NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

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

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

1   Guidance

1.1   Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if:

- their disease has progressed after one docetaxel-containing chemotherapy regimen, and
- the manufacturer provides abiraterone with the discount agreed in the patient access scheme.

1.2   People currently receiving abiraterone in combination with prednisone or prednisolone whose disease does not meet the criteria in 1.1 should be able to continue therapy until they and their clinician consider it appropriate to stop.

2   The technology

2.1   Abiraterone acetate (Zytiga, Janssen) is a selective inhibitor of androgen biosynthesis which is taken orally. It irreversibly blocks cytochrome P17 (an enzyme involved in the production of

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testosterone), thereby stopping androgen synthesis in the adrenal glands, prostate tissue and the prostatic tumour. Abiraterone has a UK marketing authorisation for use 'with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen'. For prostate cancer that was previously considered 'hormone refractory,' the term 'castration resistant' is now used because the cancer still depends on hormones to activate androgen receptors, but no longer responds to androgen-reducing treatments.

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

2.3   The cost of abiraterone is £2930 for 120 tablets (excluding VAT; British national formulary [BNF] 63, March 2012). Abiraterone is administered as a single dose of 1 g per day, taken as four 250-mg tablets. The manufacturer of abiraterone (Janssen) has agreed a patient access scheme with the Department of Health. This involves a single confidential discount applied to the list price of abiraterone. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published.

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3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of abiraterone and a review of this submission by the Evidence Review Group (ERG; appendix B). The decision problem addressed by the manufacturer considered whether treatment with abiraterone plus prednisolone was clinically effective compared with mitoxantrone (with or without prednisolone) or best supportive care for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen and whether abiraterone treatment reflected a cost-effective use of NHS resources.

3.1 The manufacturer carried out a systematic literature search to identify all relevant trials and studies of abiraterone and potential comparators for the treatment of castration-resistant metastatic prostate cancer. The manufacturer identified four studies of abiraterone following previous chemotherapy: one randomised controlled trial (COU-AA-301) and three single arm trials (COU-AA-304, COU-AA-003, COU-AA-BMA). Four randomised controlled trials comparing mitoxantrone plus prednisolone with other treatments were also identified by the manufacturer, but there were no other trials to link this evidence to the COU-AA-301 trial and enable an indirect comparison of abiraterone and mitoxantrone. The manufacturer's clinical-effectiveness evidence for abiraterone was derived solely from the COU-AA-301 trial (a phase III, placebo-controlled, randomised, double-blind, multicentre trial carried out across 130 sites in 13 countries, including the UK). In this trial, patients whose disease had progressed on or after docetaxel therapy and who had an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2 were treated with either abiraterone (four 250-mg tablets) in combination with prednisone or

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prednisolone (n = 797) or with placebo (four tablets) in combination with prednisone or prednisolone (n = 398). Patients in both groups continued treatment until disease progression was documented on the basis of the prostate-specific antigen (PSA), radiographic imaging, and clinical findings. Study follow-up was up to 60 months.

3.2   The baseline demographics and disease characteristics were similar between the two treatment groups in the COU-AA-301 trial: 93% of patients were white, the median age was 69 years and 28% of patients were 75 years or older. Among patients randomised to abiraterone plus prednisone or prednisolone (hereafter the 'abiraterone group'), 70% had previously received one prior course of docetaxel chemotherapy only (designated as the 'one prior chemotherapy' subgroup), compared with 69% of patients randomised to placebo plus prednisone or prednisolone (hereafter the 'prednisolone group'). The proportion of patients with an ECOG performance score of 2 (reflecting worse performance than a score of 0 or 1) was 10% and 11% in the abiraterone and prednisolone groups respectively. The majority of patients in both treatment groups (approximately 70%) had radiographic progression with or without PSA progression at baseline; 89% of patients in the abiraterone group and 90% of patients in the prednisolone group had bone metastases.

3.3   The primary outcome of the COU-AA-301 trial was overall survival, defined as the time from randomisation to death from any cause. A 'primary' analysis was conducted after 552 deaths (12.8 months median follow-up) for the whole (intention-to-treat) population. This was on the basis of a planned interim analysis after 534 deaths (67% of the 797 deaths at the planned final analysis). In the planned interim analysis ('primary' analysis), median survival was statistically significantly longer in the abiraterone group than in the

