Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255)

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Within the CS the clinical effectiveness of radium-223 dichloride and its cost effectiveness when compared with cabazitaxel were not formally considered. As radium-223 dichloride is a comparator for the subgroup of people with bone metastasis and no known visceral metastases, this exclusion leads to uncertainty regarding the cost-effectiveness of cabazitaxel.

Cost-effectiveness results were sensitive to the utility values that should be assigned to progressive disease, and to the choice of parametric model used for extrapolating the clinical effectiveness data. It is unclear how resolving these uncertainties would impact on the cost-effectiveness of cabazitaxel.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The probabilistic base-case ICER presented in the CS comparing cabazitaxel with mitoxantrone was £50,682. The ERG made six changes to the company's base case. These were: the use of Electronic market information tool prices in preference to British National Formulary prices for generic drug costs (including mitoxantrone); modelling vial wastage; not modelling discontinuation for reasons other than disease progression; not modelling a reduced disutility in the last three months of progressive disease; basing post-second line treatment resource use from a UK audit for all treatments; and using results from the NMA adjusted by the ERG. When taken in isolation each of these changes led to an increase in the ICER, with the largest increase attributable to the modelling of vial wastage. The combined effect of these changes was to increase the probabilistic ICER from £50,682 to [redacted]. If vial wastage is not modelled then the probabilistic ICER is £51,849.

The ERG also performed exploratory analyses regarding the long-term modelling of effectiveness data and using different utility values for progressive disease. It was noted that these uncertainties led to both increases and decreases in the base-case ICER depending on the assumptions made.

The ERG used the results from the NMA adjusted by the ERG to assess the cost-effectiveness of cabazitaxel when compared to BSC, abiraterone and enzalutamide. The ICER comparing enzalutamide with cabazitaxel was £142,180 when vial wastage was modelled and £158,873 when it was not modelled. Clinical advice given to the ERG suggests that vial wastage would be likely. Abiraterone was extendedly dominated by enzalutamide irrespective of how vial wastage was modelled. The ICER comparing cabazitaxel with BSC was £107,604 when vial wastage was modelled and £86,888 when it was not modelled: this was greater than estimated from the direct comparison with mitoxantrone and may indicate the inappropriateness of assuming proportional hazards. Analyses using the PAS-adjusted prices of abiraterone and enzalutamide, along with sensitivity analyses, are provided in a confidential appendix prepared for the Appraisal Committee only.

2 BACKGROUND

This report provides a review of the evidence submitted by the company for cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen. Cabazitaxel is licensed within the EU for use in combination with prednisone or prednisolone for the treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.[1]

Cabazitaxel was previously appraised as part of the NICE Single Technology Appraisal (STA) process (TA255), with the final appraisal determination issued in January 2012.[2] The Committee considered that the most plausible ICER was likely to be above £87,500 per quality-adjusted life years (QALYs) gained, and so did not recommend treatment with cabazitaxel. The Committee noted that key uncertainties related to the company's modelling of clinical effectiveness data and the utility values used. Cabazitaxel was available via the National Cancer Drugs Fund (CDF) until its removal in January 2015. It was later re-instated on the CDF in May 2015.

2.1 Critique of the company's description of underlying health problem

The company's submission (CS[3]) provides an appropriate overview of prostate cancer noting that prostate cancer is heterogeneous with regards to both treatment response and the types of disease progression observed. Prostate cancer is the most common form of cancer in men in the UK, and the second most common cause of cancer death. There were 41,736 incident cases, and 10,837 deaths from prostate cancer in the UK in 2012, the most recent year for which data are available.[4]

For metastatic prostate cancer (cancer that has spread to other parts of the body), there is a distinction between mHRPC and metastatic castrate resistant prostate cancer (mCRPC).[5] Tumours that progress with castrate levels of testosterone (typically taken to be lower than 50 ng per deciliter[6]) are classified as mCRPC; tumours that progress after conventional luteinising hormone-releasing hormone (LHRH) and newer hormone therapies such as abiraterone and enzalutamide are classified as mHRPC. First line therapy is typically androgen deprivation therapy or LHRH with patients with mCRPC more likely to respond to further hormonal therapies than people with mHRPC.[5] As the advanced hormonal therapies abiraterone and enzalutamide were not available at the time of the company's original submission, the terminology used for TA255 was people with mHRPC. As terminology has subsequently evolved, for the purposes of this report, the ERG shall refer to the population of interest as people with mCRPC.

