

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Abiraterone for treating metastatic
hormone-relapsed prostate cancer not
previously treated with chemotherapy**

This guidance was developed using the single technology appraisal (STA) process

1 Guidance

- 1.1 Abiraterone is not recommended for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated.
- 1.2 People currently receiving treatment initiated within the NHS with abiraterone that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Abiraterone acetate (Zytiga, Janssen) is a selective androgen synthesis inhibitor that works by blocking CYP17 (17 α -hydroxylase). It blocks androgen production in the testes and adrenal glands, and in prostatic tumour tissue. Abiraterone 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 as being very common (that is, occurring in 1 in 10 or more people): diarrhoea, urinary tract infection, hypokalaemia (low blood potassium concentrations), hypertension (high blood pressure) and peripheral oedema (swelling of the limbs). The summary of product characteristics states that 'other important adverse reactions' are 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 £2930 for 120 tablets (excluding VAT; British National Formulary [BNF] 67). Abiraterone is administered as a single dose of 1 g per day, taken as 4 250-mg tablets. The company making 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 across all indications. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by the company making abiraterone and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The clinical-effectiveness evidence presented in the company's submission came from COU-AA-302, a worldwide trial in which 9% of the trial population were from the UK. This randomised controlled trial compared abiraterone plus oral prednisone/prednisolone (referred to hereafter as abiraterone) with placebo plus prednisone/prednisolone (referred to hereafter as placebo) in 1088 people; 546 people were allocated to the abiraterone arm (1 g abiraterone daily plus 5 mg prednisone/prednisolone twice daily) and 542 people were allocated to placebo plus prednisone/prednisolone 5 mg twice daily. Patients in the trial stopped abiraterone or placebo at disease progression, if they had not already stopped for another reason (for example, because of adverse reactions). The trial had a co-primary end point of radiographic progression-free survival and death (overall survival). The company shared the overall level of significance for the trial (0.05) between radiographic progression-free survival (0.01) and overall survival (0.04). After disease progression, patients in the trial were followed up for up to 60 months after stopping treatment or until the patient was lost to follow-up, or withdrew consent; median follow-up was 27.1 months. The statistical plan called for a single pre-planned analysis for radiographic progression-free survival after 378 events had accumulated. This plan included 3 interim analyses and 1 final analysis for overall survival when 15%, 40%, 55% and 100% of the 773 deaths that the company had determined would be needed to find a difference between the 2 treatment arms had occurred. Because of the repeated analyses of overall survival, the p values at which the results could be considered statistically significant were $p < 0.0001$, 0.0005, 0.0034 and 0.040 respectively for each of the 4 analyses. The protocol stipulated that, if the effect on radiographic progression-free survival was statistically significant but the interim analysis for

overall survival was not statistically significant, then ‘the study will continue and the patients will be followed for survival until the required number of events is observed’. However, COU-AA-302 was unblinded by the company before the results for overall survival reached statistical significance (between the second and third interim analyses). This was after advice from the Independent Data Monitoring Committee (IDMC), which considered abiraterone to have a ‘highly significant advantage’ for patients, despite the p value for overall survival not meeting the criteria for statistical significance. Three people subsequently crossed over from placebo to abiraterone before the third interim analysis. The company’s submission presented data from the second interim analysis (December 2011) and the third interim analysis (May 2012).

- 3.2 COU-AA-302 included patients with metastatic hormone-relapsed prostate cancer whose disease had progressed after androgen deprivation therapy and who had no or mild symptoms, defined by a brief pain inventory (BPI) score of 0 to 3, reflecting the worst pain on a scale of 0–10 in the last 24 hours (with a score of 0 or 1 being no symptoms, and 2 or 3 being mild symptoms). Patients had an Eastern Cooperative Oncology Group (ECOG) score of 0 (no symptoms) or 1 (symptoms but able to walk). COU-AA-302 excluded people who had an estimated life expectancy of less than 6 months, people who had comorbidities for which they took more than 5 mg of corticosteroids twice daily and people who had visceral metastases. In its response to clarification questions from NICE, the company stated that the study was not designed to exclude people who would have docetaxel in clinical practice, and that some of the patients included in the trial would likely have had docetaxel in the UK. However, the company did not provide an estimate of the proportion of patients in COU-AA-302 who would be eligible for docetaxel in clinical practice. In COU-AA-302, 92.5%

and 92.3% of people had a BPI score of 3 or less in the abiraterone and placebo arms respectively.

3.3 The median treatment duration in COU-AA-302 was 13.8 months in the abiraterone arm and 8.3 months in the placebo arm. Treatment was continued until disease progression (defined by radiographic progression or unequivocal clinical progression, for example, need for alternative cancer therapy), or if the patient had adverse reactions, started a new anticancer treatment, had medications prohibited by the trial or withdrew consent to participate in the trial. At the third interim analysis, most people in both treatment arms had stopped treatment: 77.3% of people in the abiraterone arm and 89.3% of people in the placebo arm. The main reason for stopping was disease progression (57% of people in the abiraterone arm and 68% of people in the placebo arm); 8.3% of people in the abiraterone arm and 6.1% of people in the placebo arm had stopped because of an adverse event. By the third interim analysis, 50.4% of people in the abiraterone arm and 64.2% of people in the placebo arm had had subsequent treatment, about 87% of which was docetaxel in both trial arms. Eleven per cent of people in the abiraterone arm and 13% of people in the placebo arm went on to have cabazitaxel. Fourteen per cent of people in the placebo arm and 7% of people in the abiraterone arm had abiraterone again, which deviated from study protocol that prohibited retreating with abiraterone.

3.4 Radiographic progression-free survival was defined as time from randomisation to 1 of the following: progression by bone scan (adapted Prostate Cancer Working Group criteria), CT or MRI (modified RECIST criteria) and death. CT or MRI and bone scanning were performed every 8 weeks after the first 24 weeks and every 12 weeks thereafter. An independent radiologist unaware of study group assignments determined radiographic

progression-free survival, but only until unblinding, after which local radiologists determined progression. The company used intention-to-treat (ITT) analyses including all patients for efficacy analyses. Although the study protocol specified 1 analysis of radiographic progression-free survival (which was carried out in December 2010), the company did not present the results from this analysis in its submission, and continued to follow up patients whose disease had not yet progressed for radiographic progression-free survival past this point. By May 2012 (the point at which the company conducted its third interim analysis of overall survival), 292 (53.5%) of people in the abiraterone arm and 352 (64.9%) of people in the placebo arm had experienced radiological progression. The median time to radiographic progression-free survival was 16.5 months (95% confidence interval [CI] 13.8 to 16.8 months) in the abiraterone arm and 8.2 months (95% CI 8.0 to 9.4 months) in the placebo arm (hazard ratio [HR] 0.52, 95% CI 0.45 to 0.62; $p < 0.0001$).

- 3.5 At the second interim overall survival analysis (when 40% of the 773 deaths on which the study was powered had occurred), 147 people in the abiraterone arm and 186 people in the placebo arm had died. This generated an estimated hazard ratio of 0.75 (95% CI 0.61 to 0.93; $p = 0.0097$); however, this p value was not low enough to meet the pre-specified level needed to show statistical significance (0.0005, see section 3.1). At the third interim analysis (when 55% of the 773 deaths on which the study was powered had occurred), 200 (36.6%) people in the abiraterone arm and 234 (43.2%) of people in the placebo arm had died. The median overall survival in the abiraterone arm was 35.3 months (95% CI 31.2 to 35.3 months) and 30.1 months (95% CI 27.3 to 34.1 months) in the placebo arm (HR 0.79, 95% CI 0.66 to 0.96, $p = 0.0151$). Again, this p value did not meet the pre-defined value for statistical significance ($p = 0.0034$, see section 3.1).