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prednisolone group (14.8 months compared with 10.9 months, hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.54 to 0.77). Following this analysis, and because of a significant beneficial effect of abiraterone, the trial stopped. Follow-up continued, and an 'updated' analysis was conducted after 775 deaths (20.2 months median follow-up) for the whole population and the one prior chemotherapy subgroup. For the whole population, median survival continued to be statistically significantly longer in the abiraterone group than the prednisolone group (15.8 months compared with 11.2 months, HR 0.74, 95% CI 0.64 to 0.86). Subgroups with an ECOG performance score of 0–1 or 2 and subgroups who had received one or more prior chemotherapy regimens were explored by the manufacturer. For the one prior chemotherapy subgroup, median survival was also statistically significantly longer in the abiraterone group than the prednisolone group (17.0 months compared with 11.7 months, HR 0.71, 95% CI 0.60 to 0.86). The manufacturer stated that statistical testing showed that the relative overall survival benefit of abiraterone was not statistically significantly different between the one prior chemotherapy subgroup and the subgroup with more than one prior chemotherapy.

3.4   Two secondary outcomes in the COU-AA-301 trial were radiographic progression-free survival (time with no radiographically documented disease progression) and 'modified' progression-free survival (based on time to death or one of the following: PSA progression, radiographic progression, increase in glucocorticoid use, pain progression, a skeletal-related event, or initiation of a new cancer therapy). Treatment with abiraterone statistically significantly decreased the risk of radiographically documented disease progression or death compared with

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prednisolone in the primary analysis (HR 0.67, 95% CI 0.59 to 0.78, p < 0.0001). A significantly decreased risk was also observed in the updated analysis. The median radiographic progression-free survival was identical in the primary and updated analyses: 171 days in the abiraterone group and 110 days in the prednisolone group. Treatment with abiraterone also significantly decreased the risk of disease progression based on the criteria for 'modified' progression-free survival compared with prednisolone in the primary analysis (HR 0.63, 95% CI 0.55 to 0.72, p < 0.0001). A significantly decreased risk was also observed in the updated analysis (results provided as academic in confidence).

3.5   The manufacturer indicated that expert opinion had suggested that the endpoints of 'modified' progression-free survival and radiographic progression-free survival, as defined in the COU-AA-301 trial, did not necessarily represent the time at which trial participants stopped the study drug because of disease progression. On this basis, the manufacturer argued that treatment discontinuation was the most appropriate proxy for progression-free survival in the economic model. The manufacturer presented rates of time to discontinuation for both the whole population (primary and updated analyses) and the one prior chemotherapy subgroup (updated analysis only). For the whole population, the median time to treatment discontinuation for the abiraterone group was significantly longer than in the prednisolone group in the primary analysis (8 months compared with 4 months), with similar results in the updated analysis. For the one prior chemotherapy subgroup, the median time to treatment discontinuation was also significantly longer for the abiraterone group than the prednisolone group and the difference between the two groups was slightly larger than that

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observed for the whole population (results provided as academic in confidence).

3.6   Additional outcomes in the COU-AA-301 trial included PSA response rates, defined as the proportion of patients with a 50% or greater decrease in PSA confirmed by a second measurement at least 4 weeks later, and objective tumour response rates, defined according to Response Evaluation Criteria in Solid Tumours (RECIST). In the primary analysis for the whole population, confirmed PSA response was statistically significantly greater in the abiraterone group than in the prednisolone group (29.1% compared with 5.5%, p < 0.0001).

3.7   The most common adverse reactions (occurring in ≥ 10% of participants in COU-AA-301) reported in both treatment groups were anaemia, vomiting, hot flushes, anorexia, pain in extremities, diarrhoea, musculoskeletal pain, asthenia, dyspnoea, headache, urinary tract infection, weight loss and muscle weakness. For the primary analysis, the most frequently reported grade 3 or 4 adverse reactions in the abiraterone and prednisolone groups were fatigue, anaemia, back pain and bone pain. Adverse reactions relating to mineralocorticoid excess (hypertension, hypokalaemia and oedema), cardiac disorders and hepatotoxicity were more frequent in the abiraterone group than the prednisolone group (55% compared with 44%). Cardiac disorders (primarily grade 1 or 2) were more commonly reported in the abiraterone group than in the prednisolone group (13% compared with 11%, p = 0.14). Adverse reactions resulting in death or the need to discontinue study treatment were less frequent in the abiraterone group.

3.8   The manufacturer presented updated analyses for three health-related quality of life measures for which data were collected in the

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COU-AA-301 trial: the brief pain inventory short form (BPI-SF), the brief fatigue inventory short form (BFI-SF), and the functional assessment of cancer therapy-prostate (FACT-P). Neither the EQ-5D nor any other utility measure was collected in the COU-AA-301 trial. Analyses indicated that a statistically significantly greater proportion of patients in the abiraterone group compared with the prednisolone group experienced an improvement for all three outcome measures (p < 0.001). The manufacturer reported that the proportion of patients who had progression or decline in the outcome measures related to pain, functionality and fatigue did not significantly differ between the two treatment groups. However, patients in the abiraterone group experienced statistically significantly longer time to progression for all three outcome measures compared with the prednisolone group (p < 0.05). The manufacturer concluded that evidence from the COU-AA-301 trial suggests that patients receiving abiraterone are more likely to experience less pain and fatigue, have improved functional status, and have a longer time before their pain, functional status and fatigue worsen.

