NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- In the pivotal randomised controlled trial (COU-AA-301), approximately 70% of patients had received docetaxel only ('one prior chemotherapy' subgroup) whereas the other patients had received more than one type of chemotherapy. The 'one prior chemotherapy' subgroup was not predefined in the statistical plan of the trial, and when analysed, the clinical effectiveness of abiraterone in this subgroup did not differ significantly from the whole trial population. Does the Committee agree with the manufacturer that the 'one prior chemotherapy' subgroup is more relevant to the decision problem than the whole study population, and that this subgroup is generalisable to patients in the UK who are most likely to be treated with abiraterone?
- Would patients with metastatic, castrate-resistant prostate cancer (mCRPC) and a Eastern Cooperative Oncology Group (ECOG)

performance score of 2 receive abiraterone treatment in UK clinical practice?

- Mitoxantrone in combination with prednisolone was listed as a comparator in the scope. However, the manufacturer argues that because of a lack of comparative evidence between mitoxantrone and abiraterone and a lack of evidence suggesting that mitoxantrone offers any survival benefit for patients with mCRPC, the placebo plus prednisolone arm of the COU-AA-301 trial (which was used in the manufacturer's economic model) adequately represents a population treated with mitoxantrone. Does the Committee consider this to be acceptable? If not, are there estimates from other sources that could be used instead?
- Are the high rates of adherence with abiraterone treatment (an oral medication) in the COU-AA-301 trial likely to be repeated in UK clinical practice? If not, has the COU-AA-301 trial overestimated the clinical effectiveness of abiraterone?

Cost effectiveness

- The manufacturer used clinical-effectiveness data from a subgroup of the COU-AA-301 trial ('one prior chemotherapy') in the economic model, although the clinical effectiveness in this subgroup did not differ from that of the whole trial population. Should the manufacturer have used clinical-effectiveness data from the whole trial population?
- Does the Committee agree with the manufacturer that time to treatment discontinuation in the COU-AA-301 trial is the most appropriate proxy for progression-free survival as used in the manufacturer's economic model (as opposed to radiographic or modified progression-free survival)?
- The main drivers of the cost-effectiveness analysis were differences in the utility values assigned to the pre-progression and post-progression health states in the economic model, which were derived from different sources. Does the Committee consider the utility values used by the manufacturer to

be realistic given the large utility decrement assumed ([redacted]) when moving from the pre-progression to post-progression state?

- The manufacturer estimated utility values for the pre-progression state by using data from a separate study to derive a mapping function from the FACT-P data from the COU-AA-301 trial to EQ-5D utilities. Does the Committee consider the methods used by the manufacturer to be acceptable?
- The manufacturer also used these data to estimate separate utility values for the pre-progression health state for the abiraterone and placebo groups. This resulted in a higher pre-progression utility value for the abiraterone group. Does the Committee consider the separate utility values generated to be appropriate?
- To estimate overall survival and progression-free survival in the model, the manufacturer used Kaplan–Meier survival data from the COU-AA-301 trial until a small proportion (10% for overall survival and 5% for progression-free survival) of patients were still at risk and then extrapolated survival using a constant hazard rate (exponential function). Does the Committee consider this approach to be acceptable or, as suggested by the ERG, would fitting of a Weibull distribution to survival data be more appropriate?
- The manufacturer considers abiraterone to be an innovative treatment for mCRPC. Does the Committee agree?
- Does abiraterone meet the end-of-life criteria? Are there any uncertainties?

1 Background: Clinical need and practice

1.1 The prostate is a gland in the male reproductive system. Prostate cancer accounts for approximately 25% of new diagnoses of malignant cancer in men in England and Wales. The incidence of prostate cancer increases with age. Most men have histological evidence of prostate cancer by 80 years of age, but die of unrelated causes. Experts believe that the cause of prostate cancer is multi-

factorial, involving both environmental and genetic factors. It is estimated that 55–60% of men with prostate cancer will develop metastatic disease with the cancer spreading from the prostate gland to other parts of the body.

1.2 Prostate cancer can be controlled by withdrawing or blocking the male sex hormones (androgens). According to NICE clinical guideline 58 on 'Prostate cancer – diagnosis and treatment' (CG58), when prostate-specific antigen, disease symptoms or radiological evidence indicate that androgen withdrawal or blocking is no longer controlling the condition, a patient is considered to have hormone-refractory metastatic prostate cancer.

1.3 According to statistics for 1999–2002 from Cancer Research UK, 5-year survival for people with localised prostate cancer in England was at least 90% and was around 30% for those with metastatic disease. People with metastatic disease may have a variety of clinical symptoms including weight loss and lower extremity oedema caused by lymphatic node metastases obstructing venous and lymphatic tributaries. Approximately 90% of people with mCRPC have metastases to bone. These give rise to complications such as spinal cord compression or vertebral fractures and pain in up to 40% of patients.

1.4 More than 90% of people with metastatic prostate cancer initially respond to hormonal therapy. However, the disease becomes refractory to standard hormonal therapy and alternative treatment strategies are needed. 'Docetaxel for the treatment of hormone-refractory metastatic prostate cancer' (NICE technology appraisal guidance 101) recommends docetaxel as a treatment option for men with hormone-refractory metastatic prostate cancer who have a Karnofsky performance-status score of 60% or more. The

Karnofsky score attempts to quantify patients' wellbeing and ranges from 0% (death) to 100% (no complaints). For people with hormone-refractory metastatic prostate cancer that has progressed during or after docetaxel-based treatment, there are limited treatment options. These may include mitoxantrone with or without corticosteroids such as prednisolone. People with mCRPC may also receive a combination of palliative treatments, which can include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies and corticosteroids.

2 The technology

2.1 Abiraterone acetate (Zytiga, Janssen) is a selective androgen biosynthesis inhibitor which is taken orally. It blocks cytochrome P17 (an enzyme that is involved in the production of testosterone), thereby stopping androgen synthesis by the adrenals, prostate and within the tumour. Abiraterone has a UK marketing authorisation for use 'with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen'.

2.2 The summary of product characteristics lists the following common adverse reactions for abiraterone: peripheral oedema, hypokalaemia, hypertension and urinary tract infection. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of abiraterone is £2930 for 120 tablets (30 days of treatment). Abiraterone is administered as a single dose of 1 g per day, taken as four 250-mg tablets (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] December 2011). The manufacturer

of abiraterone has agreed a patient access scheme with the Department of Health. This involves a confidential [redacted] discount applied to the list price of abiraterone. The acquisition cost of abiraterone within the patient access scheme is [redacted]. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of abiraterone in combination with prednisolone within its licensed indication for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy as compared with i) best supportive care and with ii) mitoxantrone plus prednisolone. The manufacturer's approach to the decision problem was in line with the scope (table 1). The ERG considered that the manufacturer's approach to the decision problem was appropriate for the NHS.

