NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy

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 COU-AA-302 trial, people with metastatic hormone relapsed prostate cancer were considered to be asymptomatic or mildly symptomatic. The trial was not specifically designed to exclude people who may receive docetaxel in clinical practice.

  Would the participants meeting the eligibility criteria for COU-AA-302 in the UK receive docetaxel or would they receive best supportive care?

- The COU-AA-302 trial defined a stringent p value for the endpoint of overall survival for interim analyses. The study stopped before the estimate for survival reached statistical significance. What implication has this for the interpretation of the results?
- In COU-AA-302 people could switch to docetaxel on disease progression defined by radiographic progression or unequivocal clinical progression

  Does this reflect the time point when people would start docetaxel in clinical practice?

- There is limited evidence for whether treatment with abiraterone before docetaxel affects benefits from subsequent docetaxel treatment: Is docetaxel similarly effective or less effective after abiraterone than after watchful waiting?
- The original statistical plan for COU-AA-302 included 2 interim analyses for overall survival at 15% at 50% of the number of deaths required to detect a statistically significant difference between the treatment arms; this was changed to 3 interim analyses after the start of the study (after 15%, 40% and 55% of the number of deaths required to detect a difference).
- Page 17 of the manufacturer submission notes that after the 1st analysis of radiological progression free survival, the study continued to collect data of rPFS but 'it was no longer independently reviewed'. What implication has this for the interpretation of the results?

Cost effectiveness.

- The manufacturer's model is a discrete event simulation model and therefore different from the Markov model used in the appraisal of abiraterone after docetaxel.
- The model structure does not allow the possibility of dying before treatment with docetaxel (while receiving abiraterone or best supportive care prior to progression) or during post docetaxel treatments.
- The manufacturer developed a number of equations to reflect time spent on different treatments at different points in the course of treatment. These equations included adjustment for patients' baseline characteristics that affected their risk of having an event such as progressing and stopping treatment or dying (covariates). The ERG notes that:
  - The baseline characteristics which were selected to be tested as candidate covariates varied between prediction equations and the manufacturer did not provide a rationale for this
  - The same equation is used in both treatment arms and an adjustment is made for treatment, apart from one exception: for 'time from abiraterone or best

supportive care end to death' separate equations were derived for the abiraterone and best supportive care arm.

  - The modelling used only data from patients for whom data on all potential covariates were available. This was a subset of 83% of the manufacturer's ITT population.

- The manufacturer performed a survey to determine utility values of people who were mildly or asymptomatic before chemotherapy, symptomatic before chemotherapy, on chemotherapy or post chemotherapy which was not stratified by treatment. The manufacturer applied a utility increment to abiraterone taken before docetaxel based on FACT-P scores in COU-AA-302 (using a FACT-P to EQ5D mapping algorithm). The ERG noted that abiraterone was associated with more adverse events than best supportive care. The manufacturer did not adjust utility values (derived from the survey) for people who received active treatment post chemotherapy.
    - Is it possible to have better utility with a treatment associated with more adverse events?
    - The reference used by the manufacturer to the FACT-P to EQ5D mapping algorithm is a conference abstract. Has the algorithm been validated?
    - Would the utility value post-docetaxel be expected to differ between people who went on to receive an active treatment or best supportive care?
- In the current model, the ERG noted that the estimated survival following docetaxel treatment in both the abiraterone and best supportive care arms is much shorter than in the model used in TA 259 (abiraterone after docetaxel). In TA 259 survival with abiraterone taken after docetaxel was [redacted] years and with best supportive care was [redacted] years. In the current submission the survival with abiraterone taken after docetaxel (in people who received best supportive care rather than abiraterone before docetaxel) was [redacted] years and survival with best supportive care after docetaxel (in people who received abiraterone rather than best supportive care before docetaxel) was [redacted] years.

- The ICER is sensitive to the choice of extrapolation used in the prediction equations. The ERG found that using a Weibull to estimate some of the equations led to a higher ICER than using the log-logistic or log-normal curve used in by the manufacturer.
- The manufacturer suggested that abiraterone treatment given before docetaxel meets the criteria for end of life medicines.
  - The manufacturer provided an estimated life expectancy in the population receiving best supportive care of approximately 30 months based on data from COU-AA-302 and between 9 and 27 months from European Association of Urologists guidelines.
  - According to the ERG 'The manufacturer did not provide a mean survival estimate for both groups or mean survival gain, despite explicit questions in the clarification letter'. Instead the manufacturer provided a median overall survival gain of 5.2 months (from COU-AA-302).
  - The manufacturer estimated there would be around 7172 people eligible for abiraterone (both indications) in England and Wales in 2014.

  Have the criteria for end of life that is been met?
- Abiraterone is recommended following docetaxel in technology appraisal 259. Are there any additional benefits associated with receiving abiraterone earlier in the treatment pathway (before docetaxel rather than after docetaxel) that have not been captured in the QALY calculation?

1 Background: clinical need and practice

1.1 Prostate cancer develops in the prostate, a gland in the male reproductive system. The cause of prostate cancer involves both environmental and genetic factors.

1.2 In England, there were over 34,890 people newly diagnosed with prostate cancer in 2010 and there were over 9,100 deaths from prostate cancer in 2011. The incidence of prostate cancer increases with age.

1.3 Approximately 55% to 65% of people with prostate cancer develop metastatic disease; that is, the cancer spreads to other parts of the body.

In over 90% of people with metastases, the disease will initially respond to standard hormonal therapy, but eventually become resistant. This condition is described either as castration resistant prostate cancer, androgen-independent prostate cancer or hormone relapsed prostate cancer.

1.4 NICE clinical guideline 175 (‘prostate cancer’) states that once prostate cancer metastasises, the objective of treatment is to delay progression of the cancer. Stopping the body making testosterone using hormonal therapies can slow the growth of the cancer, or shrink it. Standard hormonal treatments for metastatic disease include orchidectomy (surgical removal of the testes, also known as surgical castration) or gonadotrophin-releasing hormone analogue such as goserelin, leuprorelin or triptorelin (known as medical castration). Physicians offer corticosteroid treatment third line. For metastatic hormone relapsed prostate cancer, NICE technology appraisal 101 recommends docetaxel as a treatment option for hormone-refractory prostate cancer for people with a Karnofsky performance-status score of 60% or more. Abiraterone in combination with prednisolone or prednisone is recommended as a treatment option for the treatment of adults with castration resistant metastatic prostate cancer if their disease has progressed on or after only one docetaxel-containing chemotherapy (technology appraisal guidance no. 259). Enzalutamide post-docetaxel is currently being appraised. The Appraisal Consultation Document recommended enzalutamide after docetaxel therapy if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme, but was not recommended after treatment with abiraterone. Final guidance on enzalutamide is expected for June 2014. Cabazitaxel in combination with prednisone or prednisolone is not recommended for treatment after a docetaxel containing regimen (technology appraisal guidance no. 255).

2 The technology

2.1 Abiraterone acetate (Zytiga, Janssen) is a selective androgen synthesis inhibitor which works by blocking cytochrome P17. It blocks androgen production in the testes, adrenal glands and in prostatic tumour tissue. It is administered orally in combination with prednisolone or prednisone. It is indicated for the treatment of metastatic castration resistant (hormone relapsed) prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. It is also indicated 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 adverse reactions for abiraterone: urinary tract infection, low blood potassium levels (hypokalaemia), high blood pressure and peripheral oedema (swelling of the limbs due to fluid retention) which are seen in more than 1 in 10 patients and also cardiac disorders, hepatotoxicity and fractures. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of abiraterone is £2,930 for 120 tablets (excluding VAT; British national formulary [BNF] 67). Abiraterone is administered as a single dose of 1 g per day, taken as four 250-mg tablets. The manufacturer of abiraterone (Janssen) has agreed a patient access scheme with the Department of Health. This involves a single confidential discount applied to the list price of abiraterone. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. This is the same discount that was applied in the economic evaluation for technology appraisal guidance no. 259 (abiraterone for castration resistant metastatic prostate cancer

previously treated with a docetaxel-containing regimen) that is, 30 days of treatment costs [redacted].

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 acetate in combination with prednisone or prednisolone within its licensed indication for the treatment of metastatic, castration-resistant prostate cancer in people who have not been previously treated with chemotherapy.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with metastatic hormone relapsed prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated	As scope except manufacturer considers men-only
Intervention	Abiraterone acetate in combination with prednisone or prednisolone	
Comparators	• Docetaxel • Best supportive care (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies and corticosteroids)	• Best supportive care only

The manufacturer does not consider docetaxel to be a comparator in the intended patient population because:

- Abiraterone is licenced for people with hormone relapsed prostate cancer who are mildly or asymptomatic while docetaxel is generally reserved for symptomatic patients.

- There is a lack of clinical evidence supporting the use of docetaxel in a truly asymptomatic or mildly symptomatic patient population and there is no evidence that starting chemotherapy when the patient is still asymptomatic is more effective than waiting until the patient is more highly symptomatic.