- 3.6 With respect to subgroups, the company carried out analyses of radiographic progression-free survival and overall survival in pre-defined subgroups based on baseline ECOG (0 or 1), BPI (0–1 or 2–3), bone metastasis only at study entry, age and baseline prostate-specific antigen, among others. Abiraterone resulted in a longer time to radiographic progression than placebo in all subgroups. Similarly, overall survival was longer with abiraterone than placebo in all subgroups, but in some it was not statistically significantly different.
- 3.7 The company presented safety data from COU-AA-302 safety analyses using the ‘safety population’ (1082 people from the randomised population who had had at least 1 dose of any study medication). By the third interim analysis, the company reported that statistically significantly more people having abiraterone had adverse events and serious adverse events than people having 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 had drug-related grade 3–4 adverse events with abiraterone than with placebo (HR 1.30, 95% CI 1.03 to 1.65). The most frequently reported adverse events affecting 5% or more people were fatigue, back pain, arthralgia, nausea, peripheral oedema, constipation and diarrhoea, and they were mostly grade 1 or 2. Of these, peripheral oedema and diarrhoea were more common with abiraterone than placebo (peripheral oedema was experienced by 26.0% of people with abiraterone and 20.9% of people with placebo (RR 1.24, 95% CI 1.00 to 1.54), diarrhoea was experienced by 23.4% of people with abiraterone and 18.1% of

people with placebo (RR 1.29, 95% CI 1.02 to 1.63). The most frequently reported grade 3 or 4 adverse events were hypertension, back pain and increased alanine aminotransferase (ALT).

Abiraterone was associated with more grade 3 or 4 increased ALT (5.5% compared with 0.7%, RR 7.47, 95% CI 2.65 to 21.07), increased aspartate aminotransferase (3.1% compared with 0.9%, RR 3.39, 95% CI 1.26 to 9.12) and dyspnoea (breathing difficulty) (2.6% compared with 0.9%, RR 2.79, 95% CI 1.01 to 7.69) but less hydronephrosis (retention of urine in the kidney causing swelling) (0.2% compared with 1.5% RR 0.12, 95% CI 0.02 to 0.99) than placebo.

3.8 The 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 when treatment was stopped. The company presented the results as the median time to a decrease of 10 or more points and the hazard ratio of abiraterone relative to placebo. People randomised to abiraterone 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 placebo (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.

3.9 The ERG considered that the COU-AA-302 trial was the best source of clinical evidence and identified no further relevant studies. The ERG commented that, although a large number of people dropped out of COU-AA-302, the number of people who dropped out in both treatment arms was similar.

3.10 The ERG had concerns about how the company used data from the FACT-P measure in its submission; it 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 company stated that the main drivers of reduced health-related quality of life reported by patients with metastatic hormone-relapsed prostate cancer are bone pain, fatigue, sexual disturbances and interrupted social relationships. Of these, the company only reported time to an increase in pain intensity (rather than the differences in pain intensity between the 2 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) showed no difference between the 2 treatment arms.

- 3.11 The ERG commented that there is little evidence on the efficacy of docetaxel when given after abiraterone. It identified a single-arm retrospective study of 35 patients who had had 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'.

Cost effectiveness

- 3.12 The company did not identify any published studies of cost effectiveness directly relevant to the decision problem, so it performed its own new analysis. The company 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 years, which it assumed would reflect a lifetime horizon. Costs were considered from the NHS and personal social services perspective and a 3.5% discount rate was applied. The modelled patients were assigned to either abiraterone or best supportive care (the company assumed that the

prednisone/prednisolone arm of COU-AA-302 reflects best supportive care with active monitoring). Modelled patients passed through 3 treatment phases (pre-docetaxel, on-docetaxel and post-docetaxel). In each treatment phase, patients could have active treatment or best supportive care before starting an active treatment, or have best supportive care with palliative treatment after an active treatment. The model included whether subsequent treatments were suitable after ending an active treatment; for example, if a patient's disease had progressed, the modelled patients were monitored in a phase of pre-docetaxel best supportive care to assess whether moving on to docetaxel was suitable. Patients for whom docetaxel is 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 had no further treatment until death. Likewise, after patients completed treatment with docetaxel, they were monitored for disease progression. If a patient's disease progressed while taking docetaxel and they were fit enough for further treatment, they had either abiraterone (if they had not had it before) or best supportive care. Some patients in COU-AA-302 had cabazitaxel after docetaxel. Because cabazitaxel has a survival benefit compared with best supportive care, but is not recommended by NICE in [Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen](#) (NICE technology appraisal guidance 255), the company 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.

- 3.13 The model consisted of 17 prediction equations to estimate the time to starting treatment, time to stopping treatment 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. The company constructed the equations in a series of steps, each needing a number of decisions. It decided whether a separate equation was needed for the abiraterone and placebo arm. Most of the equations were not stratified by treatment but instead the company used the same equation in each treatment arm and used 'treatment' as a predictor. However, for 'time from abiraterone or best supportive care to death', the company derived a separate equation for each treatment arm. For 10 of the equations, the company chose a parametric distribution with which to extrapolate the trial data over a longer period of time, choosing the curve with the best fit to the survival curves from the ITT population from COU-AA-302. To determine variables that were associated with the risk of an event or a patient's disease progression the company used data from 902 patients out of the 1088 ITT patient population (83%) who had complete data for the baseline variables of interest. For this, the company selected variables (covariates) that had a statistically significant association with the event/outcome of interest at a 10% level of statistical significance. The covariates differed between prediction equations. Two further variables that did not meet the 10% level of statistical significance were also included in the prediction equations by the company. The company justified this by stating that it was better to 'be inclusive' and that analyses may not have reached statistical significance because of small patient numbers. The company assessed whether there were any covariates that were dependent on each other. The company compared the model's predictions with the data from COU-AA-302.

- 3.14 The company derived utility values from 3 sources: a company-sponsored independent study, COU-AA-302, and the literature. To derive utility values associated with each treatment phase, the

company carried out a study to gather UK-specific EQ-5D data over more treatment phases than the COU-AA-302 study assessed (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 had surgical castration). The study did not compare men taking abiraterone with men not taking abiraterone and assumed that patients experienced the same utility regardless of their treatment provided that they were in the same treatment phase. Patients with mCRPC were divided into the following subgroups:

- no or mild symptoms after androgen deprivation therapy had failed; chemotherapy not yet clinically indicated (n=50)
- symptoms after androgen deprivation therapy had failed; chemotherapy clinically indicated but not started (n=50)
- after androgen deprivation therapy had failed; having chemotherapy (n=17)
- after androgen deprivation therapy had failed; post chemotherapy, completed 1 or more cycles of chemotherapy (n=46).

The company has stated that the results from this utility study are academic in confidence and cannot be reported here.

3.15 For the base case, the company supplemented the utility values derived from its survey with utility values derived from other sources. The utility value for people receiving best supportive care before death was assumed to be 0.5 based on a published study (Sandblom et al. 2004). The company also added a utility increment for people who had abiraterone (pre-docetaxel in the abiraterone arm) using utility values derived from mapping FACT-P

data from COU-AA-302 to EQ-5D (see section 3.16). The utility increment cannot be reported here because the company has stated that it is academic in confidence. The company did not apply a utility decrement for adverse events experienced on different treatments.