Table 1 Decision problem addressed in submission

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Men with metastatic, castrate-resistant prostate cancer whose disease has progressed on or after docetaxel-based chemotherapy	The manufacturer's base case focuses on patients who have received only one prior docetaxel-based chemotherapy regimen ('one prior chemotherapy' subgroup) Clinical and economic analyses on the intention-to-treat (whole) population are also presented for completeness
Intervention	Abiraterone acetate in combination with prednisolone	Abiraterone acetate (1 g once daily) in combination with 10 mg prednisolone (5 mg twice daily)
Comparators	• Best supportive care (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies and corticosteroids) • Mitoxantrone alone or in combination with prednisolone	• Best supportive care, represented by the prednisolone (10 mg) arm of the COU-AA-301 trial, which included supportive care with radiotherapy, bisphosphonates and luteinizing hormone releasing hormone (LHRH) agonists as needed. • Mitoxantrone (12 mg/m^2 every 3 weeks) in combination with prednisolone (10 mg)
Outcomes	• Overall survival • Progression-free survival • Response rate • PSA response • Adverse reactions to treatment • Health-related quality of life	• Overall survival (primary endpoint) • Progression-free survival: 1) radiographic progression-free survival 2) modified progression-free survival 3) time to treatment discontinuation • Response rate: 1) objective tumour response 2) PSA response (the number of patients achieving a decrease of PSA by at least 50%) 3) Circulating tumour cells response (the proportion of patients achieving circulating tumour cell conversion) • PSA response defined as the average PSA response • Adverse reactions to treatment • Health-related quality of life

Economic evaluation	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • 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 manufacturer submitted a survival-based decision analysis economic model that compares abiraterone acetate with prednisolone plus placebo and with mitoxantrone plus prednisolone • The manufacturer applied a time horizon of 10 years because it considered that most patients with metastatic disease will not be alive at 7 years. This time horizon is in line with models for other late-stage cancers • Costs are considered from an NHS and personal social services perspective
Other considerations	If evidence allows, consideration will be given to subgroups defined by • baseline ECOG status • extent of prior taxane exposure • time since taxane treatment	Time since prior taxane treatment was not a pre-specified stratification factor and therefore this subgroup was not explored

The manufacturer considered that the 'one prior chemotherapy' subgroup in the base case more closely reflected people with metastatic, castrate-resistant prostate cancer in England and Wales who are likely to receive abiraterone therapy. This view was shared by the ERG's clinical advisers.

The manufacturer viewed best supportive care as the main comparator for abiraterone. Following expert advice, the manufacturer considered that the treatment received by patients in the comparator arm of the COU-AA-301 trial adequately reflects best supportive care given in the UK. The ERG's clinical adviser confirmed that most patients with mCRPC in the UK whose disease has progressed on or during docetaxel therapy will receive best supportive care, which includes palliative care (for example, advice on bone preservation [on weight, diet, exercise],

hormonal treatments, drugs to strengthen bones and advice on self-management).

The manufacturer did not consider mitoxantrone in combination with prednisolone to be a relevant comparator for this appraisal, because second-line treatment with mitoxantrone is used in only about 10% of patients in the UK. The ERG's clinical advisers agreed with this estimate. However, the manufacturer provided estimates of the cost effectiveness of abiraterone compared with mitoxantrone plus prednisolone, but was unable to identify any studies comparing abiraterone with mitoxantrone in the relevant patient population. Because of evidence indicating a lack of survival benefit following treatment with mitoxantrone compared with corticosteroids in chemotherapy-naive patients, the manufacturer argued that patients treated with mitoxantrone are most appropriately represented by the prednisolone arm of the COU-AA-301 trial.

The outcomes included by the manufacturer were mostly similar to those specified in the decision problem. The manufacturer described three methods of estimating progression-free survival: radiographic progression-free survival; modified progression-free survival (defined by the manufacturer as meeting one of the criteria for discontinuation of study treatment which involved time to death or first observation of any one of the following: PSA progression, radiographic progression, increase in glucocorticoid use, pain progression, a skeletal-related event, or the initiation of a new systemic anticancer therapy); and time to treatment discontinuation. The manufacturer used the latter as a proxy for progression-free survival in its economic model. The ERG's clinical advisers confirmed that there were particular difficulties in estimating disease progression in hormone-refractory metastatic

prostate cancer and they considered the manufacturer's approach of using time to treatment discontinuation as a proxy for progression-free survival to be reasonable.

The manufacturer considers that abiraterone is an innovative technology that can extend survival and delay disease progression in people with mCRPC whose disease has progressed on or after docetaxel-based chemotherapy.
The manufacturer also considers that the end-of-life criteria should be used when assessing abiraterone. The manufacturer estimated that:

- people with mCRPC have a median overall survival of approximately 1 year
- a maximum of 3300 patients are eligible for treatment with abiraterone
- abiraterone treatment leads to a 4.6-month increase in median overall survival compared with best supportive care.

3.2 According to the manufacturer, following chemotherapy with docetaxel only a small proportion of people with mCRPC currently receive second-line chemotherapy (10% receive mitoxantrone and 10% docetaxel re-challenge). Most patients (approximately 80%) receive best supportive care (including treatment with prednisolone or other corticosteroids). In this appraisal, the manufacturer has positioned abiraterone as a second-line therapy following disease progression with docetaxel chemotherapy.

4 Clinical-effectiveness evidence

4.1 The manufacturer carried out a systematic literature search to identify all relevant trials and studies of abiraterone and potential

comparators in patients with mCRPC following first-line taxane chemotherapy. The manufacturer identified four studies of abiraterone following previous chemotherapy, including one randomised controlled trial (COU-AA-301) and three single arm studies (COU-AA-304, COU-AA-003, COU-AA-BMA). The manufacturer's clinical-effectiveness evidence was derived solely from the COU-AA-301 trial, a phase III, randomised, double-blind, multi-centre trial carried out across 130 sites in 13 countries, including the UK. In this trial, abiraterone in combination with prednisolone (797 patients) was compared with placebo plus prednisolone (398 patients) in patients with mCRPC whose disease had progressed on or after docetaxel therapy and who had a ECOG performance score of 0–2. Patients in both groups were treated until disease progression. Study follow-up was up to 60 months.

4.2 The demographics and baseline disease characteristics were similar between the two treatment groups in the COU-AA-301 trial: 93% of patients were white, median age was 69 years and 28% of patients were 75 years or older. In the abiraterone plus prednisolone (hereafter abiraterone) group, 70% of patients had previously received docetaxel chemotherapy only ('one prior chemotherapy' subgroup), compared with 69% in the placebo plus prednisolone (hereafter prednisolone) group. In the abiraterone group 10% of patients had a baseline ECOG performance score of 2. The corresponding figure in the prednisolone group was 11%. The majority of patients in both treatment groups (approximately 70%) had radiographic progression with or without PSA progression; 89% of patients in the abiraterone group and 90% of patients in the prednisolone group had bone metastasis.

4.3 The primary outcome of the COU-AA-301 trial was overall survival, defined as the time from randomisation to death from any cause (table 2). A primary analysis was conducted after 552 deaths (12.8 months median follow-up) for the whole (intention-to-treat) population. In this analysis, median survival was statistically significantly longer in the abiraterone group than the prednisolone group (14.8 months compared with 10.9 months, hazard ratio [HR] 0.646, 95% confidence interval [CI] 0.543 to 0.768). An updated analysis was conducted after 775 deaths (20.2 months median follow-up) for the whole population and the 'one prior chemotherapy' subgroup. For the whole population, median survival continued to be statistically significantly longer in the abiraterone group than the prednisolone group (15.8 months compared with 11.2 months, HR 0.740, 95% CI 0.638 to 0.859). Subgroups with ECOG performance score of 0–1 or 2 and subgroups with one or more than one prior chemotherapy regimen were not prespecified in the statistical analysis plan but were explored by the manufacturer.