The ERG considered that as the regulatory indication is for people with metastatic hormone relapsed prostate cancer for which chemotherapy is not yet clinically indicated, so it was reasonable that the manufacturer did not consider docetaxel as a comparator. However, the ERG noted that defining who receives chemotherapy on the basis of symptom severity was not clear cut. This was highlighted in the final Scope issued by NICE for this appraisal which stated: 1) recommendations in guidance such as NICE technology appraisal 101 'docetaxel for the treatment of hormone-refractory metastatic prostate cancer' include people who are asymptomatic or mildly symptomatic; 2) clinicians have stated that docetaxel is increasingly used for a patient group who are asymptomatic or mildly symptomatic in clinical practice; 3) there is a lack of clear clinical criteria to identify the patient group in the CHMP indication. The ERG interpreted the indication to reflect that the population who would receive abiraterone would then go on to receive docetaxel. The ERG therefore determined that the key comparison is whether abiraterone followed by docetaxel is more effective than best supportive care followed by docetaxel.

The manufacturer stated that prednisone or prednisolone alone can be considered best supportive care.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	• Overall survival • Progression-free survival including radiographic progression-free survival • Response rate • Prostate specific antigen (PSA) response • Adverse effects of treatment • Health-related quality of life	The following outcomes were prespecified in the protocol • Co-primary: OS, rPFS • Secondary: times to opiate use, chemotherapy, ECOG PS deterioration, PSA progression • Other: objective response rate, duration of response, health related quality of life, time to progression, time to analgesic progression • Safety adverse effects, serious adverse events, laboratory tests.

The ERG commented that radiographical progression free survival (rPFS) is not an established end point in metastatic prostate cancer. This is the first time that rPFS has been used as a co-primary end point in a clinical trial of prostate cancer in this setting and it is not clear if a rPFS benefit translates into an overall survival benefit.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	

4 Clinical-effectiveness evidence

4.1 The manufacturer carried out a systematic review and identified 3 studies which had assessed abiraterone used after androgen deprivation therapy but before chemotherapy. Two of these were open label single arm studies (COU-AA-001 and COU-AA-002) and investigated dose and

safety; the third one was a double blind randomised placebo-controlled trial (COU-AA-302) and forms the basis for the clinical effectiveness evidence presented in the manufacturer's submission.

4.2 COU-AA-302 compared abiraterone in combination with oral prednisone/prednisolone (referred to hereafter as AAP) with placebo plus prednisone/prednisolone only (referred to hereafter as PP) in 1088 people; 546 people were allocated to AAP (1 g per day with 5 mg prednisone/prednisolone twice daily) and 542 people were allocated to placebo and PP 5 mg twice daily. A patient in the trial stopped abiraterone or placebo at disease progression, if not already stopped for another reason (e.g. adverse effects). The trial had a co-primary endpoint of radiographic progression free survival (PFS) and death (overall survival, OS). The manufacturer defined the overall level of significance for the trial (0.05) between PFS (0.01) and OS (0.04). After disease progression, patients in the trial were followed up for up to 60 months after treatment discontinuation or until the patient was lost to follow up, or withdrew consent. The original statistical plan called for a single pre-planned analysis for PFS after 378 events had accumulated, and included for overall survival 2 interim and 1 final analysis. The first interim analyses was planned to coincide with the analysis for PFS and 15% of deaths required to find a difference between the two treatment arms (15% of 773 events), the second when 50% of the deaths required to find a difference had occurred (50% of 773 events) and the final when 773 events had occurred. The manufacturer amended the protocol so that the overall survival (OS) analyses included analyses after 15%, 40%, 55% and a final analysis of 100% of the events required to find a difference. The study statisticians assumed proportional hazards, a power of 85%, and a 2-tailed statistical test. Because of the repeated analysis of OS, the trials statisticians set the p value at which one could consider the results 'statistically significant' at $p<0.0001$, 0.0005, 0.0034 and 0.040 for each of the 4 analyses respectively. The manufacturer's submission presented data from the 2nd interim analysis (20/12/2011) and the 3rd

interim analysis (22/05/2012). Study COU-AA-302 was stopped early (between the 2nd and 3rd interim analyses) by the Independent Data Monitoring Committee (IDMC) because of a 'highly significant advantage' for patients receiving AAP despite the p value for OS not meeting the criteria for statistical significance. At this point the investigators unblinded the study and 3 people crossed over from PP to AAP. The 4th analysis had not been carried out at the time of the submission.

4.3 COU-AA-302 included patients with metastatic hormone-relapsed prostate cancer who were asymptomatic or mildly symptomatic after androgen deprivation therapy had failed, and for whom chemotherapy was not yet clinically indicated. Patients were classed as asymptomatic or mildly symptomatic if they had a brief pain inventory (BPI) score of 0 to 3 reflecting their worst pain on a scale of 0-10 in last 24 hours. A score of 0-1 means being asymptomatic and 2-3 mildly symptomatic. Patients also had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. In its response to clarification questions from NICE, the manufacturer stated that the study was not designed to include only people who would not yet receive docetaxel in clinical practice, and that regulators defined the population now specified in the marketing authorisation on the basis of the study results. The manufacturer stated that some of the patients included in the trial would likely have received docetaxel in the UK (see table 13 on pages 53 to 54 of manufacturer's submission for full inclusion and exclusion criteria in COU-AA-302), but did not provide an estimate of the proportion of patients in COU-AA-302 that were eligible for docetaxel in clinical practice. In COU-AA-302 92.5% and 92.3% of people had a brief pain inventory score of 3 or less in the AAP and PP arm, respectively. See table 1 below for full breakdown of patient characteristics in COU-AA-302.

Table 1: Characteristics of participants in the RCT by randomised group (ITT) (Table 14 manufacturer's submission page 53 [page 54 hard copy])

COU-AA-302 **Baseline characteristic**	**AAP** **(N=546)**	**PP** **(N=542)**
Age, years, mean (SD)	70.5 (8.8)	70.1 (8.7)
Male, %	100	100

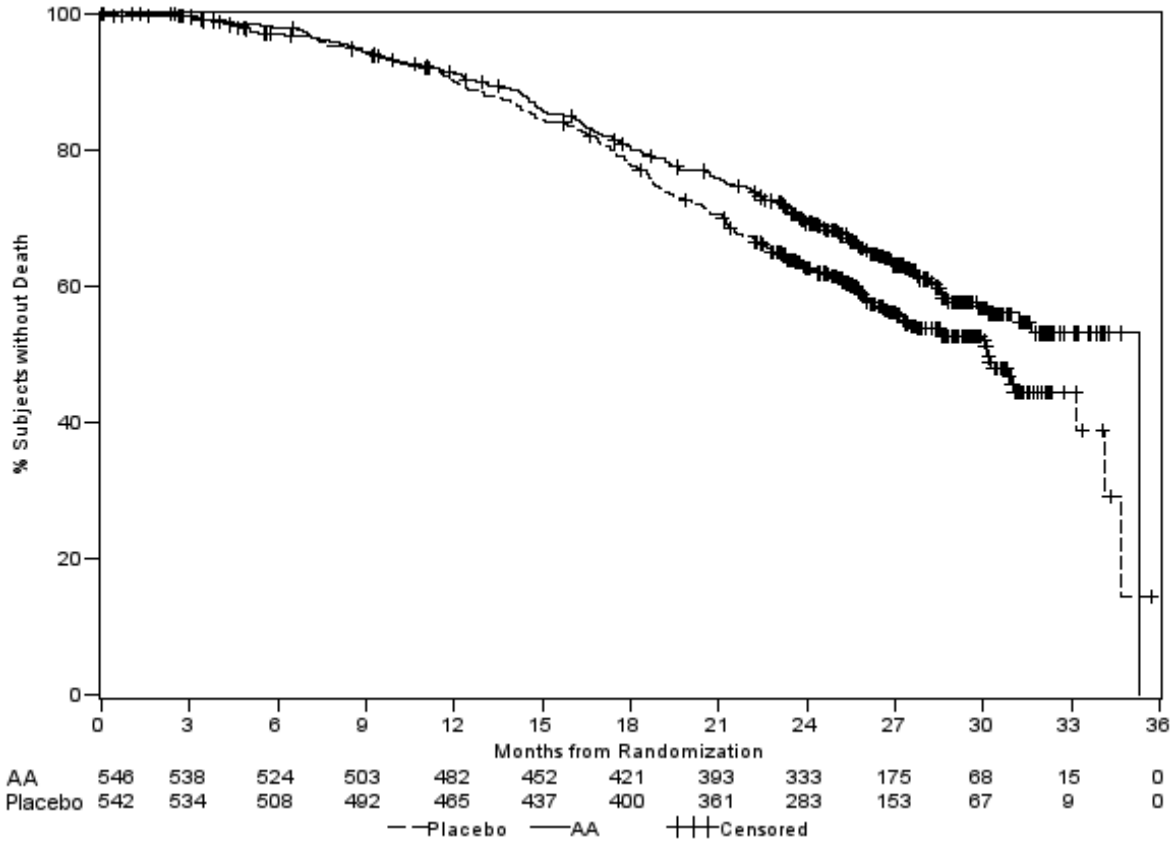
White race N n (%)	 545 520 (95.4)	 540 510 (94.4)
Weight, kg N Mean (SD)	 527 88.5 (15.1)	 520 89.6 (17.0)
Height, cm N Mean (SD)	 539 174.7 (7.5)	 536 175.2 (7.9)
Time from initial diagnosis to first dose, years N Mean (SD)	 542 6.7 (4.9)	 540 6.5 (4.8)
PSA at initial diagnosis, ng/mL N Mean (SD)	 470 174.0 (540.4)	 454 219.7 (888.8)
Baseline PSA, ng/mL N Mean (SD)	 546 133.4 (323.6)	 539 127.6 (387.9)
TNM stage at initial diagnosis, n (%) Stage I Stage II Stage III Stage IV Incomplete reporting	 1 (0.2) 86 (15.8) 52 (9.5) 201 (36.8) 206 (37.7)	 2 (0.4) 70 (12.9) 63 (11.6) 191 (35.2) 216 (39.9)
Gleason score at initial diagnosis, n (%) N <7 7 ≥8	 488 65 (13.3) 160 (32.8) 263 (53.9)	 508 64 (12.6) 190 (37.4) 254 (50.0)
Extent of disease, n (%) N Bone Bone only Soft tissue or node Bone, soft tissue, or node Other	 544 452 (83.1) 274 (50.4) 267 (49.1) 544 (100.0) 4 (0.7)	 542 432 (79.7) 267 (49.3) 271 (50.0) 542 (100.0) 7 (1.3)
Baseline BPI-SF #3 pain score (worst pain over last 24 hours), n (%) N 0–1 2–3 ≥4 Mean (SD)	 539 370 (68.6) 129 (23.9) 40 (7.4) 1.2 (1.7)	 534 346 (64.8) 147 (27.5) 41 (7.7) 1.2 (1.6)
ECOG PS, n (%) 0 1	 413 (75.6) 133 (24.4)	 409 (75.5) 133 (24.5)
Previous prostate cancer therapy, n (%) N Surgery Radiotherapy Hormonal Orchiectomy Other	 544 256 (47.1) 283 (52.0) 544 (100.0) 20 (3.7) 82 (15.1)	 542 244 (45.0) 303 (55.9) 542 (100.0) 24 (4.4) 63 (11.6)

