancer
Interventions: Drug: cabazitaxel (XRP6258); Drug: Prednisone

10 Recruiting Cabazitaxel Versus Docetaxel Both With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer

Condition: Prostate Cancer
Interventions: Drug: Cabazitaxel (XRP6258); Drug: Docetaxel (XRP6976); Drug: Prednisone

11 Recruiting Dose Escalation Study With Cabazitaxel in Combination With Daily Prednisolone in Patients With Hormone Refractory Prostate Cancer

Condition: Prostate Cancer
Interventions: Drug: Cabazitaxel (XRP6258); Drug: prednisolone

Appendix 2: Quality assessment of the manufacturer's search strategies

Facet	Elements	Review	
		Clinical effectiveness	**Cost effectiveness**
Reporting	Are the searches systematic?	Yes.	Yes.
	Are searches clearly reported?	Yes, database coverage dates, host platforms clearly provided.	Yes.
	Are all strategies given?	Yes, all reported search strategies were provided	Yes.
	Are all the appropriate searches carried out?	Yes, it is believed that the adverse events searches would be retrieved in the effectiveness search. The ERG did not find additional studies.	Yes.
	Are the searches reproducible?	Yes, despite the different host platforms used.	Yes.
	Are the results consistent with the PRISMA diagram?	Yes, clear PRISMA diagrams were given for the cabazitaxel, all RCT and non-RCT searches.	No PRISMA reported.
Source	Were the core databases searched?	Yes.	Yes including specialist economic evaluation databases e.g. HEED, NHS EED and EconLit
	Is the choice of database for the various searches consistent?	List of sources searched for cabazitaxel studies were extensive. Fewer databases were searched for all RCTs and non-RCT studies.	Search for cabazitaxel studies in the clinical effectiveness should have captured economic evaluations.
	Were other document type searches missing?	No, bibliographic reference follow-up, hand searching of conference proceedings, ongoing studies search were carried out by the manufacturer.	No.

Items from the PRESS Checklist for search strategies[94]	Translation: Is the search question translated well into search concepts?	Cabazitaxel searches (intervention terms only); all RCTs (mHRPC + first line disease + RCT filter); non-RCTs (mHRPC + intervention + non-RCT filter)	Cabazitaxel searches same as clinical effectiveness (intervention terms only); QoL searches (mHRPC + QoL filter)
	Operators: Are there any mistakes in the use of Boolean or proximity operators?	Inconsistent use of Boolean for mHRPC RCT searches (see text body).	No.
	Subject headings: Are any important subject headings missing or have any irrelevant ones been included?	No, some of the exploded MeSH subject headings/EMTREE terms may be overlapping.	No.
	Natural language: Are any natural language terms or spelling variants missing, or have any irrelevant ones been included? Is truncation use optimally?	No, but use of free-text terms should be used consistently between mHRPC RCT and non-RCT searches (see text body).	Inconsistencies of mHRPC terms between effectiveness reviews and QoL searches.
	Spelling & syntax: Does the search strategy have any spelling mistakes, system syntax errors, or wrong line numbers?	No.	Ambiguity of 'or sc.fs.' in statement 5 of the QoL Medline search. Minor typographical omission of statement 46 which should read '44 not 45'
	Limits: Do any of the limits used seem unwarranted or are any potentially helpful limits missing?	No. but justification for limiting searches since 2000 was not given for mHRPC RCT and non-RCT searches.	No.
	Adapted for database: Has the search strategy been adapted for each database to be searched?	The strategies should be adapted consistently between databases i.e. population and intervention term use differed between searches. It appears that the three searches were	Terms for mHRPC should be used consistently between effectiveness review searches.

		performed independently.	
Overall approach	Are the search strategies adequate?	Yes.	Yes.
	Are strategies sensitive?	Yes.	Yes.
	Are strategies well designed?	Yes.	Yes.
	Are there any studies missing?	Despite the minor limitations mentioned, the ERG does not consider that any studies were missing at the time of the review.	Despite the minor limitations mentioned, the ERG does not consider that any studies were missing at the time of the review.