[redacted]

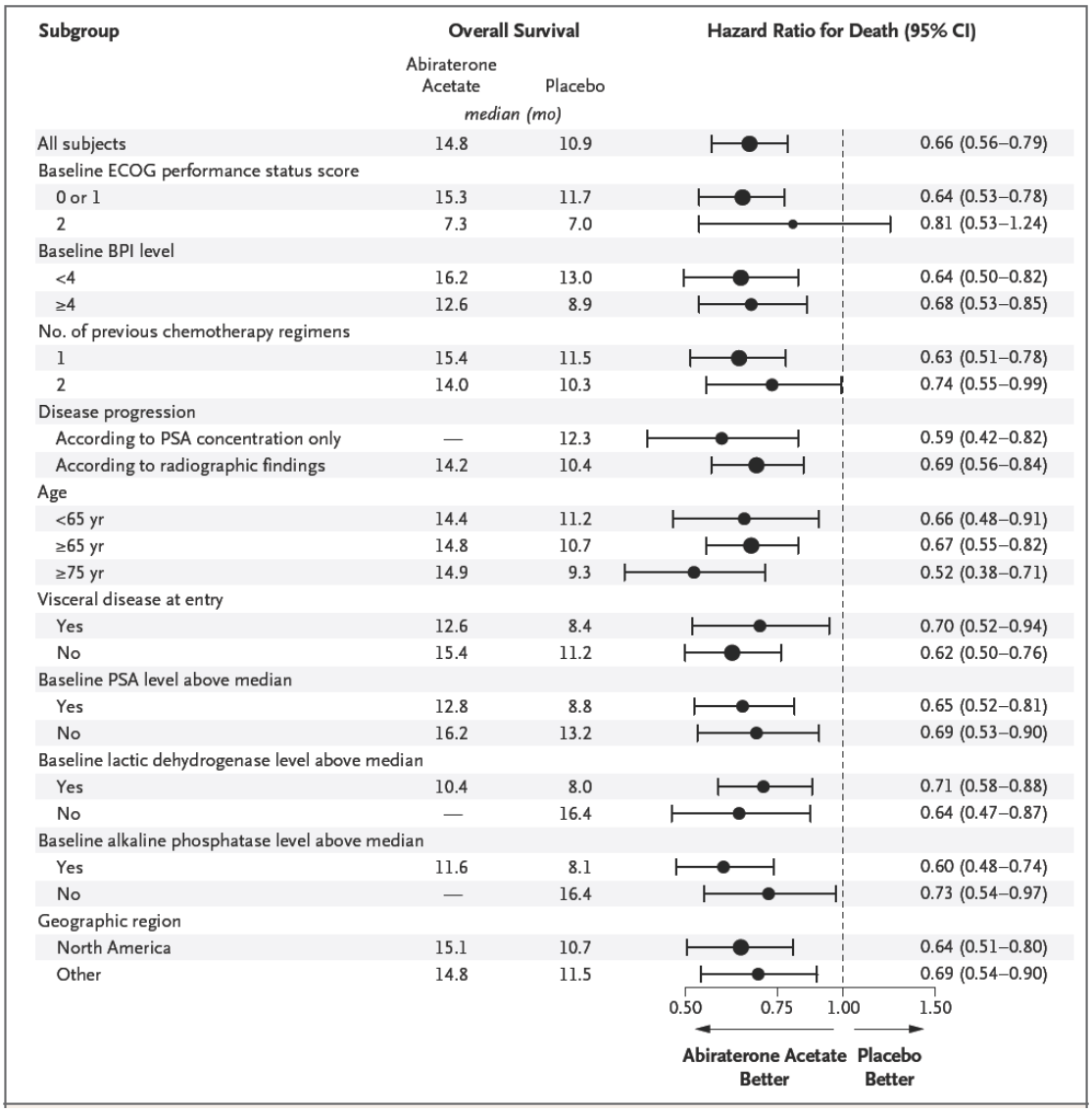
Table 2 Overall survival results from the COU-AA-301 trial

PRIMARY ANALYSIS								
Treatment arm	**Whole population**				**'One prior chemotherapy' subgroup**			
	n	Deaths n (%)	Median (95% CI)	HR[a] (95% CI)	n	Deaths (%)	Median (95% CI)	HR (95% CI)
Abiraterone	797	333 (42%)	14.8 (14.1–15.4)	0.646 (0.543–0.768)	[redacted]	NR	NR	NR
Prednisolone	398	219 (55%)	10.9 (10.2–12.0)		[redacted]	NR	NR	
Difference			3.9 months		Difference		NR	
UPDATED ANALYSIS								
Abiraterone	797	501 (63%)	15.8 (14.8–	0.74 (0.638–	[redacted]	NR	[redacted]	[redacted]

			17.0)	0.859)				
Prednisolone	398	274 (69%)	11.2 (10.4–13.1)		[redacted]	NR	[redacted]	
Difference			4.6 months		Difference		[redacted]	
[a]Hazard ratio abiraterone versus prednisolone by stratified proportional hazards model. NR, not reported								

4.4 Detailed prespecified subgroup analyses were conducted at the time of the primary analysis for the whole population to examine whether the effect on overall survival was consistent across subgroups in both treatment groups. The effect on overall survival was found to be consistent across nearly all subgroups, demonstrating a consistent and statistically significant effect in favour of abiraterone. Only the small subgroup with an ECOG performance score of 2 did not show statistically significantly longer survival with abiraterone than with prednisolone (7.3 months compared with 7.0 months, HR 0.81, 95% CI 0.53 to 1.24). See figure 1 below for more details.

Figure 1 Hazard ratios for overall survival for subgroups in the COU-AA-301 trial



4.5 A key secondary outcome in the COU-AA-301 trial was progression-free survival, which was assessed using three outcome measures: radiographic progression-free survival; modified progression-free survival; and time to treatment discontinuation. Treatment with abiraterone significantly decreased the risk of radiographically documented disease progression or death by 33% compared with prednisolone in the primary analysis (HR 0.673, 95% CI 0.585 to 0.776,

p < 0.0001) [redacted] The median radiographic progression-free survival was identical in both the primary and updated analyses: 171 days in the abiraterone group and 110 days in the prednisolone group. [redacted]

4.6 The manufacturer indicated that expert opinion had suggested that the endpoints of modified progression-free survival and radiographic progression-free survival, as defined in the COU-AA-301 trial, did not necessarily represent when treatment with abiraterone was discontinued in the trial because of disease progression. On this basis, the manufacturer argued that treatment discontinuation was the most appropriate proxy for progression-free survival. The manufacturer presented time to discontinuation rates for both the whole population (primary and updated analyses) and the 'one prior chemotherapy' subgroup (updated analysis only). For the whole population, the median time to treatment discontinuation in both the primary and updated analyses for the abiraterone group was [redacted]

4.7 Other secondary outcomes in the COU-AA-301 trial included PSA response rates, defined as the proportion of patients with a 50% or greater decrease in PSA confirmed by a second measurement at least 4 weeks later. In the primary analysis for the whole population, confirmed PSA response was statistically significantly greater in the abiraterone group than in the prednisolone group (29.1% compared with 5.5%, $p < 0.0001$).

[redacted]

4.8 Objective tumour response rates were also assessed in the COU-AA-301 trial according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria. The proportion of patients with measurable disease at baseline who had an objective response in the primary analysis (all were partial responses) was greater in the abiraterone group than in the prednisolone group (14.0% compared with 2.8%, $p < 0.0001$).

[redacted]

4.9 Because only one relevant randomised controlled trial (COU-AA-301) of abiraterone was identified in the systematic literature review, it was not possible for the manufacturer to conduct a meta-analysis. The manufacturer was also not able to conduct a network meta-analysis of abiraterone and comparator treatments because the systematic literature review did not identify any studies to link abiraterone with the comparators of interest (mitoxantrone and prednisolone, prednisolone and best supportive care) in patients who had received prior chemotherapy. In its systematic review of the literature, the manufacturer identified four randomised

controlled trials that compared mitoxantrone and prednisolone with other drugs. However, there was no other trial to link this evidence to the COU-AA-301 trial and enable an indirect comparison between abiraterone and mitoxantrone.