3.16 The company also presented utility values derived from mapping FACT-P to EQ-5D from the data collected in COU-AA-302 (see section 3.8), which it used in a scenario analysis. The company 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 company 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 results of the mapping study are academic in confidence and cannot be reported here.

3.17 The company grouped the 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 different stages of the disease pathway, the company surveyed 53 oncologists. The company applied higher resource use for patients having abiraterone than for patients on best supportive care in both the pre- and post-docetaxel setting for the first 3 months of abiraterone treatment to account for the additional monitoring as specified in the summary of product characteristics. Thereafter, the company assumed that patients incurred the same costs in both treatment arms.

3.18 The company estimated the frequency of unplanned medical resource use from trial data (for example, adverse events while on treatment) using data from COU-AA-301 (for post-docetaxel abiraterone or best supportive care) and COU-AA-302 (for pre-docetaxel abiraterone or best supportive care). COU-AA-301, the key clinical trial in [Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen](#) (NICE technology appraisal guidance 259; hereafter referred to as TA259), compared abiraterone plus prednisone/prednisolone with 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. For people having docetaxel, the company used the rates of grade 3 and 4 adverse events reported in the literature and consulted its clinical advisors on the costs of treating such events. The unplanned medical resource use associated with best supportive care was obtained from the COU-AA-301 trial. The unplanned use of resources per month were £93.79 for abiraterone, best supportive care (prednisone/prednisolone) and best supportive care (pre-docetaxel) and £380.29 while having docetaxel, best supportive care post-docetaxel, abiraterone post-docetaxel or best supportive care before death. The company also applied a one-off cost of £3598 per patient to account for palliative care in the last 3 months of the best supportive care phase.

3.19 The company applied the cost based on the patient access scheme (which is commercial in confidence) for a 1 g daily dose of abiraterone (30.4 doses per month); £2.63 a month for 10 mg prednisone/prednisolone taken daily (30.4 doses per month) (applied in both the abiraterone and best supportive care arms) and £1550.14 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 £1069.50

for a 160-mg vial of docetaxel). An additional administration cost of £214 was applied for docetaxel.

- 3.20 In the company's deterministic base-case analysis, abiraterone was associated with an incremental cost of £26,404, 0.62 life years gained and 0.57 quality-adjusted life years gained (QALYs) compared with best supportive care. The estimated incremental cost-effectiveness ratio (ICER) was £46,722 per QALY gained. The company did not present a probabilistic ICER but presented the results of a probabilistic sensitivity analysis and cost-effectiveness acceptability curves.
- 3.21 The company performed deterministic one-way sensitivity analyses. Increasing or decreasing the post-androgen deprivation therapy baseline utility had the largest effect. Decreasing the baseline utility by 20% increased the ICER to £60,418 per QALY gained whereas increasing the baseline utility by 20% decreased the ICER to £38,087 per QALY gained. The company presented 10 scenario analyses. It additionally presented its results without applying the patient access scheme price of abiraterone. The scenario without the patient access scheme had a large impact on the ICER; in all other scenario analyses, the ICER was between £45,393 per QALY gained (a scenario in which the post-docetaxel survival was assumed to be comparable in both the abiraterone and best supportive care arms) and £50,163 per QALY gained (a scenario in which utility values were derived from the mapping of FACT-P data from COU-AA-302 to EQ-5D).
- 3.22 The ERG considered that it was appropriate for the company to develop a new model, but it did not think that using a discrete event stimulation model was the simplest or most transparent approach because it was more complicated to assess face validity and internal validity than, for example, a Markov model of health states.

- 3.23 When the ERG ran the model, the ICER for the company's deterministic base case differed only slightly from that reported by the company (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 company in its submission. The ERG presented a revised summary of the company'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.
- 3.24 The ERG stated that the model structure lacked face validity because 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 abiraterone or placebo treatment.
- 3.25 The ERG commented that the model population was not the same as the COU-AA-302 ITT population because it included only a subgroup of this population with complete baseline data for covariates; the company excluded 186 patients from the ITT population (1088 people) because of missing baseline data. The company did not provide the characteristics of this subpopulation in its submission. In its clarification response, the company stated that there was not a statistically significant difference in the time to stopping treatment and overall survival between the ITT population and the population with complete baseline characteristic data.
- 3.26 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 company had applied a utility increment to the abiraterone arm relative to the best supportive care arm (see section 3.15) and that the company stated that this was based on the benefits experienced on abiraterone compared with best supportive care with respect to pain and fatigue. The ERG did not agree with this approach because, in COU-AA-302, abiraterone led to significantly more adverse events (both overall and grade 3–4) than best supportive care and the ERG considered it more appropriate to incorporate and apply separate utility decrements for each separate adverse event in the model. During clarification, the company provided 4 separate scenario analyses in which:

- The utility increment applied to the abiraterone 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 an ICER of £47,415 per QALY gained.
- The per-event costs for adverse events 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 2 treatment arms. It also considered the consistency of utility values presented for people after docetaxel treatment in the current submission and in the company's submission for [TA259](#). Following the clarification requests, the company provided a scenario in which the post-docetaxel baseline utility value of 0.780 (equivalent to the post-docetaxel utility value in TA259) was used and to which a post-

docetaxel utility increment of 0.046 was applied by either adding it to the baseline utility value of 0.78 for abiraterone post-docetaxel in the best supportive care arm or subtracting it from 0.78 for best supportive care post-docetaxel in the abiraterone arm). These analyses resulted in ICERs of between £48,316 and £47,936 per QALY gained respectively.

3.27 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 abiraterone
- the prediction equations used for time to stopping treatment, time to starting treatment 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.

Applying the first assumption (post-docetaxel disutility if not having abiraterone) to the company's base case 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 per QALY gained. The combination of these 2 scenarios (the ERG's exploratory base case) resulted in an ICER of £57,668 per QALY gained.

3.28 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 [TA259](#), which had appraised the cost effectiveness of abiraterone taken after docetaxel compared with best supportive care. 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 TA259. This increased the ‘ERG exploratory base case’ ICER from £57,688 to £65,515 per QALY gained.

3.29 The ERG performed 3 additional sensitivity analyses that it tested in its ‘exploratory base case’:

- The ERG stated that it was unclear how the company had applied the negative effect from treatment with cabazitaxel in COU-AA-302 in the model (see section 3.12). Therefore, it tested a scenario without adjusting for cabazitaxel use in COU-AA-302. This decreased the ICER from the ERG’s exploratory base-case estimate of £57,668 to £56,671 per QALY gained.
- The ERG stated that a log-logistic model, as used in the company’s base case, is often criticised for its long tail which may result in an unrealistic survival benefit. The ERG therefore used a Weibull model to extrapolate the data for time to stopping treatment with abiraterone or best supportive care, and time to death while on docetaxel treatment. This increased the ICER to £74,803 per QALY gained.
- The ERG also stated that the criticisms of log-logistic models also apply to log-normal models. The ERG therefore 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). This decreased the ICER from the ERG’s exploratory base-case estimate of £57,668 to £57,202 per QALY gained.