3.9   The manufacturer submitted an economic model to compare the cost effectiveness of the three treatments: abiraterone plus prednisolone (hereafter 'abiraterone'), prednisolone alone (hereafter 'prednisolone'), and mitoxantrone plus prednisolone, (hereafter 'mitoxantrone'). The manufacturer developed a survival-based decision model with three health states: pre-progression, post-progression and dead. People with castration-resistant metastatic prostate cancer were assumed to enter the model in the pre-progression state having already received treatment with docetaxel-based chemotherapy. The model assumed that people who experienced disease progression would enter the post-

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progression state. The model assumed that people who received abiraterone did not take it after their disease had progressed, but would continue taking prednisolone or prednisone. The model assumed that patients in the mitoxantrone and prednisolone treatment groups would also continue taking prednisolone or prednisone until death. For the analysis of abiraterone compared with mitoxantrone, the model further assumed for mitoxantrone treatment a maximum duration of 30 weeks (median duration of 12 weeks) in the base-case analysis.

3.10   For its base-case analysis, the manufacturer's preferred population was comprised of people who had received one prior chemotherapy only. The number of people remaining in each health state after each cycle of the model (3 weeks, based on the dosing cycle of mitoxantrone) was calculated directly from the overall survival and progression-free survival curves from the one prior chemotherapy subgroup of the COU-AA-301 trial. Time in the post-progression state was calculated as the difference between overall survival and progression-free survival. The model used a lifetime horizon of 10 years. The analysis took an NHS and personal social services perspective and discounted costs and benefits at 3.5%.

3.11   The key parameters of clinical effectiveness in the model were progression-free and overall survival, which, for the base-case analysis, the manufacturer derived from data from the updated analysis for the 'one prior chemotherapy' subgroup of the COU-AA-301 trial. The manufacturer assumed in the base-case analysis that progression-free survival and overall survival did not differ between treatment with mitoxantrone and treatment with prednisolone or prednisone. The manufacturer argued that this assumption was justified because available evidence suggests that mitoxantrone

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compared with corticosteroids does not extend survival in people without prior chemotherapy, and therefore it would not be expected to extend survival in people who had received chemotherapy. In the base-case analysis, the manufacturer used data from the abiraterone arm of the COU-AA-301 trial to model overall survival for abiraterone, and data from the prednisolone arm to model overall survival for mitoxantrone and for prednisolone. The manufacturer used data from Kaplan–Meier curves up to the point at which 10% of patients remained in the trial. After this, the manufacturer extrapolated the overall survival curves assuming a constant hazard rate (exponential function).

3.12   In the base-case analysis, the manufacturer modelled progression-free survival for patients taking abiraterone who had received only one prior chemotherapy. The model assumed that when patients discontinued abiraterone treatment they moved from the pre-progression to the post-progression health state. Treatment discontinuation rates were based on data from the COU-AA-301 trial for patients who had only one prior chemotherapy, and were used as a proxy for progression-free survival (see section 3.5). To estimate time spent in the pre-progression state, the manufacturer took Kaplan–Meier (time to treatment discontinuation) survival data from the one prior chemotherapy subgroup of the COU-AA-301 trial up to the point at which 5% of participants remained at risk. Beyond this 5% cut-off, the manufacturer extrapolated survival curves assuming a constant hazard rate. The manufacturer used data from Kaplan–Meier curves for patients in the prednisolone group who had received one prior chemotherapy to model progression-free survival for patients taking mitoxantrone or prednisolone. The manufacturer did not extrapolate these data further because just

over 2% of patients were still on treatment (that is, their condition had not progressed).

3.13   In the base-case analysis, the manufacturer also modelled overall survival based on Kaplan–Meier survival curves for the one prior chemotherapy subgroup from the COU-AA-301 trial. As for progression-free survival, the manufacturer extrapolated overall survival using a constant hazard but, because of greater censoring, chose a cut-off of 10% and applied it to all three treatment groups.