There are no published data for the incidence of mCRPC. However, a report from the National Cancer Intelligence Network[7] reveals that of the 36,287 diagnoses in England in 2013, 5836 (16%) were classified as Stage 4 (or metastatic) cancers, with a further 6661 diagnoses (18%) having an unknown

Table 1: Treatment received and reasons for discontinuation in the TROPIC study[11]

	Cabazitaxel (n=378)	**Mitoxantrone (n=377)**
Patients who received study treatment,	371 (98%)	371 (98%)
Median number of treatment cycles (IQR)	6 (3 to 10)	4 (2 to 7)
Number of patients completing planned 10 cycles of study treatment	109 (29.4%)	50 (13.5%)
Median relative dose intensity (IQR)	96.1% (90.1 to 98.9) [a,b]	97.3% (92.0 to 99.3) [a,b]
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 [c]	45 (12%)	15 (4%)
Number of cycles [d]	221 (9.8%)	88 (5.1%)
Treatment delays		
Number of patients [e]	104 (28%)	56 (15%)
Number of cycles [d]		
≥4 days	NR (9.3%)	NR (7.9%)
≤9 days	157 (7.0%)	110 (6.3%)
>9 days	51 (2.2%)	28 (1.6%)

IQR, interquartile range

[a] Data discrepancy in CS - p111 (CS) suggest a range (unit not specified) of 49.0% to 108.2% for cabazitaxel and 42.5% to 106% for mitoxantrone

[b] Data from de Bono *et al.*[11] and CS (p77, **Error! Reference source not found.**)

[c] One dose reduction was allowed per patient, 20 mg/m^2 for cabazitaxel or 10 mg/m^2 mitoxantrone

[d] Percentages are of total number of treatment cycles: 2251 for cabazitaxel and 1736 for mitoxantrone

[e] Delays of ≤2 weeks were allowed

cabazitaxel plus prednisone. However, clinical advisors to the ERG commented that high levels of monitoring in a trial setting would result in abnormal laboratory measurements being recorded as AEs despite the fact that these may not cause any problems for the patient. The ERG's clinicians agreed with the view expressed in the CS that rates of haematological AEs reported in the CUP and EAPs were likely to be more reflective of clinical practice. This evidence is discussed in Section 4.2.

Among non-haematological AEs, the most common in cabazitaxel-treated patients in TROPIC[11] were diarrhoea (47%), fatigue (37%), nausea (34%) and vomiting (23%). The most common AEs in patients receiving abiraterone in COU-AA-301[12] were fatigue (44%), nausea (30%), back pain (30%) and arthralgia (27%). Comparison with the enzalutamide group of the AFFIRM trial[13] was only possible for diarrhoea (21%) and fatigue (34%). The most common AEs in ALSYMPCA[14] in the relevant patient subgroup (those who had previously received docetaxel) were bone pain (53%), nausea (40%), fatigue (27%) and diarrhoea (25%).

Stable disease

Cabazitaxel and mitoxantrone are both provided in vials with the required dosage dependent on BSA (25 mg/m^2 for cabazitaxel and 12 mg/m^2 for mitoxantrone). Within the submission the company assumed that the mean BSA was 1.9 m^2 (with a standard error of 0.21 used to estimate the average number of vials required per patient), with vial sharing for cabazitaxel but not for mitoxantrone. The value of 1.9 m^2 was based on the clinical opinion of UK experts; the mean BSA observed in the TROPIC (2.01 m^2) was used in a scenario analysis. The standard error of 0.21 was based on TROPIC data. The ERG queried why the TROPIC-derived BSA was used in the base-case for the original submission (TA255), but not for this submission. The company justified this change by stating that the value of 1.9 m^2 is more likely to reflect values observed in the UK. The ERG notes that, based on the company's economic model, the threshold for an increase in vials is a BSA of [redacted] for cabazitaxel and [redacted] for mitoxantrone.

The ERG queried why it was assumed that there was no vial wastage for cabazitaxel. The company responded with:

"Sanofi believe there will be no wastage of active ingredient because patient specific doses in the form of compounded IV bags of cabazitaxel can be supplied direct to NHS hospitals".