Additional analyses presented in response to consultation on the appraisal consultation document

- 3.30 Following consultation, the company presented a sensitivity analysis that varied the treatment effect of abiraterone by 1 standard error above and below the median treatment effect of abiraterone observed in COU-AA-302, but did not present the value of the standard error. The analysis resulted in an ICER of £41,248 per QALY gained (assuming that abiraterone was more effective by 1 standard error than the median treatment effect in COU-AA-302) and £55,155 per QALY gained (assuming abiraterone was less effective by 1 standard error than the median treatment effect in COU-AA-302).
- 3.31 The company tested the sensitivity of its base-case ICER estimate to the acquisition cost of docetaxel because the NHS can procure generic versions of docetaxel at lower cost than branded docetaxel. The company tested the effect of reducing the cost of docetaxel from £1550.14 per month by 20%. This increased the ICER from £46,722 per QALY gained (base case) to £46,998 per QALY gained.
- 3.32 In response to consultation comments, the ERG provided an analysis to test whether taking into account health-related quality-of-life benefits associated with delaying chemotherapy would reduce the company's base-case ICER to below £30,000 per QALY gained. For this, the ERG tested an implausibly optimistic scenario in which people who were asymptomatic or mildly symptomatic had perfect quality of life when having abiraterone before chemotherapy (that is, a utility value of 1), and people in the best supportive care arm had perfect quality of life less the utility increment that the company applied for having treatment with abiraterone (see section 3.16). This resulted in an ICER of £38,851 per QALY gained. The ERG tested a second scenario in which people had the worst

possible quality of life while having docetaxel (a utility value of 0). This resulted in an ICER of £44,466 per QALY gained. A third scenario combined these 2 assumptions; that is, people with the best possible quality of life before docetaxel and the worst possible quality of life on docetaxel resulted in an ICER of £37,257 per QALY gained.

Estimates of life expectancy for patients for whom abiraterone is indicated; evidence provided by the company during consultation on the appraisal consultation document

- 3.33 The company presented survival data from 2 studies that it had not included in its original submission. One was a systematic literature review by Kirby et al. (2011) citing that the median survival was between 9 and 30 months for patients with castrate-resistant prostate cancer and between 9 and 13 months for people with metastatic disease. The other study was an observational analysis of a trial population (Hussain et al. 2006) documenting an association of prostate-specific androgen levels and mortality in people with prostate cancer. The company reiterated that the 2012 [European Association of Urology guidelines](#) state a mean survival of between 9 and 27 months for metastatic disease.
- 3.34 Full details of all the evidence are in the evaluation report, which can be found on the web page for abiraterone.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of abiraterone, having considered evidence on the nature of metastatic hormone-relapsed prostate cancer and the value placed on the benefits of abiraterone by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1 The Committee considered current treatment options in England for people with metastatic hormone-relapsed prostate cancer after failed androgen deprivation therapy who have no or only mild symptoms. The Committee heard from clinical specialists that, when cytotoxic chemotherapy is indicated, most people have docetaxel. However, when people have no or mild symptoms, clinicians may instead offer best supportive care including corticosteroids such as prednisolone or dexamethasone. The clinical specialists stated that they generally offered docetaxel to people with rapidly progressing disease who were fit enough for cytotoxic chemotherapy and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (or a WHO performance status consistent with this). They added that deferring docetaxel in this group would not be appropriate because the disease rapidly progresses, and patients may not be fit enough to have it at a later date. The Committee heard from the clinical specialists that older people and people with comorbidities are less likely to be fit enough to have docetaxel, and that some patients chose not to have docetaxel. The Committee heard that abiraterone received a marketing authorisation in December 2012 for use before chemotherapy, and that patients can get abiraterone through the Cancer Drugs Fund. It heard from the clinical specialists that there is no consensus on how to decide whether to offer abiraterone to patients, but that clinicians would generally use it, in addition to best supportive care, to treat people with few symptoms to delay chemotherapy, or to treat people who are unable or do not wish to have chemotherapy. The Committee also understood from the clinical specialists that they switch patients whose disease has progressed from abiraterone to docetaxel if the patients are fit enough for docetaxel. The Committee understood that, when deciding whether to offer abiraterone, corticosteroids or docetaxel, clinicians would take into account a person's fitness for

chemotherapy, performance status, symptom severity and the patient's views on taking chemotherapy.

4.2 The Committee heard from the patient experts about how important it is for patients to have the option of delaying chemotherapy. The patient experts explained that chemotherapy has adverse effects and may be particularly poorly tolerated by people who are older or who lack support from a partner or carer. The patient experts stated that some people may choose not to have cytotoxic chemotherapy to avoid its debilitating effects and to maximise their quality life, even if it may mean dying sooner. The Committee noted that the marketing authorisation for abiraterone is for people whose condition is not yet indicated for chemotherapy and so it could not appraise abiraterone as an alternative treatment to chemotherapy. The Committee concluded that chemotherapy can reduce a person's quality of life and that treatments delaying the need for chemotherapy are highly valued by patients.

4.3 The Committee discussed comments received in response to the appraisal consultation document about potential consequences of delaying chemotherapy. It noted comments from patients saying that delaying chemotherapy is highly valued because chemotherapy is associated with a reduced quality of life. It also noted comments from consultation suggesting that when delaying chemotherapy disease and performance status may worsen, and that this may lead to some people becoming unable to tolerate the side effects associated with chemotherapy or to gain the full survival advantage from the sequence of treatments now available. The Committee appreciated that abiraterone delayed the time to treatment with cytotoxic chemotherapy in COU-AA-302, and understood from abiraterone's marketing authorisation that patients on abiraterone switch to docetaxel when clinically indicated, such that chemotherapy is not delayed once needed. The Committee

concluded that there is some uncertainty about the consequences of delaying chemotherapy, but accepted the view of patients that delaying chemotherapy is of value to them.

Clinical effectiveness

- 4.4 The Committee noted that docetaxel was listed as a comparator in the final scope issued by NICE in 2012. It understood that the company did not present a comparison of abiraterone with docetaxel, noting that the marketing authorisation states that abiraterone is indicated for people for whom chemotherapy is not yet indicated. The Committee agreed that this was appropriate. It considered that a key comparison in this appraisal was of sequence a) abiraterone followed by docetaxel and subsequent treatments, with b) watchful waiting (including best supportive care) followed by docetaxel and subsequent treatments (which, in current clinical practice in England, includes abiraterone for sequence b). The Committee acknowledged that some patients may not have docetaxel at any stage. The Committee accepted that clinical trials do not typically assess treatment sequences, and that any comparisons of treatment sequences would usually be modelled.
- 4.5 The Committee considered the results from the randomised placebo-controlled trial COU-AA-302, noting that the trial recruited 9% of its patients from the UK, and that people in both arms received prednisolone/prednisone. The Committee considered that the placebo arm reflected clinical practice in England before treatment with chemotherapy in line with advice from the clinical specialists (see section 4.1). The Committee heard from the clinical specialists that the average age of people in COU-AA-302 was similar to that of the people who would be offered abiraterone in clinical practice in England. It heard that the reasons for stopping abiraterone treatment in the trial broadly reflect clinical practice in England. The Committee heard from the company that the clinical

trial included radiographic progression-free survival as a co-primary end point because this approach enabled the company to shorten the length of the trial by identifying results earlier in this patient population. It noted that the other component of the co-primary end points was overall survival with 3 planned interim analyses and a final analysis. The Committee noted that patients in the study stopped treatment with abiraterone when their disease progressed radiographically or clinically, at which point they could have treatments including docetaxel. The clinical specialists stated that, in clinical practice in England, people would get abiraterone or best supportive care until clinical progression rather than radiographic progression, at which point they would switch to docetaxel within a week if fit enough to tolerate chemotherapy. Despite these differences, the Committee concluded that COU-AA-302 generally reflected clinical practice in the UK and was relevant to address the decision problem.