BPI-SF, brief pain inventory short form; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PS, performance status; PSA, prostate-specific antigen; RCT, randomised controlled trial; SD, standard deviation; TNM, tumour–node – metastasis.

4.4 The median treatment duration in COU-AA-302 was 13.8 months in the AAP arm and 8.3 months in the PP arm. Treatment was continued until disease progression (defined by radiographic progression or unequivocal clinical progression; e.g. need for alternative cancer therapy) or if the patient had side effects, initiated a new anticancer treatment, received prohibited medications or if the patient withdrew their consent to participate in the trial. At the 3rd interim analysis 77.3% of people in the AAP arm and 89.3% of people in the PP arm had stopped treatment, the majority of people stopped treatment because of disease progression; 45 people (8.3%) in the AAP arm and 33 people (6.1%) in the PP arm stopped treatment because of an adverse event. Sixty four people (11.8%) in the AAP arm and 70 people (14.8%) of people in the PP arm had stopped treatment because of withdrawal of consent to treatment, loss to follow up or for other reasons. For a full breakdown of the reasons for treatment discontinuation see table 17 manufacturer's submission page 61. At this time 622 people (57% of the whole study population) had gone on to receive subsequent treatments (274 out of 546 people in the AAP arm (50.2%) and 348 out of 542 people in the PP arm [64.2%]). The most common subsequent treatment was docetaxel (approximately 87% of people who received subsequent treatment received docetaxel: 239 people in the AAP arm and 304 people in the PP arm). In the AAP arm 38 people received re-treatment with AAP (after progression on AAP or after docetaxel: 7.0% of all people in the AAP arm). In the PP arm, 78 people (14.4% of all people) received AAP by the time of the 3rd interim analysis, the majority of these people received AAP after docetaxel. For the full breakdown of subsequent treatments please see table 21 page 66 manufacturer's submission and for a summary of the sequence of subsequent treatments people received see Figures 39 and 40 on pages 273 and 274 of the manufacturer's submission.

4.5 The co-primary endpoints in COU-AA-302 were radiographical progression free survival (rPFS defined as time from randomisation to one of the following: progression by bone scan [adapted Prostate Cancer Working Group criteria] or CT or MRI [modified RECIST criteria] or death) and overall survival (OS). CT or MRI and bone scanning were performed every 8 weeks following the first 24 weeks and every 12 weeks thereafter. Radiographic progression free survival was determined by an independent radiologist who was unaware of study group assignments. The intention to treat population was used for all efficacy analyses. In the protocol a statistical analysis was planned for rPFS when 378 rPFS events had occurred and the first OS interim analysis (on 20/12/2010) coincided with this); rPFS continued to be measured after this point. By the 3rd interim analysis 292 (53.5%) of people in the AAP arm and 352 (64.9%) of people in the PP arm had an rPFS event. The median time to event was 16.5 (95% CI 13.8 to 16.8) months in the AAP arm and 8.2 (95% CI 8.0 to 9.4) months in the PP arm (Hazard ratio HR 0.52, 95% CI 0.45 to 0.62, $p<0.0001$). By the 3rd interim analysis 200 (36.6%) people in the AAP arm and 234 (43.2%) of people in the PP arm had died. The median overall survival in the AAP arm was 35.3 months (95% CI 31.2 to 35.3) and 30.1 months (95% CI 27.3 to 34.1) in the PP arm (HR 0.79 95% CI, 0.66 to 0.96, $p= 0.0151$). The p value for difference in median OS ($p=0.0151$) did not meet the p value required for statistical significance ($p=0.0034$).

Figure 1 Kaplan-Meier curve of OS- ITT population (COU-AA-302 study, third interim analysis) from Manufacturer's submission (figure 6 page 68 [both e- and hard copy])



4.6 The manufacturer presented results from the 3rd interim analyses for 4 secondary outcomes. People randomised to AAP showed a longer median time to opiate use for cancer pain (HR 0.71, 95% CI 0.59 to 0.85, p=0.0002); time to initiation of cytotoxic chemotherapy (including docetaxel and cabazitaxel) (HR 0.61, 95% CI 0.51 to 0.72, p<0.0001); time to PSA progression (assessed by trends in serial PSA measurements according to adapted prostate cancer working group criteria (PCWG2) (HR 0.50 95% CI 0.43 to 0.58, p<0.0001) and time to deterioration in ECOG performance status by one or more grade (HR 0.83, 95% CI 0.72 to 0.94, p=0.0052).

Table 2: Secondary outcomes – ITT population (third interim analysis – 22.05.12, 55% data cut-off) (Table 23 manufacturer's submission page 69 [page 71 hard copy]).

Endpoint	Median, months (95% CI)		Difference, months	HR (95% CI)[a]	p value[b]
	AAP	PP			
Time to opiate use for cancer pain	NE (28.3, NE)	23.7 (20.4, 30.3)	NE	0.71 (0.59, 0.85)	0.0002
Time to initiation of cytotoxic chemotherapy	26.5 (23.5, 29.1)	16.8 (14.5, 19.4)	9.7	0.61 (0.51, 0.72)	<0.0001
Time to PSA progression	11.1 (8.5, 11.2)	5.6 (5.4, 5.6)	5.5	0.50 (0.43, 0.58)	<0.0001
Time to deterioration in ECOG PS (≥1 increase)	12.3 (11.3, 14.3)	10.9 (9.5, 11.8)	1.4	0.83 (0.72, 0.94)	0.0052

SOURCE: review article [64] and COU-AA-302 study clinical study report (unpublished) [18].
[a]HR is from stratified proportional hazards model. HR<1 favours AAP.
[b]p value is from a log-rank test stratified by ECOG PS grade (0 or 1).
AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; PP, placebo plus prednisone/prednisolone; PS, performance status; PSA, prostate-specific antigen.

4.7 Response rates including prostate specific antigen response were listed as outcomes in the final scope issued by NICE for this appraisal. These were included under 'other outcomes' in COU-AA-302. The median time to confirmed PSA response was [redacted] months in the AAP arm and was [redacted] in the PP arm ([redacted], p[redacted]). The duration of response (by modified RECIST [Response Evaluation Criteria in Solid Tumours] and bone progression criteria) in people with measurable disease at baseline was [redacted] months in the AAP arm and [redacted] months in the PP arm ([redacted]). The objective response rate (complete or partial response according to RECIST criteria) in the subgroup of people with measurable disease at baseline was higher in people receiving AAP ([redacted]) than in people receiving PP ([redacted] [[redacted] [redacted], p [redacted]) (See the manufacturer's submission page 256, table 135)

4.8 The manufacturer carried out subgroup analysis of rPFS and OS in subgroups specified in an amended statistical plan based on baseline ECOG (0 or 1); BPI (0-1 or 2-3); bone metastasis only at study entry; age, baseline prostate-specific antigen, region (within or outside North America), lactate dehydrogenase and alkaline phosphatase

concentrations. AAP showed a longer time to rPFS than PP in all subgroups. Similarly, median overall survival was longer with AAP than PP in all subgroups, but in some the 95% confidence intervals surrounding the hazard ratio crossed 1 meaning there was no treatment effect (See Figures 7 and 8 on pages 66 and 67 of the manufacturer's submission).