The ERG asked their clinical advisors if they believed that there would be vial wastage for cabazitaxel. The following reply was obtained from a pharmacist:

"As far as I am aware, most centres do not buy in compounded bags as this would add to the total cost of treatment as likewise they would need to add a compounding fee to treatment. Occasionally we have been able to "save" a vial where several patients are receiving treatment on one day and as a result vials can be 'campaigned worked' (i.e. shared). This can seldom be achieved however and certainly isn't generally the rule."

The ERG noted that in addition vial wastage may occur, if people did not attend their appointment. Hence there is uncertainty over the degree of vial wastage that would occur in clinical practice. The ERG further noted that in the company's base-case there appeared to be no wastage assumed for either cabazitaxel or mitoxantrone.

Treatment with abiraterone requires 1.0g daily whilst for enzalutamide 160mg is required daily.

Costs for cabazitaxel and all three comparators were taken from the BNF June 2015.[107] A pack of abiraterone contains 120 tablets of 250mg, whilst a pack of enzalutamide contains 112 tablets of 40mg. These costs, which do not include any Patient Access Scheme or any administration costs, are displayed in Table 2. With the exception of enzalutamide, all of the treatments are in combination with 10 mg/day of prednisolone, at a 3-week cycle cost of £1.94.

Table 2: Direct treatment costs based on list prices.

Treatment	Cost per unit	Details	Cost per 3-week cycle*
Mitoxantrone	£100.00	Cost per vial	£172.87
Cabazitaxel	£3696.00	Cost per vial	£3696.00
Abiraterone	£2930.00	Cost per 120-tab pack	£2,051.00
Enzalutamide	£2734.67	Cost per 112-cap pack	£2,051.00

*Mitoxantrone and cabazitaxel are estimated by the company to require 1.73 and 1.00 vials per cycle, respectively. The PAS price is used for cabazitaxel in the main analyses. The PAS prices for abiraterone and enzalutamide are used in the confidential appendix.

It was assumed that all four treatments would require one visit to a clinical oncologist every three weeks, at a cost of £320 per visit.[27] Treatment with cabazitaxel and mitoxantrone incurred additional administration costs for pharmacist time. The hourly cost for pharmacist time used was £42,[109] it was assumed that mitoxantrone would require an hour of pharmacy time and cabazitaxel would require 15 minutes. The shorter pharmacist time required for cabazitaxel reflects the fact that cabazitaxel will be provided in prefilled bags with a tailored dose appropriate for specific patients. Hence no time is needed to make up the IV infusions. This additional time is required for mitoxantrone delivery.

Pre-medication resource use for cabazitaxel and mitoxantrone were taken from the TROPIC, as detailed in Table 63 of the CS (p165-167). The main driver of pre-medication costs was the use of primary prophylaxis, with a unit cost of £175.67. This was received by 25% of patients in the cabazitaxel arm and 10% in the mitoxantrone arm. It was assumed that patients receiving either abiraterone or enzalutamide would have the same resource use as mitoxantrone, but with no primary prophylaxis. The resulting three-weekly pre-medication costs were £87.29 for cabazitaxel, £36.32 for mitoxantrone, and £7.52 for either abiraterone or enzalutamide.

For patients with stable disease, the direct treatment costs (as detailed in Table 2), along with administration costs and pre-medication costs were incurred for either ten cycles of treatment or until disease progression or death for cabazitaxel and mitoxantrone. Patients persist on treatment until progression or death for abiraterone and enzalutamide.

In addition, patients with stable disease also required treatment with an LHRH agonist, at a cost of £52.59 every three weeks. Additional costs relating to outpatient care, inpatient care, hospice care, imaging and laboratory tests were also incurred, at a cost of £303.65 every three weeks. These two additional costs were incurred by patients as long as they remained in the stable disease state.

The costs of treating AEs were incorporated into the economic model as an additional treatment-specific cost for patients with stable disease who are receiving treatment. The rates of occurrence of

AEs as used in the economic model are described in **Error! Reference source not found.**. Costs for treating AEs were based on

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a number of additional sensitivity analyses using the economic model, and base-case settings, supplied by the company (these did not change following response to clarification questions). Due to the requirement of following the template for ERG reports the results produced from key analyses undertaken by the ERG are reported in Section 6 (Table 3).