- 4.6 The Committee was aware that the company unblinded COU-AA-302 early between the second and third interim analyses for overall survival and that, at both of these interim analyses, the results for overall survival did not show a statistically significant difference between the treatment arms according to the pre-specified statistical significance levels. The Committee heard from the company that, although there was not a statistically significant difference in overall survival between the treatment groups, the Independent Data Monitoring Committee had recommended stopping the trial (unblinding) based on the strength of the results for radiographic progression-free survival, which favoured abiraterone. It also heard that the company continued to collect observational data once the trial had been unblinded. The Committee discussed the potential effects of stopping the trial early on the size of the estimates of overall survival. The Committee noted a systematic review published in 2010 (Bassler et al.)

describing the bias in trials that stop early for benefit. Specifically, compared with trials that run to completion, trials that stop early for benefit overestimate the magnitude of the treatment effect (that is, have pooled hazard ratios around 30% lower than trials that run to completion). The company expressed the belief during consultation that this bias did not apply to oncology trials, because the review by Bassler et al included a minority of haematology/oncology trials, and because other studies indicate only a marginal bias towards overestimation in oncology trials that stopped early. However, the Committee concluded that this bias was unrelated to disease area. Overall, the Committee concluded that abiraterone compared with placebo delayed radiographic progression, but by how much abiraterone extended life was uncertain.

- 4.7 The Committee considered the adverse events reported in COU-AA-302 and noted that patients taking abiraterone experienced more adverse effects than patients taking placebo. It heard from the clinical specialists that treatment in both arms of the trial included prednisolone, which is associated with adverse effects. The Committee noted the statements submitted by patient groups, which pointed out that patients generally find the adverse effects of abiraterone mild and tolerable. The Committee concluded that abiraterone increases the risk of adverse events compared with prednisolone alone, but that patients can tolerate the adverse effects associated with abiraterone.
- 4.8 The Committee noted that the company had collected data on health-related quality of life using the Functional Assessment of Cancer Therapy (FACT-prostate cancer [P]) measure in COU-AA-302 until patients stopped abiraterone or best supportive care. The Committee noted that people having abiraterone had a longer median time to a 10-point decrease in FACT-P score than people having best supportive care. However, the Committee was not

presented with absolute values for the whole population over the full period of follow-up, nor whether the 10-point decrease represented a clinically important effect. The Committee concluded that abiraterone slowed the decrease in quality of life relative to best supportive care, but it was unclear whether this represented a clinically significant difference.

- 4.9 The Committee discussed using abiraterone in people who are not fit for chemotherapy. It heard from the clinical specialists, commentators during consultation (section 4.1) and the company that these patients currently get abiraterone through the Cancer Drugs Fund. The Committee noted, however, that COU-AA-302 included only people with a good performance status (ECOG 0 or 1) and few comorbidities (see section 3.2) and so did not include people unfit for chemotherapy. The Committee therefore considered that there was no clinical evidence available to allow it to appraise the cost effectiveness of abiraterone in this population. The Committee therefore was unable to make a separate recommendation for this group. The Committee was also aware that the population for whom chemotherapy is indicated (that is, people with more than mild symptoms), but who are unfit for chemotherapy, are not covered in the therapeutic indication addressed in this appraisal.

Cost effectiveness

- 4.10 The Committee understood that the company had developed a discrete simulation model, rather than the more commonly used Markov model, because it allowed more flexibility to reflect a sequence of treatments, and to model response to treatments that depend on previous treatments. In addition, the company had suitable patient-level data from COU-AA-302 to develop this type of model. The Committee noted that, in its submission for [Abiraterone for castration-resistant metastatic prostate cancer previously](#)

[treated with a docetaxel-containing regimen](#) (NICE technology appraisal guidance 259; hereafter referred to as TA259, which appraised abiraterone for metastatic hormone-relapsed prostate cancer taken after docetaxel), the company also had access to patient-level data but had used a Markov model. However, the Committee recognised that TA259 related to people whose disease has progressed further along the treatment pathway and who had fewer subsequent available treatments, and where therefore a less complex Markov model was appropriate. The Committee noted that the company had not validated the discrete event simulation model using information from TA259. The Committee agreed that using a discrete event simulation model was not unreasonable, but that the company's model was particularly complex. In particular, for each of the model's 17 equations predicting time to events, the Committee noted that the company made a large number of judgements when determining which variables to include in the prediction equations, which covariates to retain in the equations, and which parametric distribution to choose for extrapolation (see section 3.13 for how the company built the prediction equations). The Committee agreed that the company's model was complex and lacked transparency which made it difficult for the Evidence Review Group (ERG) to validate and critique the model.

- 4.11 The Committee was aware that, in its model, the company used data from COU-AA-302, with a median 27.1 months of follow-up from the third interim analysis at which point the study was already unblinded (see section 4.6). The Committee understood that, out of the 17 equations in the model, there were 10 equations that needed extrapolating beyond the time period of the COU-AA-302 trial during which data were collected. These included the equations that modelled time to starting or stopping treatments, and the survival of patients at different points in the treatment pathway. It noted that overall survival in the model was predicted by

combining equations that included modelled time spent in, and the number of people in, each treatment phase. The Committee discussed the way in which the company selected the parametric distribution for each of the equations in the model that needed extrapolating. The Committee was aware that the company considered the Weibull, log-normal, log-logistic exponential and gamma functions, selecting the best fitting distribution using statistical criteria and inspecting the curves visually. However, the Committee concluded that it is important to take into account face validity, and specifically whether extrapolating predicts realistic outcomes, both for the event modelled by each equation and for the model as a whole, but that the company had not done this.

- 4.12 In addition to the uncertainty surrounding the validity of the extrapolation in the model and the true magnitude of the treatment effect, the Committee understood that the company based the model on data from a subset of 902 people for whom data existed on all baseline characteristics needed to assess the covariates in the model (from the overall intention-to-treat (ITT) population of 1088 in COU-AA-302). The Committee was aware that, in its response to the appraisal consultation document, the company included the baseline characteristics for the subset of 902 people representing the modelled population, but had not tested statistically whether this population differed from the ITT population. The Committee inspected the Kaplan–Meier curve from the trial (the ITT population), and saw no difference in death rates between the abiraterone and best supportive care arms up to around 18 months. However, when inspecting the company’s modelled curves of the subgroup, the Committee noted that people having abiraterone lived longer than people having best supportive care within the first 18 months of follow-up. The Committee noted that the model results were consistent with trial results between 18 months and around 36 months of follow-up (when the trial was

unblinded). The Committee concluded that the model employing only a subgroup of patients in the trial overestimated the survival benefit of abiraterone compared with best supportive care.

4.13 The Committee further considered the extrapolations of overall survival predicted by the company's model beyond the end of the trial. The Committee noted that the company's model predicted that people who have abiraterone followed by docetaxel live longer than people in the control arm, but also that the extent of the benefit of having abiraterone followed by docetaxel was maintained for 2.5 years after the trial ended. The Committee considered that there was uncertainty about whether this outcome was plausible. The Committee concluded that the model may have overestimated the survival benefit associated with taking abiraterone after about 3 years, after which time no trial data existed on which to validate the extrapolations.

4.14 The Committee discussed the utility values used by the company in its model. It understood that the company derived utility values, by phase of treatment, from 3 sources:

- a survey it carried out in patients in the UK with metastatic hormone-relapsed prostate cancer (4 values)
- COU-AA-302 (1 value reflecting an uplift to utility experienced by people taking abiraterone before docetaxel, using FACT-P data mapped to EQ-5D)
- the literature (1 value for quality of life at the end of life).