4.9 Upon request during the clarification process the manufacturer provided the data for the subgroup of people who had gone on to receive docetaxel in COU-AA-302. The manufacturer expressed concern that the data requested was a *post hoc* analysis of patients in the COU-AA-302 trial who subsequently received docetaxel and therefore violated the principles of randomisation and in effect selected the people in both treatment arms with the worst prognosis (i.e. those showing quick progression, and requiring chemotherapy earlier). At the time of the third interim analysis 239 out of 546 people in the AAP arm and 304 out of 542 people in the PP arm had received subsequent treatment with docetaxel. Compared with the trial population as a whole, [redacted] (in the whole population 53.5% and 64.9% of people in the AAP and PP arms respectively had experienced a PFS event). The median time to PFS event in the subgroup of people who had received docetaxel at the third interim analysis was [redacted] months (95% CI [redacted]) in the AA arm and [redacted] months [redacted] in the PP arm (in the whole population the median time to PFS was 16.5 months in the AAP arm and 8.2 months in the PP arm). At the third interim analysis people who had gone on to receive docetaxel in the AAP arm had been receiving it for a median of [redacted] months ([redacted]) and people who had gone on to receive docetaxel in the PP arm had been receiving it for a median of [redacted] months ([redacted]). The median overall survival in this subgroup was [redacted]

months ([redacted]) in the AAP arm and [redacted] months ([redacted]) in the PP arm ([redacted]).

Figure 2: Time on docetaxel following AAP (green line) or PP (red line) in people who had started docetaxel by third interim analysis. This figure is commercial in confidence (from manufacturer's response to clarification – additional response to question A3)

[redacted]

4.10 The manufacturer did not submit meta-analyses or mixed treatment analyses as it identified only a single RCT that compared AAP with PP in the treatment of asymptomatic or mildly asymptomatic patients with metastatic hormone relapsed prostate cancer.

4.11 The manufacturer presented safety data from COU-AA-302 safety analyses using the 'safety population' (1082 people from the randomised population who had received at least 1 dose of any study medication). By the third interim analyses the manufacturer reported statistically significantly more people receiving AAP had adverse events and serious adverse events than people receiving placebo (relative risk (RR) 1.02, 95% CI 1.01 to 1.04 for 'treatment emergent' adverse events and RR 1.28, 95% CI 1.07 to 1.54 for serious adverse events. Adverse events reported as 'unlikely, possibly, or related to abiraterone, prednisone/prednisolone or placebo' were classified as drug related

adverse events. No statistically significant difference in the rates of drug-related serious adverse events were reported RR 1.14, 95% CI 0.81 to 1.61 but more people experienced drug related grade 3-4 adverse events with AAP than PP (HR 1.30, 95% CI 1.03 to 1.65) (see table 25 pages 73 and 74 manufacturer's submission). The most frequently reported adverse events affecting 5% or more people were fatigue, back pain, arthralgia, nausea, peripheral oedema, constipation, diarrhoea and were mostly grade 1 or 2. Of these peripheral oedema and diarrhoea were more common with AAP relative to PP (experienced by 26.0% or people with AAP and 20.9% of people with PP. RR 1.24 (1.00 to 1.64). The most frequently reported grade 3 or 4 adverse events were hypertension, back pain and increased alanine aminotransferase (ALT). AAP was associated with more grade 3 or 4 increased ALT (5.5% vs. 0.7%, RR 7.47 95% CI 2.65 to 21.07), increased aspartate aminotransferase (3.1% vs. 0.9%, RR 3.39, 95% CI 1.26 to 9.12) and dyspnoea (breathing difficulty) (2.6% vs. 0.9% RR 2.79, 95% CI 1.01 to 7.69); but less hydronephosis (retention of urine in the kidney causing swelling) (0.2% vs. 1.5% RR 0.12 95% CI 0.02 to 0.99) than PP. The European Public Assessment Report for abiraterone stated that adverse events of special interest for abiraterone included events related to mineralocorticoid excess (hypertension, hypokalaemia, and fluid retention), cardiac disorders and hepatotoxicity. The total incidence of these (grade 1 to 5) was 68.6% in the AAP arm and 51.3% in the PP arm. The most commonly reported subcategories of AEs of special interest were fluid retention (29% AAP, 24% PP), hypertension (22% AAP, 14% PP), cardiac disorders (21% AAP, 18% PP), hepatotoxicity (19% AAP, 11 % PP) and hypokalaemia (17% AAP, 13% PP).

4.12 Health related quality of life of patients in COU-AA-302 was measured using the Functional Assessment of Cancer Therapy (FACT- general (G) and prostate cancer (P) subscale on the first day of treatment and after 12, 20 and 28 weeks and every 12 weeks thereafter as well as at treatment discontinuation. The manufacturer presented the results as

median time to a decrease in 10 or more points, and also as the hazard ratio for AAP compared with PP. The manufacturer presented the median time to a 10 point decrease for both total FACT P score and subscales including the prostate cancer scale (PCS); total outcomes index (TOI); FACT-G; physical well-being (PWB); social/ family well-being (SFWB); emotional well-being (EWB) and functional well-being. People randomised to AAP showed a longer median time to a 10 point decrease in total FACT-P score (12.7 months, 95% CI 11.1 to 14.0) than people randomised to PP (8.3 months, 95% CI 7.4 to 10.6), HR 0.79 (95% CI 0.67 to 0.93, p=0.0046). The analysis of FACT subscales showed a similar effect (See table 24, page 70 of the manufacturer's submission for full results including the subscales).

4.13 The ERG noted that the manufacturer's searches for this appraisal were an update of previous searches undertaken to support an earlier submission relating to technology appraisal 259 (abiraterone after docetaxel). The manufacturer did not change the search strategies. In this update, the manufacturer focused on studies specific to the current indication. The ERG concluded that the COU-AA-302 trial is most likely the best source of clinical evidence and identified no further relevant studies.

4.14 The ERG commented that a large number of people dropped out of COU-AA-302, but that the number of people who dropped out in both treatment arms was similar. The ERG stated that neither the second nor third interim analysis overall survival results met the pre-specified statistical significance levels (that is, $p < 0.0005$ at the second interim analysis and a $p < 0.0034$ at the third interim analysis [see section 4.2]).

4.15 The ERG had concerns about how the manufacturer used data from the FACT-P measure in the submission. The ERG stated that the manufacturer presented the results only as time to event data, and did not provide scores by treatment arm for baseline or follow up. The ERG

commented that the manufacturer stated that ‘the main drivers of reduced health-related quality of life reported by patients with mCRPC are bone pain, fatigue, sexual disturbances and interrupted social relationships’. Of these, the manufacturer only reported time to an increase in pain intensity, (rather than the differences in pain intensity between the two treatment arms). The time to an increase in the worst pain intensity (an increase in baseline BPI score of 30% or more on 2 consecutive occasions) did not differ between the treatment arms (manufacturer’s submission table 137 page 257).

4.16 As the marketing authorisation implies that people after using abiraterone go on to receive docetaxel, the ERG considered that abiraterone followed by docetaxel should be compared with watchful waiting followed by docetaxel. The ERG commented that there is very little evidence regarding how effective docetaxel is after abiraterone. It identified a single arm retrospective study of 35 patients who had received abiraterone followed by docetaxel suggesting that the effectiveness of docetaxel following abiraterone might be ‘seriously reduced’. In their discussion the authors of the study commented that the “activity of docetaxel post-abiraterone appears lower than anticipated and no responses to docetaxel were observed in abiraterone refractory patients”. The ERG considered the data from COU-AA-302 for the subgroup of people who had received docetaxel by the 3rd interim analysis, noting the limitations of this data outlined by the manufacturer (see section 4.9). The ERG commented that although for the whole study population there was a difference in OS with AAP compared with PP (although this did not meet the level of statistical significance pre-specified in the study protocol), [redacted] was seen in the subgroup who had received docetaxel . The ERG suggested that as the median time on docetaxel treatment was [redacted] months in the AAP group and [redacted] months in the PP group this might not be long enough to assess whether the effect of docetaxel is lower after treatment with abiraterone than after best supportive care. The ERG speculated that if the

effectiveness of docetaxel was lower when taken after abiraterone a longer period on docetaxel treatment would result in an even greater difference in relative effectiveness of docetaxel with or without prior abiraterone.

5 Comments from other consultees

5.1 The professional groups explained that people with metastatic castrate-resistant prostate cancer who are asymptomatic or have mild symptoms would either receive: abiraterone (through the cancer drugs fund where this is available), best supportive care (including low dose steroids and further hormonal treatments) or docetaxel. Patients with advanced, symptomatic prostate cancer are considered eligible for chemotherapy/docetaxel. People with a poorer performance status, significant co-morbid factors, advancing age and the presence of asymptomatic disease with slowly rising prostate specific antigen (PSA) levels would not be offered chemotherapy.