4.10 Adverse reactions were recorded in the COU-AA-301 trial for all patients who were randomised and received any study medication (abiraterone, n = 791, prednisolone, n = 394). The manufacturer presented the incidence of adverse reactions for both the primary and updated analyses but not for the 'one prior chemotherapy' subgroup. Commonly reported adverse reactions (≥ 10%, mostly grade 1 or 2) in both treatment groups were anaemia, vomiting, hot flush, anorexia, pain in extremity, diarrhoea, musculoskeletal pain, asthenia, dyspnoea, headache, urinary tract infection, weight loss and muscular weakness. For the primary analysis, the most frequently reported grade 3 or 4 adverse reactions in the abiraterone and prednisolone treatment groups were fatigue, anaemia, back pain and bone pain. The incidence of frequently reported adverse reactions are summarised in table 3.The incidence of individual grade 3 or 4 adverse reactions did not increase by more than 2% for either treatment group between the primary and updated analyses.

Table 3 Incidence of frequently reported adverse reactions for the primary analysis in the COU-AA-301trial

	All grades		**Grade 3 or 4**		
Event, n (%)	**Abiraterone (n = 791)**	**Prednisolone (n = 394)**	**Event, n (%)**	**Abiraterone**	**Prednisolone**
Fatigue	346 (44%)	169 (43%)	Fatigue	66 (8%)	39 (10%)
Back pain	233 (30%)	129 (33%)	Anaemia	59 (8%)	29 (7%)
Arthralgia	215 (27%)	89 (23%)	Back pain	47 (6%)	38 (10%)
Nausea	233 (30%)	124 (32%)	Bone pain	44 (6%)	29 (7%)
Constipation	206 (26%)	120 (31%)			
Bone pain	194 (25%)	110 (28%)			

4.11 Adverse reactions of special interest, which included events related to mineralocorticoid excess (hypertension, hypokalaemia and oedema), cardiac disorders and hepatotoxicity, were more frequent in the abiraterone group than the prednisolone group (55% compared with 44%). However, the incidence of grade 3 or 4 events was low in both treatment groups. Cardiovascular events (primarily grade 1 or 2) were more commonly reported in the abiraterone group than the prednisolone group (13% compared with 11%, p = 0.14). The proportion of patients discontinuing treatment because of adverse reactions was similar between the abiraterone and prednisolone groups (19% compared with 23%, p = 0.09). A higher proportion of patients in the prednisolone group (15%) died because of treatment-related adverse reactions compared with the abiraterone group (11%). The COU-AA-301 trial also reported skeletal-related events, which were defined as a pathological fracture, spinal cord compression, palliative radiation or surgery to the bone.

[redacted]

4.12 The manufacturer presented updated analyses for three health-related quality of life measures for which data were collected in the COU-AA-301 trial: the brief pain inventory short form (BPI-SF); the brief fatigue inventory short form (BFI-SF); and the functional assessment of cancer therapy-prostate (FACT-P).

[redacted]

[redacted] The manufacturer concluded that evidence from the COU-AA-301 trial suggests that patients receiving abiraterone are more likely to experience reduced pain, improved functional status and decreased fatigue and have more time before their pain, functional status and fatigue worsens.

4.13 The ERG considered that the clinical-effectiveness evidence submitted by the manufacturer was of good quality. This included the systematic literature searches conducted and the single randomised controlled trial (COU-AA-301) of abiraterone in combination with prednisolone in men with mCRPC that was identified. The ERG had minor concerns about the generalisability of the results from the COU-AA-301 trial because only 12 of the 130 study centres were in the UK, and because of under-representation of ethinc groups other than white people in the trial population. The ERG also noted that, although the 'one prior chemotherapy' subgroup corresponded to the licensed population and to patients who are likely to receive abiraterone in UK clinical practice, use of this subgroup reduced statistical power for comparison of outcomes between the two treatment groups.

5 Comments from other consultees

5.1 Statements from clinical specialists indicated that the aim of treatment in mCRPC is to improve survival and control symptoms effectively. Clinical specialists noted that, following progression after hormonal therapy, the next line of therapy for this patient group is often chemotherapy with docetaxel. There is currently no NICE-approved treatment that offers a survival benefit in patients whose condition has progressed after docetaxel chemotherapy.

The clinical specialists stated that both abiraterone (in combination with prednisolone) and cabazitaxel (which is currently being appraised by NICE) have been shown to improve survival in this patient group. It was noted, however, that these two drugs are not directly comparable because not all patients in the COU-AA-301 trial would have been considered fit enough to be enrolled in the trial for cabazitaxel (TROPIC). It was also stated that a third drug, alpharadin, may offer improved survival for patients who have not received docetaxel therapy and have troublesome bone pain.

5.2 It was noted by clinical specialists that as well as improving overall survival abiraterone is effective in controlling symptoms and reducing skeletal-related adverse reactions. In addition, abiraterone is an oral medication taken once daily and clinical specialists stated that adverse reactions are considered manageable. The clinical specialists and other consultees also stated that abiraterone should only be prescribed in secondary care by medical or clinical oncologists with a special interest in urological malignancies.

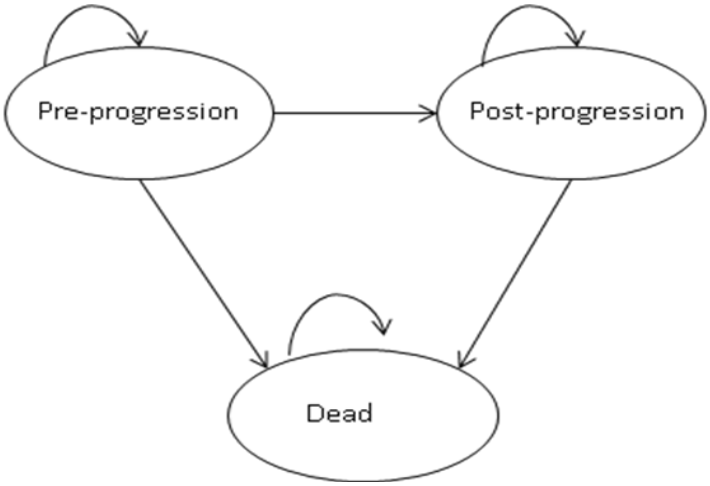
5.3 Statements from patient groups indicated that abiraterone would make a significant difference to people with mCRPC by offering the possibility of extending life when only very limited treatment options, apart from palliative care, are available. According to the patient experts, by potentially extending life abiraterone could enable people with mCRPC to spend more time with family and friends and could improve quality of life by increasing hope and mental wellbeing when limited treatment options are available. A further advantage of abiraterone treatment noted by patient experts was that it is taken orally at home and does not need frequent hospital visits.

6 Cost-effectiveness evidence

6.1 The manufacturer's systematic review did not identify any published studies that evaluated the cost effectiveness of abiraterone for the treatment of mCRPC following previous cytotoxic chemotherapy.

6.2 The manufacturer submitted an economic model comparing abiraterone with prednisolone and with mitoxantrone plus prednisolone (hereafter mitoxantrone). The manufacturer developed a survival-based decision model with three health states: pre-progression (progression-free survival), post-progression and dead. The model is shown in figure 2. People with mCRPC were assumed to enter the model in the pre-progression state having already received treatment with docetaxel-based chemotherapy. It was assumed that people who experienced disease progression would enter the post-progression state. People receiving abiraterone were assumed to discontinue abiraterone treatment when they entered the post-progression state. Prednisolone treatment was assumed to continue until death for all comparators (including the prednisolone group) but a fixed maximum duration of 30 weeks was assumed for mitoxantrone treatment in the base-case analysis.

Figure 2. Schematic of manufacturer's economic model



6.3 The number of people remaining in each health state at each model cycle was calculated directly from the overall survival and progression-free survival curves from the 'one prior chemotherapy' subgroup of the COU-AA-301 trial. Time in the post-progression state was calculated as the difference between overall survival and progression-free survival. The model assumed a cycle length of 3 weeks based on the dosing cycle of mitoxantrone, and used a lifetime horizon (10 years). An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%.