The Committee considered that, when a trial includes quality-of-life data (as in COU-AA-302; see section 4.8), in line with its Guide to the Methods of Technology Appraisal (2013), NICE prefers that these data are used to derive utility values in the model. However, the Committee had concerns about the utility mapping study that the company used to map FACT-P data from COU-AA-302 to EQ-

5D because the company did not provide evidence that the mapping function had been validated or that the assumptions for the mapping function had been tested in sensitivity analyses. Furthermore, the Committee questioned the company's choice of when to apply utility values derived from its mapping study or from other sources. It noted that, in its base case, the company used the trial data mapped to EQ-5D data to estimate only the utility increment associated with having abiraterone. The Committee questioned whether or not it was appropriate for the company to include an increment in utility associated with taking abiraterone, given that patients on abiraterone experience more adverse events than patients on best supportive care. The Committee noted the ERG's concerns that the company applied this increment only to people who take abiraterone before docetaxel, but not to people who take abiraterone after docetaxel. The Committee was aware that, for the post-docetaxel treatment phase in the model, the company chose lower utility values (based on its survey) than in its previous submission for [TA259](#), which appraised abiraterone after docetaxel. The Committee was unconvinced by the company's argument presented in the meeting that the post-docetaxel population in TA259 differed from the post-docetaxel population in its current model. However, it acknowledged that the company had included a scenario in its response to clarification in which the post-docetaxel utility value was the same as that used in TA259, and in which people who had abiraterone after docetaxel had a utility increment of 0.046. Lastly, the Committee noted that the company, in presenting FACT-P data in COU-AA-302 as time to worsening, made it extremely difficult to compare these data with data from other trials of treatments for metastatic hormone-relapsed prostate cancer. Overall, the Committee was not persuaded that the company had modelled utility appropriately, and noted that the sensitivity analyses around the sources of the utility values and

effect of abiraterone on quality of life presented by the company and the ERG slightly increased the ICERs.

4.15 The Committee considered the cost-effectiveness results, noting that the company's base-case incremental cost-effectiveness ratio (ICER) was £46,700 per quality-adjusted life year (QALY) gained. The Committee was concerned that the company had not presented a probabilistic ICER in its submission, and was aware that the ICERs from the company's one-way sensitivity analyses and scenario analyses generally ranged from £45,000 to £49,000 per QALY gained. The Committee noted that some of the one-way sensitivity analyses had a larger impact on the ICER. When the company increased the utility value for the pre-docetaxel treatment phase, changed the discount rate, used a Weibull rather than a log-logistic model to extrapolate first-line treatment duration, or used utility data mapped from FACT-P to EQ-5D instead of utilities derived from survey data, the ICER increased to over £50,000 per QALY gained. The Committee also noted that, following consultation on the appraisal consultation document, the company presented a sensitivity analysis that lowered the treatment effect of abiraterone from COU-AA-302 by 1 standard error and that this increased the ICER to £55,000 per QALY gained. The Committee concluded that the company's estimate of cost effectiveness was sensitive to assumptions around treatment effect.

4.16 The Committee discussed the cost of docetaxel used by the company in its base-case model, which seemed high considering that the NHS now purchases non-proprietary docetaxel, and that the company used a price listed in the British National Formulary (BNF). The Committee was aware that NICE methods for technology appraisal encourage companies to use actual rather than list prices. The Committee considered that it was unlikely that the cost of docetaxel assumed in the company's model reflects the

cost paid for docetaxel in the NHS in England. It noted that the additional sensitivity analysis provided by the company in its response to the appraisal consultation document, including the cost of docetaxel reduced by 20%, resulted in an ICER of £47,000 per QALY gained. The Committee concluded that the price paid for docetaxel in England may be less than the value tested by the company in that sensitivity analysis, but that the ICER was relatively insensitive to changes in the cost of docetaxel.

4.17 The Committee considered the ERG's analyses exploring the uncertainty around the company's modelling of survival, which were based on the subset of 902 people with complete baseline characteristics. It noted that the ERG had conducted a scenario analysis using the ITT population from COU-AA-302 to produce prediction equations with the only covariate being whether a patient had abiraterone or best supportive care. The Committee noted that this resulted in an ICER of £57,300 per QALY gained. The Committee heard from the company that it believed that using treatment as the only covariate would result in the model outputs being less similar to the trial results than a model using multiple covariates. The Committee accepted that the ERG's approach might underestimate any survival benefit of abiraterone before docetaxel, but it considered that the company's base case might overestimate it (see sections 4.12 and 4.13). The Committee understood that the company had used a log-logistic or log-normal distribution to replace, and to extrapolate from, trial data. The ERG suggested that these distributions have a long tail that may give implausible results because they generate improbably large values during the relatively long extrapolation period. For example, the Committee heard from the ERG that the model predicted that patients wait about 6 months to start docetaxel after having stopped abiraterone, which the Committee appreciated differed from clinical care in England based on testimony from the clinical

specialists who described patients switching treatment within a week of progression (see section 4.3). The Committee therefore questioned the validity of the model. The Committee noted that replacing log-logistic distributions with Weibull distributions increased the ERG's exploratory base-case ICER from £57,700 to £74,800 per QALY gained. The Committee concluded that the choice of parametric distribution used in the prediction equations was a key driver of cost effectiveness in the model. Because the Committee had not been presented with data with which it could assess the clinical and biological plausibility of the company's modelled extrapolations, it could not determine whether the company's or the ERG's preferred extrapolation was more appropriate. However, it concluded that it did not need to pursue this issue further because in both sets of analyses the ICERs were above the range normally considered cost effective.

4.18 The Committee discussed whether abiraterone could be considered an efficient use of NHS resources. Taking into account the issues considered in sections 4.3.11 to 4.3.17, it concluded that all ICERs estimated both by the company and the ERG fell substantially above the range normally considered cost effective, that is, £20,000 to £30,000 per QALY gained.

4.19 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all of the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of extension to life are robust, and the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.20 To address whether metastatic hormone-resistant prostate cancer at this stage of therapy is associated with a mean life expectancy of less than 24 months, the Committee noted in its first meeting that the median overall survival in the control arm of COU-AA-302 was about 30 months. The Committee heard from the company in the first meeting that it had estimated the mean survival for the best supportive care arm as 32 months. The Committee also heard from the company during the first meeting, that estimates from COU-AA-302 were in line with survival of patients randomised to best supportive care in the PREVAIL trial of enzalutamide for metastatic hormone-relapsed prostate cancer in people who had not previously had chemotherapy, a population similar to that addressed in the current appraisal. The Committee recognised that the criterion of short life expectancy had previously been met in [TA259](#), where abiraterone is used after docetaxel at a later phase in the disease process.

4.21 The Committee considered the company's comments received during consultation that people treated in the NHS would have a lower life expectancy than people in COU-AA-302 because, in the trial, people had active treatments after docetaxel including

‘Sipuleucel-T, cabazitaxel, ketoconazole and retreatment with abiraterone’. However, the Committee believed that the NHS did not offer worse care than the international trial because the clinical specialists commented that people in the NHS might be more likely than patients in the trial to have docetaxel, which prolongs life compared with best supportive care. Also, the Committee heard from a research organisation during consultation that ‘abiraterone is now used as standard treatment after docetaxel and has extended the life of thousands of men in the UK’. In addition, the Committee noted that, in England, although not recommended by NICE, patients often get cabazitaxel, which has a proven survival benefit, through the Cancer Drugs Fund. The Committee believed that ketoconazole had not been proven to improve survival in patients with metastatic hormone-resistant prostate cancer, and including it in the clinical trial therefore would not affect survival outcomes. The Committee concluded that the life expectancy of people in the best supportive care arm of COU-AA-302 reflected that of patients in the NHS because the subsequent active treatments in the best supportive care arm in COU-AA-302 were similar to those patients receive in routine clinical practice in the NHS.