5.2 The professional and patient groups stated that docetaxel benefits patients not only by improving survival but also improving symptoms and quality of life benefits. However, a patient group stated side effects of docetaxel include fatigue, increased risk of infection, liver damage, hair loss, numbness of the hands and feet, memory loss and confusion, loss of appetite amongst others. These side effects can be debilitating and some people, particularly if they have no or minimal symptoms, or do not want to consider docetaxel yet. The patient groups commented that the side effects of abiraterone are generally mild and manageable, but can include symptoms such as build-up of fluids in the ankles, headaches, loss of appetite and diarrhoea. The professional groups stated that clinicians must take care when using abiraterone in patients with a history of cardiovascular disease, since a small percentage may develop hypertension and heart failure from the mineralocorticoid effect. Both patient and professional groups commented that as abiraterone acetate is

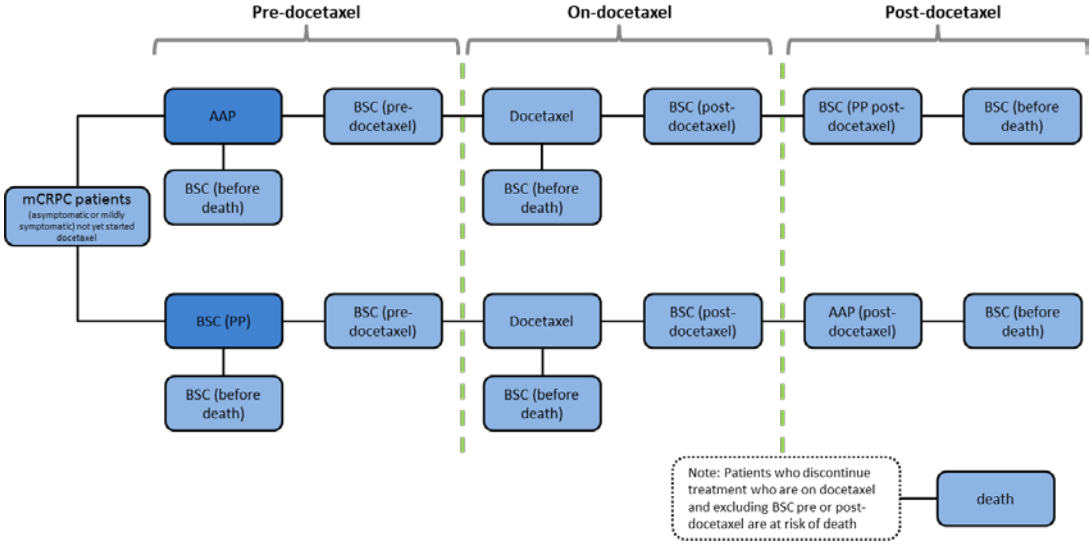
taken as a tablet, patients need not travel to a cancer centre, and will have relatively little impact on service delivery in the clinical setting. . Consultees considered that delaying chemotherapy use is an advantage of abiraterone before docetaxel.

6 Cost-effectiveness evidence

6.1 The manufacturer did not identify any published cost-effectiveness studies directly relevant to the decision problem so it performed its own new analysis. The manufacturer produced an individual time-to-event model (discrete event simulation), tracking patients at an individual level through a sequence of treatments until they reached a maximum age of 100 which it assumed reflects a lifetime horizon. Costs were considered from the NHS and personal social services perspective and a 3.5% discount rate was applied. People entering the model were assigned to either an abiraterone or best supportive care strategy (the prednisone/prednisolone arm of COU-AA-302 was assumed to reflect best supportive care with an active monitoring strategy). People were modelled through 3 treatment phases (pre-docetaxel, on-docetaxel and post-docetaxel). In each treatment phase people could receive active treatment, or receive best supportive care before starting an active treatment, or receive best supportive care with palliative treatment after an active treatment (see Figure 3 below). The model took into account a person's suitability for subsequent treatment after ending an active treatment; for example, if a person's disease progressed, the modelled patients were monitored in a pre-docetaxel best supportive care phase and their suitability to move on to receive docetaxel was assessed. Patients for whom docetaxel would be considered unsuitable (people with a Karnofsky performance status of 60% or more [approximately an ECOG performance status of less than 2]) transitioned to best supportive care and receive no further treatment until death. Likewise, after patients completed treatment with docetaxel patients were monitored for disease progression. When progression occurred, if people fit enough for further treatment, people either received

abiraterone if they had not received it before, or best supportive care. Some people in COU-AA-302 had received cabazitaxel after docetaxel. As cabazitaxel has a survival benefit compared with best supportive care, but is not recommended by NICE (technology appraisal 255), the manufacturer adjusted post docetaxel survival estimates from COU-AA-302 to exclude the survival benefit associated with cabazitaxel. It was assumed that after all treatment options were explored and the disease was progressing best supportive care would evolve into an approach involving palliative care.

Figure 3 Manufacturer's model pathway (figure 10 manufacturer's submission page 86 [page 90 hard copy])



6.2 The model consisted of 17 prediction equations to estimate the time to treatment discontinuation, time to treatment start and time to death within the treatment phases and also to estimate the disease status of the patient at a particular position in the modelled treatment pathway. Parametric curves with the best fit to the survival curves from the ITT population from COU-AA-302 were used to extrapolate this data over a longer time period than the trial. To determine variables which affected the risk of an event or disease status the manufacturer used data from 902 patients out of the 1,088 ITT patient population (83%) who had complete data for the baseline variables of interest. For this, the manufacturer

selected variables (predictors) which had a statistically significant association with the event/outcome of interest at a 10% level of statistical significance. The baseline variables tested for association with the outcome and the variables included in the final prediction equation differed between prediction equations (see manufacturer's tables 146-153 pages 279-282). Two variables which did not meet the 10% level of statistical significance were also included by the manufacturer in the prediction equations. The manufacturer justified this by stating that it was better to be inclusive and in some cases statistical significance may not have been reached because of small patient numbers. The majority of equations were not stratified by treatment, rather the same equation was used in each treatment arm and 'treatment' was used as a predictor. However, for 'time from abiraterone or best supportive care to death' a separate equation was derived for each treatment arm.

Table 3 Summary of the prediction equations used in manufacturer's model

Prediction equations	Distribution
Time to treatment discontinuation	
Time to AAP/BSC (PP) end (table 143 page 279)	Log-logistic (+weibull)
Time from docetaxel start to docetaxel end (table 145 page 280)	Weibull
Time from post-docetaxel treatment start to end (table 147 page 280)	Weibull
Time to treatment start	
Time from AAP/BSC (PP) end to docetaxel start (table 144 page 279)	Log-normal
Time from docetaxel end to post-docetaxel start (table 146 page 280)	Weibull
Time to death	
Time from AAP end to death + Time from BSC (PP discontinuation to death (table 148 page 280)	Weibull (both equations for each treatment arm)
Time to docetaxel start to death (table 149 page 281)	Log-logistic
Time from docetaxel end to death (table 150, page 281)	Weibull
Time from post-docetaxel treatment end to death (table 151 page 281)	Weibull
Patient disease status equations	
ECOG at discontinuation of AAP/BSC (table 152	n/a

page 281-2)	
ECOG at start of docetaxel ((table 152 page 281-2)	n/a
ECOG at docetaxel discontinuation (table 152 page 281-2)	n/a
ECOG at start of post docetaxel treatment (table 152 page 281-2)	n/a
PSA progression at AAP/BSC PP end (table 153 page 282)	n/a
Radiographic progression at AAP/BSC PP end (table 153 page 282)	n/a
Opiate use at AAP/BSCPP end (table 153 page 282)	n/a

6.3 To derive utility values associated with each treatment phase the manufacturer performed an independent study to gather UK specific EQ 5D data over a broader range of treatment phases than the COU-AA-302 study was designed to assess (including the 'on docetaxel' and 'post docetaxel' treatment phases). This 'UK mCRPC patient utility study' was an online survey of 163 men with mCRPC in the UK who had previously taken anti-androgen tablets for more than 1 month but had since stopped (unless they had undergone orchidectomy [surgical castration]). The study was non-comparative and assumed that patients experienced the same utility regardless of the treatment they received provided that they are in the same treatment phase. Patients with mCRPC were divided into the following subgroups.

- Mildly or asymptomatic after failure of androgen deprivation therapy; chemotherapy not yet clinically indicated (N=50)
- Symptomatic after failure of androgen deprivation therapy; chemotherapy clinically indicated but not started (N=50)
- After failure of androgen deprivation therapy; receiving chemotherapy (N=17)
- After failure of androgen deprivation therapy; post chemotherapy, completed 1 or more cycles of chemotherapy (N=46)

For the base case these utility values were supplemented with utility values derived from other sources. The utility value for people who were

receiving best supportive care before death was assumed to be 0.5 based on a published study (Sandblom et al). The manufacturer also added a utility increment for people who received AAP (pre-docetaxel in the AAP arm) [redacted] using utility values derived from mapping FACT-P data from COU-AA-302 to EQ-5D (methods for mapping from FACT-P to EQ-5D are described in the next section). The manufacturer did not apply a utility decrement based on adverse events experienced on different treatments.