The following exploratory analyses had a notable effect on the base-case ICER reported in the CS.

For the company's base-case it was assumed that wastage would not occur for either cabazitaxel or mitoxantrone. As discussed in Section 5.2.8, the ERG believes that wastage could still occur. Hence an analysis was conducted that allowed for wastage. This was implemented in the company's model by setting the cost for mitoxantrone and cabazitaxel to be the cost per vial (instead of the cost per mg).

The ERG changed the post-second line treatment mix so that it was no longer treatment-specific, with both resource use estimates and the proportion receiving BSC taken from a UK clinical audit used instead.[25] The rationale for this change is summarised in Section 5.2.12. The change was achieved by changing the drop-down box of cell 'Post2ndChemoMix' (sheet 'Resource input') from 'TROPIC (arm-specific)' to 'Country-specific (general)', and by setting the proportion receiving BSC for all treatments to be 0.80 (sheet 'Cost treatment').

The ERG examined how sensitive the model results were to including a dose-reduction for both cabazitaxel and mitoxantrone. These reductions were removed by setting cells Rel_dose_int_caba and Rel_dose_int_mitox both equal to one.

For the comparison between cabazitaxel and mitoxantrone, the choice of parametric curve for extrapolation was based on minimising the goodness of fit to both TROPIC arms. The ERG explored the impact on the ICER of minimising the goodness of fit to the TROPIC arms separately (hence allowing for different parametric models to be used for the two treatments). This led to modelling OS with the Weibull curve for cabazitaxel and the log-logistic curve for mitoxantrone. For PFS the log-logistic curve was used for cabazitaxel and the log-normal curve was used for mitoxantrone.

The ERG noted that, based on their goodness of fit to the observed data, the use of log-logistic curves for both OS and PFS was a plausible alternative to the curves used in the base-case, although the ERG notes the statements made in the CS (p187)[25] that these had less face validity regarding long-term projection of survival. The ERG enacted these changes using the options in the 'RUN MODEL' sheet.

The ERG explored the sensitivity of the model results to the choice of progressive disease. The utility value used in the base-case was 0.6266, based on data from the UK EAP. Based on the standard error of 0.060 derivable from the UK EAP data, a normal 95% CI for the utility value for progressive disease is 0.510 to 0.743. These values were used in the economic model by changing the cell 'utility_value_PD' to these values. It should be noted that when using the latter estimate, the modelled utility will increase for people who progressed after receiving less than four cycles of treatment. Hence these results should be viewed with caution.

The company did not consider radium-223 dichloride to be a valid comparator, and so did not include it within their NMA. The ERG believes that this exclusion was inappropriate, as discussed in Section 3.3. When queried about this exclusion (clarification question A1), the company did provide summary statistics comparing OS amongst the TROPIC population with OS amongst the ALSYMPCA population with previous docetaxel use. This comparison is reproduced in **Error! Reference source not found.** (comparable measures of PFS were not reported by the two trials):

The ERG notes that the differences in OS (both absolute and relative) are similar for cabazitaxel and radium-223 dichloride. Hence, the cost-effectiveness of cabazitaxel in comparison with radium-223 dichloride is likely to be driven mainly by the costs of the two drugs. The list price for a course of radium-223 dichloride (£4040) is [redacted] the PAS price for a cycle of cabazitaxel ([redacted]). Radium-223 dichloride is taken for a maximum of six courses, whereas in the company's economic model cabazitaxel is taken for a maximum of ten cycles. In clinical practice there is no restriction on the maximum number of cycles for which cabazitaxel may be taken, although the median number of treatment cycles observed in both the TROPIC trial[11] and the UK EAP[50] was six. Data on the median number of treatments for radium-223 dichloride is not available. [redacted]. A consideration of the effect of the PAS for radium-223 dichloride on cost-effectiveness is discussed in a confidential appendix.

The following analyses did not materially affect the company's reported base-case ICER.
The company included a disutility to HRQoL to reflect the potentially worsening HRQoL for people with progressive disease in their last three months of life. The ERG had concerns with how this was implemented in the economic model, as discussed in Section 5.2.12. Hence an analysis was performed that removed this disutility. This was achieved by setting cells B3 to B6 on sheet 'Utility death' each equal to zero.