6.4 The key clinical effectiveness parameters used in the model were progression-free and overall survival, which were derived from the updated analysis for the 'one prior chemotherapy' subgroup of the COU-AA-301 trial. It was assumed that progression-free survival and overall survival for mitoxantrone treatment was the same as for the prednisolone treatment group in the base-case analysis. The manufacturer argued that this was justified because of clinical evidence indicating no overall survival benefit for mitoxantrone compared with corticosteroids in chemotherapy-naive populations and therefore no overall survival benefit in the post-chemotherapy

population. In the base-case analysis, overall survival in both treatment groups was modelled using Kaplan–Meier survival data taken directly from the COU-AA-301 trial to the point at which 10% of patients were still contributing data. The manufacturer justified this because censoring at the end of the trial period made the tails of the Kaplan–Meier curves less reliable. Beyond this 10% cut-off point, overall survival curves were extrapolated assuming a constant hazard rate.

6.5 Transition from the pre-progression to the post-progression health state was determined by treatment discontinuation rates from the COU-AA-301 trial, which were used as a proxy for progression-free survival (see section 4.6). As for overall survival, progression-free survival in the abiraterone treatment group was modelled in the base case using Kaplan–Meier survival data taken directly from the COU-AA-301 trial and was truncated at a point at which 5% of men remained at risk. The manufacturer justified this lower cut-off because there was less censoring than for overall survival. Beyond this 5% cut-off point, survival curves were extrapolated assuming a constant hazard rate. For the prednisolone treatment group, the Kaplan–Meier data for survival on treatment were virtually complete with just over 2% of patients still on treatment, and so no extrapolation was applied.

6.6 For mitoxantrone treatment, the manufacturer applied the progression-free and overall survival curves from the prednisolone treatment group in the base-case analysis. The key differences between the mitoxantrone and prednisolone groups in the model were that: treatment costs differed (maximum mitoxantrone treatment duration was 30 weeks); mitoxantrone was associated with more adverse reactions with a subsequent impact on costs and health-related quality of life; and there was a health-related

quality of life gain from reduced pain for mitoxantrone treatment. The maximum duration of mitoxantrone treatment (ten 3-weekly cycles) was informed by the TROPIC trial, which compared prednisolone plus cabazitaxel with mitoxantrone for the treatment of mCRPC following previous docetaxel chemotherapy.

6.7 No utility data were collected during the COU-AA-301 trial. Therefore, the manufacturer undertook a two-stage analysis to convert FACT-P data from the COU-AA-301 trial into utility values. In the first stage, the manufacturer analysed data from a separate cross-sectional study of patients with mCRPC across five European countries (including the UK) who completed FACT-P and EQ-5D questionnaires. The data set from this study was used to develop an algorithm to map data from FACT-P to EQ-5D using an ordinary least squares (OLS) regression model. In the second stage, FACT-P data from both treatment groups in the COU-AA-301 trial ('one prior chemotherapy' subgroup) were converted to EQ-5D utilities and regression analysis was applied to derive a treatment effect. There was no explicit modelling of adverse reactions within the treatment model by the manufacturer, who assumed that any differences in adverse reactions between the treatment groups were reflected in the treatment group coefficient in the regression model. Although the EQ-5D data set was not specific to UK patients with mCRPC, utility values were converted using the UK EQ-5D tariff.

6.8 As a result of this analysis, the manufacturer applied a pre-progression (baseline) utility value of [redacted] for patients in the prednisolone treatment group and a utility increment of [redacted] was added for the abiraterone treatment group, resulting in a pre-progression utility value of [redacted]. This treatment effect was also applied to the mitoxantrone group in the base-case analysis. In

order to estimate the impact of grade 3 or 4 adverse reactions on pre-progression utility for mitoxantrone treatment, the manufacturer conducted a separate, parallel regression, which estimated an average utility decrement of [redacted] for the 'one prior chemotherapy' subgroup. The manufacturer estimated that, based on the average number of grade 3 or 4 adverse reactions reported for abiraterone (from the COU-AA-301 trial) and mitoxantrone (from the mitoxantrone arm of the TROPIC trial), mitoxantrone resulted in a net increase of 32% in grade 3 or 4 adverse reactions compared with abiraterone, resulting in a utility decrement of [redacted] for mitoxantrone. The pre-progression utility value for mitoxantrone was therefore [redacted].

6.9 For the post-progression health state, the manufacturer noted that FACT-P data were not collected beyond the point of disease progression (treatment discontinuation) in the COU-AA-301 trial. Based on a systematic literature review, the manufacturer identified a study that estimated EQ-5D utility values in the year before death in Swedish men with prostate cancer (Sandblom et al. 2004). In this study, utility values ranged from 0.58 in men with 8–12 months to live to 0.46 in those with less than 4 months to live. The manufacturer used a utility value of 0.50 for the post-progression state, based on the average utility observed for men in the last 8 months of life in this study. The health state utility values used in the economic model are summarised in table 4.

Table 4 Health state utility values used in the manufacturer's economic model

Health state	Utility value	SE	Reference in submission
Pre-progression state (base case)	[redacted]	[redacted]	Utility analysis from COU-301-AA trial
Post-progression state	0.50	0.08	Sandblom et al. (2004)

On-treatment utility gain for abiraterone and mitoxantrone (base case)	[redacted]	[redacted]	Utility analysis from COU-301-AA trial
Adverse reactions utility decrement (applied to mitoxantrone only)	[redacted]	[redacted]	Utility analysis from COU-301-AA trial

6.10 The manufacturer included the costs of drug treatment, including drug acquisition, administration and monitoring costs. Under the terms of the patient access scheme approved by the Department of Health, the monthly cost of abiraterone was [redacted], based on a daily dose of 1 g, which resulted in a total cost of [redacted] per 3-week cycle. For mitoxantrone, in which dosing is determined by body surface area, a surface area of 2.02 m^2 was assumed, based on the average observed in the TROPIC trial. Based on a cost of £100 per 20-mg vial, and assuming two vials were needed, the cost of mitoxantrone used in the model was £200 per 3-week cycle. It was also assumed that mitoxantrone treatment would need one outpatient visit per 3-week cycle, resulting in a total cost of £448.45 per 3-week cycle. The cost of prednisolone was £1.03 for a 28-tablet (5 mg) pack (£1.55 per 3-week cycle). This cost was included for all three treatments and was assumed to continue until death. The costs of mitoxantrone and prednisolone were taken from the 'British national formulary' (BNF; edition 61).

6.11 The model also included the costs of scheduled, disease-related patient follow-up consisting of clinical visits, diagnostic imaging tests and clinical laboratory tests to monitor the status of the disease. To estimate scheduled UK medical resource utilisation in each treatment group, the manufacturer conducted a clinical consensus meeting. Based on statistical analysis of data from the COU-AA-301 trial, the manufacturer estimated that unscheduled

medical resource utilisation (including grade 3 or 4 adverse reactions) was similar between the abiraterone and prednisolone treatment groups while on treatment. Therefore, a one-off fixed cost of unplanned, event-related resource utilisation in the pre- and post-progression states was applied to all treatment groups. For those receiving mitoxantrone, the extra costs of treating grade 3 or 4 adverse reactions were assigned to the incremental rates of adverse reactions for mitaxontrone compared with abiraterone treatment. The costs of concomitant medication, (including bisphosphonates in the pre- and post-progression states for all three treatment groups, and granulocyte colony-stimulating factor [G-CSF] to treat febrile neutropenia in the abiraterone and mitoxantrone groups) were also included in the model. Based on results from the UK subpopulation of the COU-AA-301 trial, it was assumed that [redacted] of people in each treatment group would receive three cycles of cabazitaxel (currently being appraised by NICE) in the post-progression state. The manufacturer also estimated terminal treatment resource utilisation and costs based on clinical expert opinion, which were applied for the last 3 months of life in each treatment group (for further details see pages 118–124 of the manufacturer's submission). The costs applied in the model are summarised in table 5.