Table 4: Summary of the utility values associated with each model phase (Modified from table 42 manufacturer's submission page 113 [page 123 hard copy])

Utilities	Value	SE (distribution)	Source
Post-Androgen deprivation therapy baseline. People asymptomatic or mildly symptomatic but chemotherapy not yet clinically indicated	[redacted]	[redacted]	UK mCRPC patient utility study (a survey of 163 UK men with metastatic hormone relapsed prostate cancer)
AAP on-treatment utility increment (applied to AAP arm)	[redacted]	[redacted]	COU-AA-302 mapping study (mapped EQ-5D from FACT-P scores collected in COU-AA-302)
BSC (pre-docetaxel) , people are symptomatic and chemotherapy is indicated but has not started	[redacted]	[redacted]	UK mCRPC patient utility study
Docetaxel, utility associated with taking chemotherapy	[redacted]	[redacted]	UK mCRPC patient utility study
Post-docetaxel	[redacted]	[redacted]	UK mCRPC patient utility study
BSC (before death)	0.500	0.08	Sandblom et al. 2004 (A population based study of quality of life during the year before death in men with prostate cancer)

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.

6.4 The manufacturer also presented utility values derived from mapping FACT-P to EQ-5D from the data collected in COU-AA-302 (see section 4.12) which it used in a scenario analysis. The manufacturer used data from an observational study of patients with mCRPC in 6 European countries (including the UK) in which both EQ-5D and FACT-P data were available to develop an algorithm to map FACT-P data to EQ-5D using an

ordinary least squares regression model and the UK EQ-5D tariff. The manufacturer applied this mapping algorithm to map FACT-P data from patients in both treatment groups in the COU-AA 302 study to EQ-5D utility values. The manufacturer also considered two further scenarios for utility values. In the first the utility values used were a mixture of utility values derived from the UK mCRPC patient utility study and from FACT-P to EQ-5D mapping. The second scenario applied the utility decrement used in the ongoing enzalutamide appraisal for the end of life (the decrement between 16 to 8 months before death to 8 to 0 months before death) to the post docetaxel utility value derived from the mCRPC utility survey (i.e. [redacted] – 0.085 = [redacted]) in order to determine the best supportive care before death utility value.

Table 5: Results of the FACT-P to EQ-5D Mapping Study and other scenario's assessed (modified from tables 43 and 61 manufacturer's submission pages 115 and 144 [pages 126 and 158 hard copy])

State	FACT-P to EQ-5D mapping		Mixed	BSC (before death) enzalutamide
	Utility value	SE	Utility value	Utility value
Post-ADT baseline (asymptomatic and mildly symptomatic)	[redacted]	[redacted]	[redacted]	[redacted]
AAP on-treatment utility increment	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel utility decrement	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (PP post-docetaxel)	[redacted]	[redacted]		
AAP (post-docetaxel)	[redacted]	[redacted]		
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

AAP, abiraterone acetate plus prednisolone; AE, adverse event; BPI, brief pain inventory; BSC, best supportive care; SE, standard error.

6.5 The manufacturer grouped use of medical resources into 'scheduled' and 'unscheduled'. Scheduled resources included disease-related tests including imaging diagnostic and clinical laboratory tests. To determine the frequency of scheduled follow up appointments over a 3 month period during the pre-docetaxel, on docetaxel, post-docetaxel, best supportive care and palliative care stages of the disease pathway, the manufacturer

surveyed 53 oncologists and 50 urologists. In the model, the manufacturer applied higher resource use for AAP patients than for patients on best supportive care in both the pre- and post-docetaxel setting for the first 3 months of AAP treatment as per the SPC. Thereafter, the manufacturer assumed that patients incur the same costs in both treatment arms. In the base-case analysis, the manufacturer used values provided by oncologists and in scenario analyses the manufacturer used values from urologists (see table 6 below for the frequency of visits and associated costs).

Table 6: Scheduled oncologist medical resource use costs (table 55 manufacturer's submission page 138 [page 151 hard copy])

	Median, £	25th percentile, £	75th percentile, £
AAP	217.22*	129.24	266.77
BSC (PP)	82.40	43.56	158.26
BSC (pre-docetaxel)	82.40	43.56	158.26
Docetaxel	203.46	107.22	248.79
BSC (post-docetaxel)	116.01	47.69	159.14
BSC (PP post-docetaxel)	116.01	47.69	159.14
AAP (post-docetaxel)	198.76*	96.76	223.37
BSC (before death)	39.96	21.54	124.59

*Cost applied for the first 3 months, and then the equivalent cost of BSC (PP) thereafter (section 7.5.4)
AAP, abiraterone acetate plus placebo; AE, adverse event; BSC, best supportive care; MRU, medical resource utilisation; PP, placebo plus prednisolone.

6.6 The manufacturer estimated the frequency of unplanned medical resource use (e.g. adverse events while on treatment) based on data from COU-AA-301 (for post-docetaxel AAP or best supportive care) and COU-AA-302 (for pre-docetaxel AAP or best supportive care). COU-AA-301, the key clinical trial in technology appraisal 259, compared abiraterone in combination with prednisone/prednisolone to prednisone/prednisolone alone in people whose disease had progressed on or after docetaxel therapy and who had an ECOG performance status of 0 to 2. The manufacturer assumed that resource use while on docetaxel would be similar to that experienced while on abiraterone after docetaxel with the addition of the costs of treating grade 3 or 4 adverse events associated with docetaxel. It used the rates of grade 3 and 4 adverse events reported

in the literature to be experienced on docetaxel and consulted it's clinical advisors on the costs of treating such events (see table 36 page100 manufacturer's submission). The manufacturer assumed that patients who receive best supportive care before death incur a similar level of unplanned medical resource use regardless of their previous treatment history. For these people, the manufacturer used the costs associated with medical care from the COU-AA-301 trial. The trial-based unplanned use of resources per month were £93.79 for AAP, BSC (PP) and BSC (pre-docetaxel) and £380.29 while receiving docetaxel, BSC post-docetaxel, abiraterone post docetaxel or BSC before death (table 56 page 138 manufacturer's submission). The manufacturer also applied a one-off cost of £3,598 per patient to account for palliative care in the last 3 months of the best supportive care phase.

6.7 The drug costs used in the model were: [redacted] per month for a 1g daily dose of abiraterone (30.4 doses per month); £2.63 a month for 10mg prednisone/prednisolone taken daily (30.4 doses per month) (applied in both the abiraterone and best supportive care arms.) and £1,550.14 per month for docetaxel (based on a dosing frequency of once every 3 weeks for a patient of average weight (based on the patient characteristics in COU-AA-302) and with a cost of £1,069.50 for a 160 mg vial of docetaxel. An additional administration cost of £214 was applied for docetaxel.

6.8 The manufacturer presented a breakdown of the proportion of people who transitioned through each treatment phase and the duration of time spent in each phase. The manufacturer noted that in both the on-docetaxel treatment phase and the post-docetaxel treatment phase people who had received best supportive care rather than abiraterone before docetaxel gained more QALYs. The manufacturer suggested that this was because people who received best supportive care as their first treatment were more likely to receive docetaxel treatment following disease progression than were patient whose disease had progressed on AAP and would have longer treatment duration with docetaxel and post-docetaxel treatments.

Furthermore, the manufacturer said that people who had received best supportive care rather than AAP before docetaxel could go on to receive an active treatment (AAP) after docetaxel whereas people who received AAP before docetaxel were assumed in the model to have no further active treatments available to them after docetaxel. Tables 7 to 9 below summarise the survival and QALYs gained as people progress through the treatment pathways following initial treatment with AAP or best supportive care before docetaxel.

Table 7: Summary of proportion of patients and respective duration in each treatment phase (table 68 manufacturer's submission page 149 [page 164 hard copy])

Treatment phase	AAP		BSC (PP)	
	% in each treatment phase[a]	Mean duration (years)	% in each treatment phase[a]	Mean duration (years)
Pre-docetaxel				
1st-line active treatment	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel				
Post-docetaxel active treatment[b]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

*Percentage (among the total starting population) who reach each 'state' in the treatment pathway.
[b]AAP arm: BSC (PP post-docetaxel); BSC (PP) arm: AAP (post-docetaxel).

Table 8: Summary of Life Years gained by pre/on/post-docetaxel status (table 69 manufacturer's submission page 150 [page 165 hard copy])

		AAP	BSC (PP)
Total LY gained		[redacted]	[redacted]
Pre-docetaxel survival (Include pre-docetaxel treatment and BSC)	% entered this phase	[redacted]	[redacted]
	Mean survival within this phase of those who entered the phase	[redacted]	[redacted]
On-docetaxel survival	% entered this phase	[redacted]	[redacted]
	Mean survival within this phase of those who entered the phase	[redacted]	[redacted]
Post-docetaxel survival (exclude post-docetaxel BSC)	% entered this phase	[redacted]	[redacted]
	Mean survival within this phase of those who entered the phase	[redacted]	[redacted]

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; LY, life year; OS, overall survival; PP, placebo + prednisolone.