The ERG performed three sensitivity analyses concerning the stable disease utility values. These were:

1. Use of the weighted mean utility from the UK EAP (0.737) for all cycles.

Table 3: Overview of ERG changes to the model

Individual changes made	Cabazitaxel		Mitoxantrone		Incremental values		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Costs (£)	QALYS	
Company deterministic base-case	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.232	49,327
Company probabilistic base-case	NR	NR	NR	NR	11,829	0.233	50,682
Changes made							
A1) Use eMIT prices*	[redacted]	[redacted]	[redacted]	[redacted]	11,994	0.232	51,667
A2) Discontinuation for reasons other than disease progression not modelled	[redacted]	[redacted]	[redacted]	[redacted]	11,693	0.232	50,370
A3) Reduced disutility in the last 3 months of progressive disease not modelled	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.230	49,691
A4) Post-second line treatment resource use and proportion receiving BSC both from UK audit for all treatments.	[redacted]	[redacted]	[redacted]	[redacted]	11,353	0.232	48,908
A5) Network meta-analysis results using a weakly informative prior (does not affect the comparison with mitoxantrone).	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.232	49,327
A6) Cost of cabazitaxel and mitoxantrone based on vial cost (assuming wastage).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.232	[redacted]
A7) Use of log-logistic curves for both overall and progression-free survival.	[redacted]	[redacted]	[redacted]	[redacted]	12,627	0.309	40,887
A8) Parametric curves for OS and PFS	[redacted]	[redacted]	[redacted]	[redacted]	9,347	0.137	68,168

based on lowest AIC value (no requirement for same parametric form for both arms)**							
A9) Use of the 95% low confidence interval value for progressive disease (0.510).	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.207	55,248
A10) Use of the 95% high confidence interval value for progressive disease (0.743).	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.257	44,560
ERG Deterministic base-case 1 (changes A1 to A6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.230	[redacted]
ERG Probabilistic base-case 1 (changes A1 to A6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.231	[redacted]
ERG Deterministic base-case 2 (changes A1 to A5)	[redacted]	[redacted]	[redacted]	[redacted]	11,823	0.230	51,308
ERG Probabilistic base-case 2 (changes A1 to A5)	[redacted]	[redacted]	[redacted]	[redacted]	12,133	0.234	51,849

BSC: Best supportive care. ICER: Incremental cost-effectiveness ratio. NR: Not reported. OS: Overall survival. PFS: Progression-free survival. QALYS: Quality-adjusted life-years.

*Note: when the company used eMIT prices (in response to clarification question B7), the reported total costs for cabazitaxel and mitoxantrone were £28,902 and £16,906 respectively, resulting in an ICER of £51,675. The ERG was unable to replicate these values.

** For cabazitaxel the Weibull curve is used for OS and the log-logistic curve for PFS. For mitoxantrone the curves are the log-logistic and the log-normal, respectively.

Under the ERG base-cases (using the results of probabilistic sensitivity analyses), the ICER comparing cabazitaxel with mitoxantrone was [redacted] if vial wastage occurs and £51,849 in the absence of vial wastage. Clinical advice given to the ERG suggests that vial wastage would be likely. The sensitivity analyses performed (A7 to A10) showed that the ICER was also sensitive to the methods employed for extrapolating clinical effectiveness data, and the utility value used for progressive disease. In addition, the ERG noted that when choosing the parametric form to extrapolate OS (and allowing cabazitaxel and mitoxantrone to have different parametric forms), the difference in goodness of fit statistics were less than 0.2% for both treatments. The models with the lowest goodness of fit statistics provided estimated mean survival times of 1.54 and 1.36 years for cabazitaxel and mitoxantrone respectively (ICER: £73,592). The models with the second lowest goodness of fit statistics provided estimated mean survival times of 1.82 and 1.20 years for cabazitaxel and mitoxantrone respectively (ICER: £35,947).

Based on the ERG base-cases, the cost-effectiveness of cabazitaxel when compared with abiraterone, enzalutamide or BSC is displayed in Table 4 (assuming vial wastage) and Table 5 (with no vial wastage). The company's model was amended to include BSC as a comparator. It was assumed that BSC was represented by mitoxantrone with respect to per-cycle costs and utility values. The effectiveness of BSC was modelled in the same manner as for abiraterone and enzalutamide by using HRs for BSC derived from the NMA as updated by the ERG (see Section 4.5 for more details).