Table 5 Health states and associated costs applied in the manufacturer's economic model

Health state	Item	Cost	Source in manufacturer's submission
Pre-progression (monthly cost)	Mitoxantrone on-treatment cost (scheduled MRU)	[redacted]	Clinical consensus meeting
	Mitoxantrone off-treatment cost (scheduled MRU)	[redacted]	Clinical consensus meeting
	Abiraterone on-treatment costs (scheduled MRU) first 3 months	[redacted]	Clinical consensus meeting
	Abiraterone on-treatment costs (scheduled MRU) after 4 months	[redacted]	Clinical consensus meeting
	Prednisolone (scheduled MRU)	[redacted]	Clinical consensus meeting

	Abiraterone and mitoxantrone groups therapeutic use of G-CSF (0.3% of patients)	£686.38/model cycle	BNF 61
	All treatments (concomitant bisphosphonate use in 37% of patients)	£48.54	BNF 61
	All treatments one-time cost (unscheduled MRU)	[redacted]	COU-AA-301 MRU analysis,
Post-progression (monthly cost)	All treatments (scheduled MRU)	[redacted]	Clinical consensus meeting
	All treatments (unscheduled MRU)	[redacted]	COU-AA-301 MRU analysis,
	All treatments (concomitant bisphosphonate use in 100% of patients)	£132.38	BNF 61
	All treatments one-time cost of subsequent treatment ([redacted])	[redacted]	BNF 61
	All treatments (terminal treatment in last 3 months)	[redacted]	Clinical consensus meeting

The manufacturer's base-case deterministic cost-effectiveness results (including the patient access scheme) for the 'one prior chemotherapy' subgroup (table 6) showed that mitoxantrone plus prednisolone resulted in higher costs and lower quality-adjusted life years (QALYs) than a combination of abiraterone and prednisolone (extendedly dominated). The comparison between abiraterone and prednisolone resulted in an incremental cost-effectiveness ratio (ICER) of £52,851 per QALY gained (incremental costs [redacted]; incremental QALYs [redacted]). The manufacturer's base-case probabilistic cost-effectiveness results were very similar. The manufacturer's base-case deterministic cost-effectiveness results for the whole trial population (intention-to-treat) showed that mitoxantrone was again extendedly dominated by abiraterone and prednisolone whereas the comparison between abiraterone and prednisolone resulted in an ICER of £63,233 per QALY gained (incremental costs [redacted]; incremental QALYs [redacted]).

Table 6 Manufacturer's base-case deterministic results ('one prior chemotherapy' subgroup)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Prednisolone	[redacted]	[redacted]	[redacted]					
Mitoxantrone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£170,550	Extendedly dominated
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,851	£52,851
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

6.12 The manufacturer conducted a number of one-way sensitivity analyses on various model input parameters, which included: altering the time horizon (4, 6, 8 years), varying the discount rates for costs and benefits (0 and 6%), using a Weibull parametric approach to estimate survival beyond the Kaplan–Meier cut-off point for progression-free and overall survival, using alternative utility estimates for pre- and post-progression health states and abiraterone treatment effect, and varying a number of cost input parameters (±50%). The results of these one-way sensitivity analyses indicated that the ICERs were fairly robust to changes in most input parameters (see table 7). Only when the utility value for the pre-progression state was changed from [redacted] to 0.538 did the cost-effectiveness results change significantly, resulting in an ICER for abiraterone compared with prednisolone of £77,000 per QALY gained. In one scenario analysis, the manufacturer assumed that mitoxantrone offered a progression-free survival advantage compared with prednisolone (HR 0.77). This scenario resulted in an ICER of £21,038 per QALY gained for mitoxantrone compared with prednisolone and an ICER of £62,843 per QALY gained for abiraterone compared with mitoxantrone. In a scenario without the patient access scheme for abiraterone, the ICER for abiraterone compared with prednisolone was [redacted] per QALY gained. Results of the probabilistic sensitivity analysis showed

that, at a cost-effectiveness threshold range of £20,000 to £30,000 per QALY gained, prednisolone had the highest probability (100%) of being cost effective. Abiraterone had the highest probability of being cost effective when the cost-effectiveness threshold was above £50,000 per QALY gained.

Table 7. Results of manufacturer's one-way sensitivity analyses

Input parameter	Alternative values	ICER for abiraterone versus prednisolone	ICER for abiraterone versus mitoxantrone
Base case		£52,851	£46,617
Time horizon	4 years	£57,057	£50,146
	6 years	£54,066	£47,646
	8 years	£53,141	£46,863
Discount rate – costs	0	£55,309	£49,142
	0.06	£51,279	£45,005
Discount rate – benefits	0	£49,164	£43,252
	0.06	£55,461	£49,006
Overall survival approach	Kaplan–Meier plus 10% cut-off plus Weibull projection	£56,484	£49,817
	Kaplan–Meier plus 5% cut-off plus constant hazard projection	£54,195	£47,796
	Kaplan–Meier plus 5% cut-off plus Weibull projection	£57,298	£50,537
	Parametric (Weibull-placebo, Weibull-Abiraterone)	£56,339	£49,691
	Lower end of the 95% CI of Kaplan–Meier	£50,679	£44,516
	Higher end of the 95% CI of Kaplan–Meier	£55,438	£48,886
Progression-free survival approach	Kaplan–Meier plus 5% cut-off plus Weibull projection	£53,301	£46,878
	Kaplan–Meier plus 10% cut-off plus constant hazard projection	£53,091	£46,755
Median treatment – mitoxantrone	2 cycles	-	£50,128
	7 cycles	-	£43,849
Baseline utility	0.538 (Collins, 2007)	£77,040	£69,640
	0.85 (Krahn, 2003)	£48,451	£42,548
Utility increment abiraterone	[redacted]	£54,353	£48,014
	[redacted]	£51,708	£45,556
Utility in progression	0.40 (–20%)	£51,421	£45,290
	0.60 (+20%)	£54,364	£48,024
	0.46 (Sandblom 2004)	£52,270	£46,077
	0.70	£55,965	£49,518
Utility grade 3/4 adverse reactions	[redacted]	-	£45,983

Scheduled follow-up costs	–50% +50%	£51,147 £54,555	£45,699 £47,534
Unplanned MRU cost	–50% +50%	£53,486 £52,217	£47,285 £45,948
Subsequent treatment costs	No cabazitaxel	£52,930	£46,700
GCSF use	No G-CSF	£52,758	£46,541
Bisphosphonate use	50% in progression-free survival and progression	£53,347	£47,139
Adverse event costs – all	–50% +50%	- -	£47,179 £46,054
Terminal care costs	None +20%	£52,960 £52,829	£46,731 £46,594

6.13 The ERG commented that the manufacturer submitted a relatively straightforward economic model comparing the relevant comparators following docetaxel chemotherapy, and closely adhered to the NICE reference case requirements for economic analysis. The ERG acknowledged that the base-case analysis was appropriately based on the 'one prior chemotherapy' subgroup from the COU-AA-301 trial.

6.14 The ERG commented that the factors with the most influence on the cost effectiveness of abiraterone compared with prednisolone and mitoxantrone were the differences in the EQ-5D utility values attached to the pre- and post-progression health states, which were derived from different sources. The ERG noted that the pre-progression utility value of [redacted] for the abiraterone treatment group, which was estimated from the FACT-P mapping function, was similar or higher than EQ-5D utility values for men of similar age taken from a survey of the general UK population living in the community (Kind et al. 1998). This survey reported average EQ-5D visual analogue scores of between 0.800 and 0.750 for men aged between 60 and 79 years. The ERG's clinical advisers suggested that, because the COU-AA-301 trial may have been

oversubscribed, the population selected would be fitter, more aware and more mobile than generally seen in clinical practice.