Table 9: Summary of QALY gain by pre/on/post-docetaxel status (table 70 manufacturer's submission page 150 [page 165 hard copy])

	AAP	BSC (PP)	Increment	Absolute Increment, %
Total QALYs	[redacted]	[redacted]	**0.57**	100
Pre-docetaxel QALYs	[redacted]	[redacted]	0.71	124.6
On docetaxel QALYs	[redacted]	[redacted]	–0.10	17.5
Post-docetaxel QALYs	[redacted]	[redacted]	–0.04	7.0

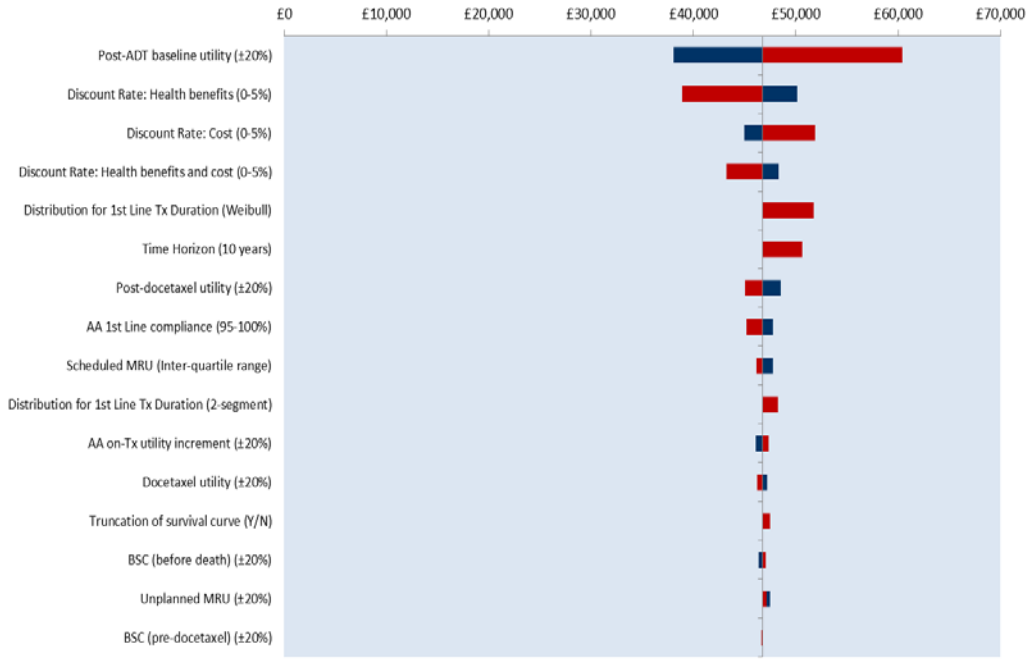
6.9 In the manufacturer's deterministic base case analysis, abiraterone was associated with an incremental cost of £26,404, 0.62 extra life years and 0.57 extra quality adjusted life years (QALYs) compared with BSC. The estimated incremental cost effectiveness ratio (ICER) was £46,722 per QALY gained. The manufacturer did not present a probabilistic ICER but presented the results of a probabilistic sensitivity analysis. This analysis suggested that at £40,000 per QALY gained, abiraterone has a 0% probability of being cost effective. At £50,000 per QALY gained abiraterone has a 38% probability of being cost effective.

Table 10: Base-case results (with PAS) (table 72 manufacturer's submission page 152 [page 167 hard copy])

Technology	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.57	46,722

6.10 The manufacturer performed deterministic 1-way sensitivity analyses. Increasing the post androgen deprivation therapy baseline utility value by 20% to [redacted] had the largest effect and increased the ICER to £60,418 per QALY gained. For full deterministic one way sensitivity analyses see table 73, page 153 manufacturer's submission.

Figure 4 Tornado diagram of 1 way sensitivity analyses (Figure 15 manufacturer's submission page 154 [page 169 hard copy]) Red bars are when the higher values are used blue bars are when the lower values are used.



AA, abiraterone acetate; ADT, androgen deprivation therapy, BSC best supportive care; MRU, medical resource utilisation; N, no; Tx, treatment; Y, yes.

6.11 The manufacturer presented 11 scenario analyses, as summarised below. The scenario without the PAS had a large impact on the ICER; in all other scenario analyses the ICER was between £45,393 to £50,163 per QALY gained.

- Two scenarios explored the assumptions about the use of medical resources, using the urologist estimates rather than the oncologist estimates decreased the ICER to £46,344 per QALY gained, using the combined estimates from the urologists and oncologists decreased the ICER to £46,480 per QALY gained.
- Three scenario analyses explored different utility value assumptions: using utility values from the FACT-P to EQ-5D mapping increased the ICER to £50,163, using the mixed source utility values decreased ICER to £46,114 per QALY gained, and applying the utility decrement used in

the enzalutamide appraisal in order to determine the best supportive care before death decreased the ICER to £46,289 per QALY gained (see section 6.4).

- One scenario analysis applied the cost of dexamethasone rather than prednisolone at all appropriate stages in the model (£0.06 per 10 mg dose). This increased the ICER to £46,929 per QALY gained.
- One scenario analysis varied the prediction equations for post docetaxel survival to generate comparable survival estimates in both the AAP and BSC arms. This reduced the ICER to £45,393.
- Two scenario analyses explored different post-docetaxel treatment options: assuming no active treatments were available post docetaxel increased the ICER to £48,833 per QALY gained, including enzalutamide as a post docetaxel active treatment option for all people who received AAP pre-docetaxel and 56.2% of people who received BSC pre-docetaxel increased the ICER to £48,546 per QALY gained.
- One scenario allowed all people to receive docetaxel irrespective of their ECOG performance status; this increased the ICER to £48,146.

6.12 The ERG considered that it was appropriate for the manufacturer to develop a new model, but did not think using a discrete event stimulation model was the simplest or most transparent approach as it made it more complicated to assess face validity and internal validity than, for example, a Markov model of health states.

6.13 When the ERG ran the model, the ICER for the manufacturer's deterministic base case differed only slightly from that reported by the manufacturer (that is, the ICER was £46,756 per QALY gained rather than £46,722 per QALY gained). The ERG also noted that there was a small error in the cost effective acceptability curves presented by the manufacturer in its submission. The ERG presented a revised summary of the manufacturer's probabilistic sensitivity analysis suggesting that the probability of abiraterone being cost effective assuming £30,000, £40,000

or £50,000 per QALY gained was 0%, 10% and 67% respectively (see page 98 of the ERG report for these corrected results).

6.14 The ERG stated that the model structure lacked face validity as it did not allow the possibility of dying during abiraterone treatment or best supportive care with prednisone/ prednisolone before docetaxel treatment or during post docetaxel treatments. It noted that in COU-AA-302, 5 patients had died before the end of AAP or PP treatment. The ERG requested that the manufacturer provide a model which allowed the possibility of dying during pre- docetaxel AAP and BSC treatment and during post-docetaxel treatment. The manufacturer responded that it was unable to produce the necessary risk equations because of the small number of patients who died while on pre-docetaxel and post-docetaxel treatments and instead clarified that in the model that these patients died the day after they stopped treatment.

6.15 The ERG commented that although the manufacturer stated that the model population was the same as the COU-AA-302 ITT population, the modelled population was in fact a subgroup of this population with complete baseline data for covariates. 186 patients from the ITT population (1088 people) were excluded because of missing baseline data. The manufacturer did not provide the characteristics of this subpopulation. In its clarification response the manufacturer stated that the time to treatment discontinuation and overall survival were not statistically significantly different between the ITT population and the population with complete baseline characteristic data. The ERG did not agree with the manufacturer's statement that model predictions were consistent with the trial results as it was not the ITT population that was used (but a subset) and therefore the model results were probably not fully comparable with the ITT results of the COU-AA-302.

6.16 The ERG considered that using the EQ-5D utility values from the UK mCRPC utility study was the preferred approach given the uncertainty

surrounding the mapped utility values based on the FACT-P responses from COU-AA-302. The ERG considered whether the utility value for the pre-docetaxel treatment phase would be expected to be different between treatment arms. In the base case the ERG noted that the manufacturer had applied a utility increment of [redacted] to the AAP arm relative to the BSC arm and that the manufacturer stated that this was based on the benefits experienced on AAP compared with best supportive care with respect to pain and fatigue. The ERG did not agree with this approach as in COU-AA-302, AAP led to [redacted] (both overall and grade3/4) than BSC and considered it more appropriate to incorporate and apply separate utility decrements for each separate AE in the model. During clarification the manufacturer provided 4 separate scenario analyses in which:

- The utility increment of [redacted] applied to the AAP arm was removed. This resulted in an ICER of £50,120 per QALY gained
- The utility decrements for each separate adverse event were applied separately. This resulted in a ICER of £47,415 per QALY gained
- The per-event costs for AEs for the pre- and post- docetaxel treatment phases were incorporated. This resulted in an ICER of £46,686 per QALY gained.
- Combining the 3 scenarios above resulted in an ICER of £50,880 per QALY gained

The ERG considered whether the post docetaxel utility values would be expected to be different between the two treatment arms. It also considered the consistency of utility values presented for people after docetaxel treatment in the current submission and in the manufacturer's submission for technology appraisal 259. Following the clarification requests the manufacturer provided a scenario in which the post docetaxel baseline utility value was 0.780 derived from FACT-P to EQ5D mapping using data from COU-AA-301 (and equivalent to the post-docetaxel utility value in TA 259) was used and a post-docetaxel utility

increment of 0.046 was applied by either adding it to the baseline utility value of 0.78 for AAP post docetaxel in the BSC arm or subtracting it from 0.78 for BSC post docetaxel in the AAP arm). These analyses resulted in ICERs of between ICERs of £48,316 and £47,936 respectively.