Table 4: Cost-effectiveness results comparing cabazitaxel with BSC, abiraterone and enzalutamide (ERG base-case assuming vial wastage)

Treatment	Total values		Incremental cost-effectiveness ratio (£)
	Costs (£)	QALYs	
Deterministic results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£111,543 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£136,902 compared with cabazitaxel
Probabilistic sensitivity analysis results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£107,604 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£142,180 compared with cabazitaxel

BSC: Best supportive care. QALYs: Quality adjusted life years.

Table 5: Cost-effectiveness results comparing cabazitaxel with BSC, abiraterone and enzalutamide (ERG base-case assuming no vial wastage)

Treatment	Total values		Incremental cost-effectiveness ratio (£)
	Costs (£)	QALYs	
Deterministic results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£85,934 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£152,914 compared with cabazitaxel
Probabilistic sensitivity analysis results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£86,888 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£158,873 compared with cabazitaxel

BSC: Best supportive care. QALYs: Quality adjusted life years.

Based on the ERG base-case assumptions (using the results of probabilistic sensitivity analyses) the ICER for cabazitaxel compared with BSC is estimated to be £107,604 with vial wastage and £86,888 without vial wastage.. Abiraterone does not lie on the efficiency frontier, as the ICER comparing abiraterone with cabazitaxel is greater than that comparing enzalutamide with abiraterone regardless of the assumption made concerning vial wastage, and hence abiraterone is extendedly dominated by enzalutamide. Compared with cabazitaxel, the ICER for enzalutamide is £142,180 with vial wastage and £158,873 without vial wastage.

It should be noted that the ICERs comparing cabazitaxel with BSC are substantively greater than those comparing cabazitaxel with mitoxantrone, as reported in **Error! Reference source not found.**. This shows that the estimated cost-effectiveness results are sensitive to the modelling approach employed for extrapolating clinical effectiveness data. For the NMA results (which are used when comparing cabazitaxel with BSC and the two advanced hormonal therapies), an assumption of proportional hazards is required. The ERG has already noted that this assumption is questionable, and that the NMA results should be treated with caution, as discussed in Section 4.4.

Sensitivity analyses for the comparison between cabazitaxel, BSC, abiraterone and enzalutamide were not performed as the list prices used for abiraterone and enzalutamide do not reflect the true cost to the NHS. Cost-effectiveness results and sensitivity analysis based on the PAS for abiraterone and enzalutamide are reported in a confidential appendix.

known visceral metastases radium-223 dichloride is a comparator in the NICE final scope, so excluding it will lead to uncertainty in the cost-effectiveness of cabazitaxel for both clinical pathways. In addition, not including BSC in the alternative practice pathway also leads to uncertainty about the cost-effectiveness of cabazitaxel.

The ERG's estimate of the ICER comparing cabazitaxel with mitoxantrone was [redacted] when modelling vial wastage and £51,849 when this was not modelled. The ERG also considered the cost-effectiveness of cabazitaxel when compared with BSC, abiraterone and enzalutamide. Effectiveness data were taken from the NMA adjusted by the ERG. The ICER comparing cabazitaxel with BSC was £107,604 when vial wastage was modelled and £86,888 when it was not modelled. Abiraterone was extendedly dominated by enzalutamide irrespective of how vial wastage was modelled. The ICER comparing enzalutamide with cabazitaxel was £142,180 when vial wastage was modelled and £158,873 when it was not modelled.

8.1 Implications for research

There are no direct comparisons of the clinical and cost effectiveness of cabazitaxel and any of abiraterone, enzalutamide or radium-223 dichloride. Hence there is a need for RCTs that directly compare these treatments, collects sufficient evidence on resource use and costs, and is powered to detect clinically meaningful changes in both OS and PFS. Trials comparing different sequences of treatment involving cabazitaxel and the advanced hormonal agents would also be beneficial.

Further research into the utility of people with mCRPC, particularly for people with progressed disease and how this utility varies over time, would help to reduce the uncertainty in the cost-effectiveness results. Uncertainty would also be reduced if longer-term data concerning the effectiveness of cabazitaxel (and each of the comparators) were available.