- 4.22 The Committee considered the company’s argument that COU-AA-302 is not a relevant source of data to estimate mean life expectancy. It noted that COU-AA-302 excluded patients with significant comorbidities and a life expectancy of less than 6 months (see section 3.2), which would make the life expectancy in the control arm longer than in the real-world population. However, the Committee noted that both the clinical specialists and the company had stated that COU-AA-302 was generalisable to clinical practice in England and reflected patients who would be offered abiraterone in England. The Committee considered the company’s additional argument that it had designed COU-AA-302 to measure relative risk and not absolute risk (death rates).

However, the Committee was aware that the trial was designed to measure overall survival, and that the company had used the absolute death rates in its submission to calculate the difference in median survival between abiraterone and best supportive care. The Committee considered that all trials can provide information other than estimates of relative effectiveness which are in fact based on absolute rates. It concluded that COU-AA-302 provides a reasonable estimate of the median life expectancy for people with metastatic hormone-resistant prostate cancer for whom abiraterone is indicated, and that mean values generally exceed median values.

- 4.23 The Committee considered the company's review of the published literature on estimates of survival for people with metastatic hormone-resistant prostate cancer. It noted that this included estimates from the 2012 European Association of Urology guidelines, an observational analysis from a clinical trial of androgen deprivation therapy, and a systematic review of observational studies of people with castrate-resistant prostate cancer. In addition, the Committee considered a clinical trial of docetaxel compared with best supportive care cited by a professional consultee organisation. The Committee noted that the median survival estimates across these publications ranged from 9 to 30 months (see section 3.33). However, it was concerned about the reliability of the estimates. Firstly, it had not been presented with evidence that the guidelines included a systematic review. Secondly, the estimate from the 2012 European Association of Urology guidelines had not been included in the 2013 and 2014 updates of this guideline. Instead, these updates referred to the median survival estimates from the docetaxel trials and trials of other technologies such as cabazitaxel, enzalutamide, sipuleucel-T and abiraterone. Thirdly, the primary finding from an observational analysis of a clinical trial of androgen deprivation therapy showed

how prostate-specific androgen levels are associated with mortality, but did not provide life expectancy data for the population. Fourthly, it was unclear whether the populations included in the systematic review of observational studies were generalisable to the population in the UK for whom abiraterone is indicated. Finally, the trial comparing docetaxel and mitoxantrone mainly included people at a later stage of treatment, who would be expected to have a shorter life expectancy than the population for whom abiraterone is considered in this appraisal.

- 4.24 The Committee also considered studies informing the life expectancy of patients that the company had not included in its response to the consultation document. It noted that these included the PREVAIL trial (section 4.20) and published data from NHS patients in England, specifically data from the South West Public Health Observatory following 2700 men from 1999–2002 to 2006 who were resident in England and had metastatic prostate cancer. The Committee noted that the observatory data suggest a median survival of about 2.5 years. The Committee acknowledged that this population would include people who had metastatic prostate cancer still responding to androgen deprivation therapy and who would be expected to have a longer life expectancy than the population for whom abiraterone is indicated, but would also include patients at a later stage of disease who would be expected to have a shorter life expectancy. It recognised that the data were collected before life-extending treatments such as enzalutamide and abiraterone (post-docetaxel) were available in England and so would likely underestimate life expectancy in current English clinical practice. The Committee concluded that current mean life expectancy for people with metastatic hormone-relapsed prostate cancer for whom chemotherapy is not yet indicated was unlikely to be less than 24 months.

4.25 Having determined that abiraterone did not meet the 'end of life' criterion on life-expectancy, the Committee discussed the criteria of small patient population and whether abiraterone extended life by more than an average of 3 months. It noted that the company, in its response to the appraisal consultation document, estimated that 6782 people would be eligible for the pre- and post-docetaxel marketing authorisations in England, but that a proportion of the population eligible for abiraterone after docetaxel would not receive abiraterone if they had received it before docetaxel. The Committee concluded that the eligible population for England did not exceed 7000 and that abiraterone therefore met the end of life criterion for a small patient population. The Committee referred to its previous conclusion that there is uncertainty about the survival benefit with abiraterone. It considered that the median of 5.2 months may overestimate the true treatment effect because the trial was stopped early, and that the modelled mean benefit of 7.44 months was likely to overestimate the true values because of the choice of the extrapolation curves. However, the Committee agreed that it is likely that abiraterone when given before docetaxel leads to a life extension of 3 months. However, because the 24 month life expectancy criterion had not been met, the Committee concluded that the end-of-life criteria did not apply to abiraterone taken before docetaxel in the treatment pathway.

4.26 The Committee considered whether abiraterone was innovative and whether it had substantial, demonstrable and distinctive benefits not adequately captured in the modelling of the QALYs. The Committee noted that, although abiraterone is not a new technology, it is the first treatment available for this position in the treatment pathway and, in this regard, was innovative. It then considered whether the model captured the benefits of either having abiraterone at an earlier point in the treatment pathway when people had higher quality of life, or delaying the need for

cytotoxic chemotherapy, such as docetaxel. The Committee agreed that the model predicted that people in the abiraterone arm have more time with better utility before docetaxel than people on best supportive care, and that the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling. In its first meeting, the Committee had agreed that taking into account the benefit of delaying chemotherapy would be extremely unlikely to reduce the ICER for abiraterone to within the range usually considered a cost-effective use of NHS resources. It noted, in its second meeting, that the ERG’s sensitivity analysis exploring the utility values before and on docetaxel confirmed this previous conclusion (see section 3.32) and also the company’s own sensitivity analysis on utility values (see section 3.21). The Committee concluded that abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources. Therefore, the Committee could not recommend abiraterone for people with metastatic hormone-relapsed prostate cancer who have no or mild symptoms and who have not previously been treated with chemotherapy.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title: Abiraterone for metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy	Section
Key conclusion		
Abiraterone is not recommended within its marketing authorisation for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated		1.1
All ICERs estimated both by the company and the ERG fell substantially above the range normally considered cost effective, that is, £20,000 to £30,000 per QALY gained. The company’s base case ICER was £46,700 per QALY gained.		4.18, 4.15, 4.17
The Committee concluded that current mean life expectancy for people with metastatic hormone-relapsed prostate cancer for whom chemotherapy is not yet indicated was unlikely to be less than 24 months, and abiraterone at this stage in the treatment pathway did		4.24 4.25