Appendix 3: The assumed distributions used within the probabilistic sensitivity analyses for parameters deemed non-key by the ERG

Variables following the Beta Distribution	Alpha	Beta	Mean	95% CI
'Normed' Body-Surface Area (mean = 2.01)	66.77	82.72	2.01	1.89 - 2.12
Disutilities				
Neutropenia	30.00	303.30	0.09	0.06 - 0.12
Febrile Neutropenia	28.98	212.48	0.12	0.08 - 0.16
Diarrhoea	31.46	637.93	0.05	0.03 - 0.06
Fatigue	29.86	287.81	0.09	0.06 - 0.12
Asthenia (weakness)	29.86	287.81	0.09	0.06 - 0.12
Leukopenia	30.00	303.30	0.09	0.06 - 0.12
Back pain	30.71	414.39	0.07	0.04 - 0.09
Anaemia	28.80	201.63	0.12	0.08 - 0.17
Thrombocytopenia	30.00	303.30	0.09	0.06 - 0.12
Pulmonary embolism	28.12	165.83	0.14	0.09 - 0.19
Dehydration	27.92	156.98	0.15	0.10 - 0.20
Nausea	30.49	373.36	0.07	0.05 - 0.10
Bone pain	30.71	414.39	0.07	0.04 - 0.09
Deep vein thrombosis	27.61	144.97	0.16	0.10 - 0.21
Neuropathy	29.11	221.85	0.11	0.07 - 0.15
Proportion patients per BSC type				
Analgesics	14.62	19.38	0.43	0.27 - 0.59
Steroids	70.05	67.30	0.51	0.42 - 0.59
Palliative Radiotherapy	81.65	108.23	0.43	0.36 - 0.50
Bisphosphonates	119.35	582.71	0.17	0.14 - 0.19
Proportion patients per drug (BSC)				
Co-codamol	71.50	71.50	0.50	0.41 - 0.58
Diclofenac	71.50	71.50	0.50	0.41 - 0.58
Dexamethasone	71.50	71.50	0.50	0.41 - 0.58
Prednisone	71.50	71.50	0.50	0.41 - 0.58
Strontium-89	71.50	71.50	0.50	0.41 - 0.58
External beam RT	71.50	71.50	0.50	0.41 - 0.58
Proportion patients requiring inpatient care due to AEs				
Neutropenia	15.08	738.92	0.02	0.01 - 0.03
Febrile Neutropenia	565.50	188.50	0.75	0.71 - 0.78
Diarrhoea	75.40	678.60	0.10	0.07 - 0.12
Fatigue	7.54	746.46	0.01	0.00 - 0.01
Asthenia	7.54	746.46	0.01	0.00 - 0.01
Leukopenia	15.08	738.92	0.02	0.01 - 0.03
Back pain	113.10	640.90	0.15	0.12 - 0.17
Anaemia	113.10	640.90	0.15	0.12 - 0.17
Thrombocytopenia	37.70	716.30	0.05	0.03 - 0.06
Pulmonary embolism	603.20	150.80	0.80	0.77 - 0.82
Dehydration	188.50	565.50	0.25	0.21 - 0.28
Nausea	0.00	0.00	N/A	N/A
Bone pain	15.08	738.92	0.02	0.01 - 0.03
Deep vein thrombosis	226.20	527.80	0.30	0.26 - 0.33
Neuropathy	0.00	0.00	N/A	N/A
End-of-life care (share of patients)				
Hospice home	115.00	460.00	0.20	0.16 - 0.23
Palliative care at home	71.50	71.50	0.50	0.41 - 0.58

Nurse visits	28.00	7.00	0.81	0.65 - 0.91
GP visits	115.00	460.00	0.20	0.16 - 0.23
Palliative hospital outpatients visits	71.50	71.50	0.50	0.41 - 0.58
Palliative care - hospital inpatient	0.00	0.00	N/A	N/A
Share of patients on BSC post-2nd line – Caba	19.74	23.26	0.46	0.31 - 0.60
Share of patients on BSC post-2nd line – Mitox	19.74	23.26	0.46	0.31 - 0.60
Share of patients getting GCSF prophylaxis – Caba	107.04	312.89	0.25	0.21 - 0.29
Share of patients getting GCSF prophylaxis – Mitox	129.95	1211.12	0.10	0.08 - 0.11

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