3.14   In the model, the key differences between the mitoxantrone group and the prednisolone group were the treatment durations (maximum duration of mitoxantrone treatment was 30 weeks) and costs (mitoxantrone was associated with more adverse reactions and therefore higher costs). The 30-week maximum duration of mitoxantrone treatment (ten 3-weekly cycles) was taken from the TROPIC trial, which compared cabazitaxel plus prednisolone with mitoxantrone plus prednisolone in patients with metastatic prostate cancer who had received docetaxel chemotherapy. Mitoxantrone was associated with less pain than prednisolone, and the manufacturer assumed that this lower level of pain was equal to that for abiraterone. However, because more treatment-related adverse reactions with mitoxantrone were observed in the TROPIC trial, mitoxantrone was associated with a smaller gain in health-related quality of life compared with abiraterone.

3.15   Utility values for the pre-progression and post-progression health states were identified by the manufacturer in two studies that specifically collected EQ-5D utility values in men with metastatic prostate cancer (Sandblom et al. 2004; Sullivan et al. 2007). Sandblom et al. estimated utility values in Swedish men (n = 1442) with prostate cancer (metastatic or non-metastatic) in the year

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before death. The manufacturer stated that this study provided good estimates of utility for the post-progression health state but did not provide an accurate estimate of utility for people who had stable disease after receiving further treatment following progression on or after docetaxel treatment (defined as the pre-progression health state for the purpose of the analysis) in the UK. Sullivan et al. collected utility values for men (n = 280) with metastatic prostate cancer in an observational study carried out across Europe, Australia and North America at baseline and at 3, 6 and 9 months follow-up. The baseline utility was 0.635 for the whole cohort and 0.715 for the UK subgroup (n = 29). The manufacturer stated that Sullivan et al. had not provided separate utility values for people whose disease had progressed and those whose disease had not progressed, and therefore the study did not provide suitable utility values for the post-progression health state.

3.16   Therefore, to estimate utility values for the pre-progression state, the manufacturer undertook a two-stage analysis to convert FACT-P data from the COU-AA-301 trial into EQ-5D utility values. In the first stage, the manufacturer analysed data from a manufacturer-sponsored cross-sectional study in five European countries (including the UK) of 291 patients with castration-resistant metastatic prostate cancer who completed both FACT-P and EQ-5D questionnaires. The data were used to develop an algorithm to map FACT-P data to EQ-5D using an ordinary least squares (OLS) regression model and the UK EQ-5D tariff. In the second stage, the manufacturer used this mapping algorithm to convert FACT-P data from patients in both treatment groups in the COU-AA-301 trial who had only one prior chemotherapy to EQ-5D utility values. The manufacturer then applied a separate regression analysis to derive an effect of treatment on utility. The manufacturer did not explicitly

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model adverse reactions, but instead assumed that any differences in adverse reactions between patients taking abiraterone or prednisolone were reflected in the overall utility values estimated from the FACT-P mapping algorithm.

3.17 In the base-case analysis the manufacturer applied different pre-progression utility values to the abiraterone and prednisolone groups (utility values provided as academic in confidence). The manufacturer also applied the pre-progression utility value for abiraterone to the mitoxantrone group. In order to estimate the impact of grade 3 or 4 adverse reactions from mitoxantrone on the utility of the pre-progression state, the manufacturer conducted a separate regression, which estimated an average utility decrement based on the occurrence of at least one adverse reaction. The manufacturer estimated that, based on the average number of grade 3 or 4 adverse reactions reported for abiraterone (from the COU-AA-301 trial) and mitoxantrone (from the TROPIC trial), mitoxantrone increased the occurrence of grade 3 or 4 adverse reactions by 32% compared with abiraterone. This resulted in a small utility decrement for mitoxantrone compared with abiraterone (utility values provided as academic in confidence).

3.18 The manufacturer noted that the COU-AA-301 trial did not collect FACT-P data beyond the point of disease progression (treatment discontinuation). Therefore, the manufacturer used the study by Sandblom et al. to provide an estimate of utility for the post-progression state. In this study, utility values ranged from 0.58 in men with 8–12 months to live to 0.46 in those with less than 4 months to live. Based on the average utility observed for men in the last 8 months of life, the manufacturer used a utility value of 0.50 for the post-progression state in the economic model. This

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post-progression utility value was applied for all three treatment groups.