6.15 The ERG noted that because most patients in the cross-sectional study data set used to derive the mapping function were receiving a course of chemotherapy, both their FACT-P scores and EQ-5D utilities would tend to be lower than patients in the COU-AA-301 trial. It was argued that this could have resulted in the FACT-P mapping function derived from this separate data set being applied to FACT-P values outside the reliable range of the mapping function, which increases the uncertainty around the manufacturer's derived utility values. The ERG also noted that the FACT-P mapping function was applied to a restricted set of patients who reported FACT-P values at baseline and at follow-up in the COU-AA-301 trial, enabling changes from baseline to be estimated. It was noted that the FACT-P values at baseline for those reporting values at follow-up may have been higher in the prednisolone group than the abiraterone group and that patients in the prednisolone group may have shown a smaller change because they had less severe disease.

6.16 The ERG noted that the utility values used in the manufacturer's model implied utility decrements for discontinuing treatment (disease progression) of [redacted] for abiraterone and [redacted] for prednisolone. However, the ERG had some concerns regarding the manufacturer's approach to the regression and, in the absence of access to individual patient data, the ERG's exploration of alternative approaches was necessarily limited. The ERG suggested that, for the utility value of 0.500 assigned to the post-progression state, this will tend to worsen the cost effectiveness of abiraterone because it will reduce the QALY gain from time spent in the pre-progression state for the abiraterone

treatment group. The ERG also noted that the utility decrement applied when moving from stable to progressive disease health states in the ongoing appraisal of cabazitaxel for the second-line treatment of hormone-refractory metastatic prostate cancer was lower than that used in this appraisal.

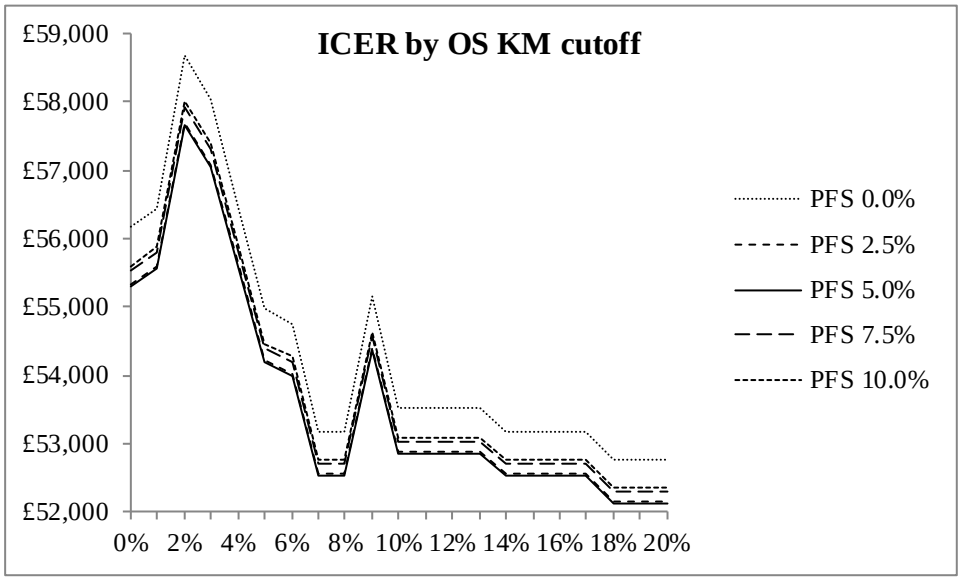
6.17 The ERG noted that the manufacturer's choice of a 10% at-risk cut-off before extrapolation of overall survival was somewhat arbitrary, although sensitivity analyses by the manufacturer showed that applying different cut-off points had little impact on the ICERs for abiraterone compared with prednisolone. The ERG also noted that a similar approach was taken by the manufacturer when estimating time to progression. However, the ERG noted that there was some inconsistency with this approach, because extrapolation in the abiraterone group was from a cut-off of 5% of patients remaining at risk, whereas for the prednisolone group Kaplan–Meier survival data were used without any extrapolation. The ERG noted that within the economic model, the use of Kaplan–Meier data for the prednisolone treatment group resulted in 2% of patients remaining in the pre-progression state. The ERG also noted that the shape of the Kaplan–Meier curve for treatment discontinuation was unusual, with a large proportion of patients discontinuing treatment over a narrow period of a few weeks at approximately 60 days into treatment. The ERG considered that this was unlikely to represent actual disease progression and that true progression would be better represented by fitting a parametric distribution.

6.18 The ERG noted that there was some uncertainty around the most appropriate functions for extrapolating overall survival and progression-free survival in the manufacturer's model. The ERG commented that by using patient-level Kaplan–Meier data from

the trial for overall survival (up to the cut-off) the manufacturer considered all time points. However, when extrapolating overall survival using the constant hazard, only two time points were used (baseline and cut-off hazards). The ERG considered that this approach was less reasonable than informing the extrapolation with all available event data time points which would be the case if a parametric distribution were fitted to the data. The ERG also argued that the use of patient-level Kaplan–Meier data may represent over-fitting and may be less appropriate than employing well-fitting parametric distributions.

6.19 The ERG conducted exploratory analyses around the Kaplan–Meier cut-off points that were used in the manufacturer's extrapolation of progression-free survival and overall survival from the COU-AA-301 trial data (figure 3). For overall survival, the ICERs for abiraterone compared with prednisolone increased for cut-off points between 0 and 2%, decreased between 3 and 8% before peaking again at 9%. Beyond a cut-off point of 10%, the ICERs for abiraterone compared with prednisolone decreased very slightly (see figure 3). The ERG noted that varying the cut-off points used to extrapolate progression-free survival for the abiraterone treatment group between 0 and 10% had a very small impact on the ICERs. The ERG noted that the 5% cut-off point used in the manufacturer's base-case analysis resulted in the lowest ICER for abiraterone compared with prednisolone.

Figure 3 ICERs for abiraterone compared with prednisolone according to Kaplan–Meier curve cut-off for extrapolation of overall and progression-free survival



6.20 The ERG conducted further exploratory analyses to assess the impact of using alternative parametric functions to extrapolate overall survival and progression-free survival beyond the Kaplan–Meier cut-off points in the COU-AA-301 trial. In response to requests from the ERG for clarification, the manufacturer indicated that the Weibull distribution was the best parametric fit for overall survival in the abiraterone group, the log-normal distribution for overall survival in the prednisolone group, and the log-logistic distribution for progression-free survival for both abiraterone and prednisolone. The ERG noted that when these were applied to the manufacturer's economic model, the overall survival curve for prednisolone crossed the overall survival curve for abiraterone at the 49th cycle time point. Therefore, the ERG applied the abiraterone overall survival curve to the prednisolone treatment group beyond this time point. As a result, the manufacturer's ICER for abiraterone compared with prednisolone increased to £63,942 per QALY gained.

6.21 The ERG agreed with the manufacturer that the log-normal distribution should not be used to extrapolate overall survival because it exhibited a long tail that resulted in a proportion of patients with clinically implausible long survival. The ERG also noted that, when the log-logistic distribution was fitted to treatment discontinuation for the abiraterone treatment group, the resulting curve crossed the extrapolated part of the overall survival curve (from the manufacturer's base case) so that some patients were still in the pre-progression state when they died, which was also clinically implausible. The ERG considered that the Weibull distribution should be used to estimate overall survival and progression-free survival in both treatment groups rather than the exponential distribution used by the manufacturer. However the ERG acknowledged that both models were based on data associated with considerable uncertainty. When the Weibull parametric distribution was fitted to overall survival in both treatment groups and progression-free survival was extrapolated using constant hazard in the abiraterone treatment group, the ICER for abiraterone compared with prednisolone was £56,339 per QALY gained. When the Weibull parametric distribution was fitted to overall survival and progression-free survival in both treatment groups, the ICER for abiraterone compared with prednisolone was £58,116 per QALY gained (see table 8 for further details).