6.17 The ERG noted that the post docetaxel survival in the current model was much lower than at the same point in the care pathway in technology appraisal 259 which had appraised the cost effectiveness of abiraterone taken after docetaxel compared with best supportive care. See table 11 below. The ERG modified the prediction coefficients for the 'time from post-docetaxel treatment continuation to death' equation so that the post docetaxel survival was similar to that estimated in technology appraisal 259. The effect of this scenario alone was not tested on the manufacturer's base case, rather it was tested in combination with other assumptions that comprised the 'ERG exploratory base case' see sections 6.18 and 6.19

Table 11: Comparison of post-docetaxel survival with TA 259 (table 5.16 ERG report page 100)

Undiscounted LYs	AA[a]	BSC (PP)[a]	Difference
TA 259 (post-docetaxel N=832)	[redacted]	[redacted]	[redacted]
Current TA (post-docetaxel N=104)[b,c]	[redacted]	[redacted]	[redacted]

Abbreviations: LY, life year; AA, abiraterone acetate; BSC, best supportive care; PP prednisone/prednisolone.

[a] Post-docetaxel treatment; in the current assessment patients treated initially treated with BSC (PP) in the pre-docetaxel phase are eligible for Post-docetaxel treatment with AAP whilst patients treated initially treated with AA in the pre-docetaxel phase are not eligible for retreatment with AA.

6.18 The ERG stated that its preferred base case would include:

- A disutility of 0.046 to be applied in the post-docetaxel phase for patients not on active treatment
- The prediction equations used for time to treatment discontinuation, time to treatment start and time to death to be derived from the full

ITT population in COU-AA-302, to account for treatment effect on risk only and not include other risk predictors based on baseline characteristics (see table 5.17 ERG report page 103 for these equations).

Applying the first assumption (post-docetaxel disutility if not receiving active treatment) to the manufacturer's base case (the recalculated manufacturer's base case see section 6.13) resulted in an ICER of £46,952 per QALY gained. Applying new risk equations based on the ITT population resulted in an ICER of £57,337. The combination of these two scenarios (the ERG's exploratory base case) resulted in an ICER of £57, 668 per QALY gained (table 12). A summary of the life year and QALY gain by treatment phase (pre/on/post docetaxel) status is given in table 13 below. The ERG performed a probabilistic sensitivity analysis and found that at £30,000, £40,000 or £50,000, the probability of abiraterone being considered cost effective relative to best supportive care would be 0%, 0% and 6% respectively.

Table 12 Overview of additional analyses undertaken by the ERG to determine the 'ERG exploratory base case' (table 6.1 page 108 ERG report)

Technology	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER, £/QALY
MS Base case					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	26,404	0.57	46,722
Recalculated MS Base case (see section 6.13)					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	26,423	0.57	46,756
Scenario 1: Post-docetaxel on treatment disutility applied for people not on active treatment					
BSC (PP)	[redacted]	[redacted]			
AAP	[redacted]	[redacted]	26,423	0.56	46,952
Scenario 2:Updated prediction equations based on ITT population using treatment as only covariate					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	24,757	0.43	57,337
ERG exploratory base case (combines scenario 1 and 2)					
BSC (PP)	[redacted]	[redacted]	–	–	–

AAP	[redacted]	[redacted]	24,757	0.43	57,688

Table 13: Summary of life year and QALY gain by pre/on/post docetaxel status using the assumptions in the 'ERG exploratory base case'

	AAP		BSC (PP)		Difference	
	LY	QALY	LY	QALY	LY	QALY
Pre-docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	0.61	0.57
On docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	-0.17	-0.10
Post-docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	-0.04	-0.04
Total	[redacted]	[redacted]	[redacted]	[redacted]	0.40	0.43

6.19 The ERG performed 4 additional sensitivity analyses which it tested in its 'exploratory base case':

- The ERG stated that it was unclear how the manufacturer had applied the negative effect from treatment with cabazitaxel in COU- AA-302 was applied in the model (see section 6.1). Therefore it tested a scenario without adjusting for cabazitaxel use in COU-AA-302. This decreased the ICER to £56,671 per QALY gained
- The ERG assumed that survival after docetaxel was the same as in technology appraisal 259 (see section 6.19). This increased the ICER to £65,515 per QALY gained.
- The ERG used a Weibull model to extrapolate the data for time to discontinuing treatment with abiraterone or BSC, and time to death while on docetaxel treatment. The ERG used this rather than the log-logistic model than the manufacturer had used in the base case because the log-logistic distribution is often criticised for its long tail which may result in an unrealistic survival benefit. This increased the ICER to £74,803 per QALY gained.
- The ERG used a Weibull model to extrapolate time to stopping docetaxel treatment and time to death after post-docetaxel active treatment rather than a log-normal distribution (as was used in the base case) as the criticisms of the log-logistic model also apply to the log normal model. This decreased the ICER to £57,202 per QALY gained.

Table 14: Additional sensitivity analyses (based on ERG exploratory base case) (table 6.2 ERG report page 109)

Technology	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER, £/QALY
ERG exploratory base case[c]					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	24,757	0.43	57,688
Cabazitaxel negative treatment effect removed					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	24,821	0.44	56,671
post-docetaxel survival as in TA 259					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	24,159	0.37	65,515
Weibull instead of Log-logistic used to extrapolate time to AAP/BSC discontinuation					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	19,620	0.26	74,803
Weibull instead of Log-normal used to extrapolate time to docetaxel treatment discontinuation and time to death after post docetaxel active treatment					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	24,565	0.43	57,202

7 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The control arm of the COU-AA-302 study shows that patients with asymptomatic and mildly symptomatic hormone relapsed prostate cancer had a life expectancy of approximately 30 months. However the manufacturer stated that as patients in the trial have gone on to receive other clinical trial technologies post-docetaxel and therefore the survival observed for these patients is probably not reflective of the average mCRPC patient in the UK. It gave 2 further estimates: 9-27 months for asymptomatic disease (from European Association of Urology guidelines published 2013) and 18-22 months from a systematic review of '10 years of docetaxel based therapies in adenocarcinoma' in which the disease is symptomatic
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	In COU-AA-302 people receiving abiraterone had a 5.2 month increase in median OS compared with BSC with PP.
The treatment is licensed or otherwise indicated for small patient populations	The manufacturer estimated that there would be 7,172 people eligible for treatment with AAP across both the pre-docetaxel and post-docetaxel indications.

The ERG commented that it was unlikely that the life expectancy in this patient group will be less than 24 months as in COU-AA-302, 63% of people receiving best supportive care were still alive and that the median survival is 30.1 months. The ERG commented that the manufacturer was unwilling to provide mean survival estimates so the mean survival gain experienced with abiraterone taken before docetaxel is not available.

8 Equality issues

8.1 During the scoping process for this appraisal it was noted that making recommendations for men with prostate cancer may exclude people who have undergone gender reassignment. Therefore all recommendations should be for people with prostate cancer rather than men with prostate cancer. The manufacturer and ERG did not identify any further potential equality issues.

9 Innovation

9.1 The manufacturer stated that abiraterone has a unique mechanism of action and it is the first treatment to be evaluated in and licensed for this stage of the disease (people with asymptomatic or mildly symptomatic metastatic castrate resistant prostate cancer not yet clinically indicated). If further noted that no other treatment options have been shown to improve survival in this patient population. It suggested that the reduced stress and impact on family and social activities experienced taking abiraterone at home rather than attending hospital and the release of hospital clinic slots and increase in consultant availability for other patients are unlikely to be quantified in the QALY calculation. The manufacturer also highlighted that as patients would have the opportunity to receive AAP earlier in the course of their disease (i.e. post-ADT, pre-chemotherapy rather than post-chemotherapy), they not only gain additional survival but are also able to preserve their health related quality of life earlier in the disease process, rather than extending their life at a time when they are likely to have a poorer health related quality of life.

9.2 One professional group stated that the recommendations in technology appraisal guidance 259 exclude many patients with castrate resistant prostate cancer from being treated with this drug, if they have declined or have not been offered docetaxel on grounds of medical co-morbidity or age. A Patient group stated that it would be hugely beneficial if patients

were not required to experience the debilitating effects of chemotherapy before they could receive abiraterone.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Prostate cancer. NICE clinical guideline 175 (2014).
- Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours. NICE technology appraisal guidance 265 (2012)
- Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. NICE technology appraisal guidance 259 (2012)
- Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. NICE technology appraisal guidance 255 (2012)
- Docetaxel for the treatment of metastatic prostate cancer. NICE technology appraisal guidance 101 (2006).

Under development

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

- Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen. NICE technology appraisal. Expected date of issue June 2014.

NICE pathways

- There is a NICE pathway on prostate cancer which is available from http://pathways.nice.org.uk/pathways/prostate-cancer

Appendix B: Clinical efficacy section of the draft European public assessment report

- The EPAR is published and is available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002321/WC500137814.pdf