<p>not meet the end-of-life criterion for short life expectancy.</p> <p>The Committee considered that abiraterone is innovative because it is the first treatment available for this position in the treatment pathway and that the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling. The Committee agreed that taking into account the benefit of delaying chemotherapy would be extremely unlikely to reduce the ICER for abiraterone to within the range usually considered a cost-effective use of NHS resources.</p>		4.26
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee understood from the patient experts that chemotherapy can reduce a person's quality of life and that treatments delaying the need for chemotherapy are highly valued by patients.</p>	4.2
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Although abiraterone is not a new technology, it is the first treatment available for this position in the treatment pathway and, in this regard, is innovative.</p> <p>The Committee concluded that there is some uncertainty about the consequences of delaying chemotherapy, but accepted the view of patients that delaying chemotherapy is of value to them.</p>	4.26 4.3
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>There is no consensus on how to decide whether to offer abiraterone to patients, but clinicians generally use it, in addition to best supportive care, to treat people with few symptoms to delay chemotherapy, or to treat people who are unable or do not wish to have chemotherapy.</p>	4.1, 4.3
<p>Adverse reactions</p>	<p>Patients generally find the adverse effects of abiraterone mild and tolerable. Abiraterone increases the risk of adverse events compared with prednisolone alone, but patients can tolerate the adverse effects associated with abiraterone.</p>	4.7
<p>Evidence for clinical effectiveness</p>		

Availability, nature and quality of evidence	The clinical-effectiveness evidence came from the randomised placebo-controlled trial COU-AA-302 that recruited 9% of its patients from the UK.	4.5
Relevance to general clinical practice in the NHS	The Committee concluded that COU-AA-302 generally reflected clinical practice in the UK and was relevant to address the decision problem.	4.5
Uncertainties generated by the evidence	The Committee was aware that the company unblinded COU-AA-302 early between the second and third interim analyses for overall survival and that, at both of these interim analyses, the results for overall survival did not show a statistically significant difference between the treatment arms according to the pre-specified statistical significance levels.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None were identified.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that abiraterone compared with placebo delayed radiographic progression, but by how much abiraterone extended life was uncertain.	4.6
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee understood that the company had developed a discrete simulation model, rather than the more commonly used Markov model, because it allowed more flexibility to reflect a sequence of treatments, and to model response to treatments that depend on previous treatments. In addition, the company had suitable patient-level data from COU-AA-302 to develop this type of model.	4.10

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee agreed that the company’s model was complex and lacked transparency which made it difficult for the Evidence Review Group (ERG) to validate and critique.</p> <p>The Committee concluded that it is important to take into account face validity, and specifically whether extrapolating predicts realistic outcomes, both for the event modelled by each equation and for the model as a whole, but that the company had not done this.</p>	<p>4.10</p> <p>4.11</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee had concerns about the company’s utility mapping study, which was used to map FACT-P data from COU-AA-302 to EQ-5D, because it had not been provided with evidence that the study had been validated or that the assumptions for the mapping function had been tested in sensitivity analyses. There were also inconsistencies in the utility values used in this appraisal and in NICE technology appraisal 259.</p> <p>The Committee agreed that taking into account the benefit of delaying chemotherapy would be extremely unlikely to reduce the ICER for abiraterone to within the range usually considered a cost-effective use of NHS resources.</p>	<p>4.14</p> <p>4.26</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>None were identified.</p>	<p>4.16</p>

<p>What are the key drivers of cost effectiveness?</p>	<p>The choice of parametric distribution used in the prediction equations was a key driver of cost effectiveness in the model. However, because the Committee had not been presented with data with which it could assess the clinical and biological plausibility of the company's modelled extrapolations, it could not determine whether the company's or the ERG's preferred extrapolation was the more appropriate.</p> <p>The company's estimate of cost effectiveness was sensitive to assumptions around treatment effect.</p>	<p>4.17</p> <p>4.15</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee concluded that all the ICERs estimated both by the company and the ERG fell substantially above the range normally considered cost effective, that is, £20,000 to £30,000 per QALY gained. The company's base-case ICER was £46,700 per QALY gained and its sensitivity analysis resulted in ICERs from £45,000 to above £50,000 per QALY gained. The ERG presented an 'exploratory base case' of £57,300 per QALY gained. Additional sensitivity analyses resulted in ICERs of £57,200 to £74,800 per QALY gained.</p>	<p>4.15, 4.17, 4.18</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>The company 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 across all indications.</p>	<p>2.3</p>

End-of-life considerations	<p>The Committee concluded that abiraterone was licensed for a small patient population, and it is likely that abiraterone when given before docetaxel leads to a life extension of 3 months.</p> <p>The Committee concluded that current mean life expectancy for people with metastatic hormone-relapsed prostate cancer for whom chemotherapy is not yet indicated was unlikely to be less than 24 months, and abiraterone at this stage in the treatment pathway did not meet the end-of-life criterion for short life expectancy.</p>	4.19-25
Equalities considerations and social value judgements	No equality issues were raised during the appraisal committee meetings.	n/a

5 Implementation

5.1 NICE has developed [tools](#) [\[update link\]](#) to help organisations put this guidance into practice (listed below). [\[NICE to amend list as needed at time of publication\]](#)

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Prostate cancer: diagnosis and treatment](#) NICE clinical guideline 175 (2014)
- [Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen](#) NICE technology appraisal guidance 316 (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

- Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases. NICE technology appraisal guidance, publication expected September 2014.
- Sipuleucel-T for the first line treatment of metastatic hormone relapsed prostate cancer. NICE technology appraisal guidance, publication expected February 2015.

7 Date for review of guidance

- 7.1 The guidance on this topic will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
June 2014

8 Appraisal Committee members, guideline representatives and NICE project team

8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)

Professor of Public Health, University of Exeter Medical School

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Mr Matthew Campbell-Hill

Lay member

Professor Imran Chaudhry

Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

Dr Lisa Cooper

Echocardiographer, Stockport NHS Foundation Trust

Dr Maria Dyban

General Practitioner, Cardiff

Mr Robert Hinchliffe

Clinical Senior Lecturer (Higher Education Funding Council for England; HEFCE) in Vascular Surgery and Honorary Consultant Vascular Surgeon, St George's Vascular Institute

Dr Neil Iosson

Locum General Practitioner

Mrs Anne Joshua

Pharmaceutical Advisor NHS 111/NHS Pathways

Dr Rebecca Kearney

Clinical Lecturer, University of Warwick

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research

at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Mr Christopher O'Regan

Head of Health Technology Assessment and Outcomes Research, Merck Sharp & Dohme

Dr Sanjeev Patel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay member

Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Mr Cliff Snelling

Lay member

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Mr David Thomson

Lay member

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Mary Hughes

Technical Lead

Zoe Charles

Technical Adviser

Jeremy Powell

Project Manager

9 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Kleijnen Systematic Reviews:

- Riemsma R, Ramaekers B, Tomini F et al. (2014) Abiraterone for the treatment of chemotherapy naïve metastatic castration-resistant prostate cancer.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were also invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Companies/sponsors:

- Janssen

II. Professional/specialist and patient/carer groups:

- British Association of Urological Surgeons
- British Uro-Oncology Group
- Cancer Research UK
- Prostate Cancer UK
- Royal College of Nursing
- Royal College of Physicians
- Tackle Prostate Cancer
- The Urology Foundation

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Commissioning Support Appraisals Service

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Collaborating Centre for Cancer
- Sanofi

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on abiraterone by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr John Graham, Consultant Clinical Oncologist and Director, National Collaborating Centre for Cancer, nominated by the National Collaborating Centre for Cancer – clinical specialist
- Dr Simon Hughes, Consultant Clinical Oncologist, Guys and St Thomas' NHS Trust, nominated by the British Uro-oncology Group – clinical specialist
- David Smith, Hon. Secretary, Tackle Prostate Cancer, nominated by Tackle Prostate Cancer – patient expert
- Stuart Watson, volunteer, Prostate Cancer UK, nominated by Prostate Cancer UK – patient expert

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

- Janssen