Table 8 Additional ERG sensitivity analyses for extrapolation of overall survival and progression-free survival

	Overall survival		Progression-free survival		ICER versus	
	Abiraterone	**Prednisolone**	**Abiraterone**	**Prednisolone**	**Prednisolone**	**Mitoxantrone**
Base case	KM, 10%, h(t)=k	KM, 10%, h(t)=k	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£52,851	£43,437
1	Weibull	Weibull	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£56,339	£49,691
2	Weibull	Weibull	Weibull	KM, 0%, h(t)=1	£57,111	£50,191
3	Weibull	Weibull	Weibull	Weibull	£58,116	£51,279

4	Weibull	Log-normal (truncated)	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£64,159	£56,691
5	Weibull	Log-normal (truncated)	Weibull	Weibull	£66,820	£59,157
6	Weibull	Weibull	Log-logistic	Log-logistic	£56,211	£49,984
7	Weibull	Log-normal (truncated)	Log-logistic	Log-logistic	£63,942	£57,057
8	Log-normal	Log-normal	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£44,578	£39,425
KM – Kaplan Meier, x% KM data cut, h(t)=k from baseline to data cut assumed for extrapolation beyond data cut Log-normal (truncated) assumed to follow abiraterone overall survival Weibull curve at crossover at cycle 49						

6.22 In addition to fitting the Weibull distribution to estimate overall survival and progression-free survival, the ERG made further minor changes to cost and utility parameters in the economic model. These included revisions to administration costs in order to reflect oncology outpatient consultation costs, follow-up chemotherapy administration costs for mitoxantrone, variation in the average body surface area for mitoxantrone and changes to the percentages of patients receiving biphosphonates following progression. Further corrections were made to reflect the manufacturer's regression analysis of the utility for progression-free survival while receiving prednisolone. As a result of these changes, mitoxantrone continued to be extendedly dominated whereas the ERG's base-case ICER for abiraterone compared with prednisolone increased to £60,084 per QALY gained.

6.23 The ERG conducted additional one-way sensitivity analyses for this revised base-case model. Sensitivity analyses with variation of the costs for unplanned medical resource use resulted in ICERs for abiraterone compared with prednisolone ranging from £60,492 to £67,554 per QALY gained. Sensitivity analyses with variation in utility estimates resulted in ICERs for abiraterone compared with prednisolone ranging from £63,281 to £72,469 per QALY gained. When overall survival for prednisolone was

extrapolated using the truncated log-normal distribution, the ICER for abiraterone compared with prednisolone was £70,217 per QALY gained. Mitoxantrone continued to be extendedly dominated in all sensitivity analyses. A summary of the ERG's exploratory sensitivity analyses for the revised base-case model are presented in table 9.

Table 9. Summary of the ERG's exploratory one-way sensitivity analyses for the revised base-case model

Input parameter	Alternative values	ICER for abiraterone versus prednisolone
Baseline		£60,084
Overall survival approach	Log-normal for prednisolone	£70,217
Unplanned progression-free survival MRU	£106 per week	£67,554
Survival with progression MRU	Fixed cost	£60,492
Utility gain abiraterone versus prednisolone	[redacted]	£65,911
Utility gain abiraterone versus prednisolone	[redacted]	£63,281
Utility prednisolone pre-progression	[redacted]	£72,469
Utility post-progression	[redacted]	£63,326
Utility prednisolone pre-progression, post-progression	0.715, 0.645	£67,140
MRU, medical resource use		

6.24 The ERG noted that the manufacturer applied a half cycle correction to direct drug costs and other ongoing costs in the base-case model. The ERG argued that, although this is appropriate for ongoing costs such as adverse reactions which may be spread over a 3-week cycle, this is less appropriate for direct drug costs which are usually incurred at the start of the cycle. The ERG also noted that the abiraterone pack size (30 days' treatment) was not consistent with the 3-week cycle length used in the model, which may have underestimated any possible

drug wastage. To account for this, the ERG argued that the curve for survival on treatment should be revised from a 3-weekly cycle to a daily cycle. When the ERG made these changes to the revised base-case model, there were higher incremental costs for abiraterone and an increase in the ICER by approximately £2500 per QALY gained for abiraterone compared with prednisolone.

7 End-of-life considerations

Criterion	Manufacturer's submission	ERG's assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The control arms of the TROPIC and COU-AA-301 trials indicate that after first-line docetaxel treatment patients have a short life expectancy of approximately 1 year	Not applicable
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Abiraterone offers men with hormone-refractory metastatic prostate cancer a 4.6-month increase in median overall survival compared with best supportive care. The economic model estimates that the mean overall survival that could be expected for patients in England and Wales would be [redacted] years or [redacted] months	The ERG presented alternative estimates of mean overall survival for abiraterone, which used the Weibull distribution to extrapolate overall survival beyond the COU-AA-301 trial period. This resulted in a mean undiscounted overall survival gain for abiraterone of [redacted] years ([redacted] months)
The treatment is licensed or otherwise indicated for small patient populations	Of the 4400 patients with hormone-refractory metastatic prostate cancer estimated to receive docetaxel in the UK, approximately 75%	Not applicable

	would be eligible for treatment with abiraterone (3300 patients). It is estimated that no more than 50% of these patients would actually receive treatment with abiraterone	

8 Equalities issues

8.1 Consultees highlighted that prostate cancer is more common in men over 60 years and that in the UK African-Caribbean men are three times more likely to develop prostate cancer than white men of the same age. Consultees also noted that men from lower socioeconomic groups are less likely to survive prostate cancer than men from more affluent backgrounds. Consultees further commented that it is important to ensure that these men are not denied access to abiraterone (if approved by NICE) because of factors related to their age, ethnicity and/or socioeconomic status. It is also understood that people who have proposed, started or completed male to female gender reassignment can develop prostate cancer and therefore this appraisal refers to people rather than men.

9 Innovation

The manufacturer considers abiraterone an innovative technology that offers a step change; that is, it will alter the treatment pathway for patients whose disease progresses after chemotherapy and where there are currently no treatment options to extend survival or delay disease progression that are supported by NICE guidance.

Abiraterone offers a significant survival advantage over best supportive care and improves or maintains patient quality of life. The manufacturer also commented that, in contrast to intravenous treatments used in clinical practice in the UK in this patient population, abiraterone treatment can be taken orally at home, without the medical resource utilisation of healthcare professional time and medical equipment associated with intravenous administration.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Prostate cancer: diagnosis and management. NICE clinical guideline 58 (2008). Available from http://guidance.nice.org.uk/CG58
- Intraoperative red blood cell salvage during radical prostatectomy or radical cystectomy. NICE interventional procedure guidance 258 (2008). Available from http://guidance.nice.org.uk/IPG258
- Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. NICE technology appraisal guidance 101 (2006). Available from http://guidance.nice.org.uk/TA101
- Laparoscopic radical prostatectomy. NICE interventional procedure guidance 193 (2006). Available from http://guidance.nice.org.uk/IPG193
- Crytotherapy as a primary treatment for prostate cancer. NICE interventional procedure guidance 145 (2005). Available from http://guidance.nice.org.uk/IPG145
- Crytotherapy for recurrent prostate cancer. NICE interventional procedure guidance 119 (2005). Available from http://guidance.nice.org.uk/IPG119
- High-intensity focused ultrasound for prostate cancer. NICE interventional procedure guidance 118 (2005). Available from http://guidance.nice.org.uk/IPG118

Under development

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

- Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Technology appraisal in preparation. Earliest anticipated date of publication February 2012.