3.19   The manufacturer included the costs of drug treatment as costs of drug acquisition, administration and monitoring. Under the terms of the patient access scheme approved by the Department of Health, the cost of a 3-week cycle of abiraterone, based on a daily dose of 1 g, is commercial in confidence and not reported here. Dosing of mitoxantrone is determined by body surface area. The manufacturer assumed a value of 2.02 m², based on the average body surface area observed in the TROPIC trial. Based on a cost of £100 per 20-mg vial, and assuming a patient needs two vials, the cost of mitoxantrone used in the model was £200 per 3-week cycle. The model also assumed that a person receiving treatment with mitoxantrone would need one outpatient visit per 3-week cycle, resulting in a total cost of £448.45 per 3-week cycle. The cost of prednisolone was £1.03 for a 28-tablet (5-mg) pack (£1.55 per 3-week cycle at 10 mg daily). Because patients were taking prednisolone with abiraterone and with mitoxantrone, this cost was included for all three treatments and was assumed to continue after treatment with abiraterone and with mitoxantrone was discontinued until death. The costs of mitoxantrone and prednisolone were taken from the BNF (edition 61).

3.20   The model also included the costs of scheduled follow-up consisting of clinical visits, diagnostic imaging and clinical laboratory tests to monitor the status of the disease. To estimate scheduled UK medical resource utilisation in each treatment group, the manufacturer convened a clinical consensus panel, consisting of five oncologists and three oncology nurse specialists. Based on statistical analysis of data from the COU-AA-301 trial, the manufacturer estimated that unscheduled medical resource

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utilisation (because of unplanned clinical events) would be similar for patients whether taking abiraterone or prednisolone alone. Therefore, the manufacturer applied a one-off fixed cost of unplanned, event-related resource utilisation in the pre- and post-progression states to patients taking abiraterone or prednisolone alone. For patients receiving mitoxantrone, the manufacturer assigned the extra costs of treating grade 3 or 4 adverse reactions based on data from the TROPIC trial. The costs of other drugs (including bisphosphonates in the pre- and post-progression states for people taking any of the three treatments, and granulocyte colony-stimulating factor [G-CSF] to treat febrile neutropenia in the abiraterone and mitoxantrone groups) were also included in the model. Based on results from the UK subpopulation of the COU-AA-301 trial, in which a small proportion of patients received subsequent chemotherapy treatments, including taxanes and anthracenediones, the manufacturer assumed that a proportion of people in each treatment group would receive three cycles of cabazitaxel (currently being appraised by NICE) in the post-progression state. The manufacturer also estimated resource utilisation and costs for end-of-life care based on clinical expert opinion. These costs were applied for the last 3 months of life for patients taking any of the three treatment regimens.

3.21   The manufacturer's original base-case deterministic cost-effectiveness results for the one prior chemotherapy subgroup showed that mitoxantrone was extendedly dominated, that is, the incremental cost-effectiveness ratio (ICER) of mitoxantrone compared with prednisolone was higher than that of the next most effective alternative (abiraterone). The comparison between abiraterone and prednisolone alone resulted in an ICER of £52,851 per QALY gained (incremental costs and incremental QALYs

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provided as commercial in confidence). The manufacturer's original base-case probabilistic ICERs were similar. The manufacturer's original base-case deterministic cost-effectiveness results for the whole trial population showed that mitoxantrone was extendedly dominated by abiraterone and prednisolone alone whereas the comparison between abiraterone plus prednisolone and placebo plus prednisolone resulted in an ICER of £63,233 per QALY gained (incremental costs and incremental QALYs provided as commercial in confidence).

3.22   The manufacturer conducted a number of one-way sensitivity analyses on various model parameters which included: altering the time horizon from 10 years to 4, 6, or 8 years, varying the discount rates for costs and benefits from 3.5% each to 0% and 6%, using a Weibull instead of an exponential function to extrapolate survival beyond the cut-off point of the Kaplan–Meier curve for both progression-free and overall survival, using alternative estimates of utility for pre- and post-progression health states and for the effect on utility of treatment with abiraterone, and varying a number of cost input parameters (±50%). The results of these one-way sensitivity analyses indicated that the original base-case ICERs were fairly insensitive to changes in most, but not all, of the input parameters. Decreasing the baseline utility value for the pre-progression state to 0.538 increased the ICER significantly, resulting in an ICER for treatment with abiraterone compared with prednisolone of £77,000 per QALY gained. In one scenario analysis, the manufacturer assumed that patients taking mitoxantrone remained in the pre-progression state for longer than patients taking prednisolone only (HR 0.77). This scenario resulted in an ICER of £21,038 per QALY gained for mitoxantrone compared with prednisolone and an ICER of £62,843 per QALY

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gained for abiraterone compared with mitoxantrone. Results of the probabilistic sensitivity analysis showed that prednisolone had the highest probability (100%) of being cost effective at a level of £20,000 to £30,000 per QALY gained, whereas abiraterone had the highest probability of being cost effective at over £50,000 per QALY gained.

3.23 The ERG was satisfied with the methodological quality of the COU-AA-301 trial and considered that it provided persuasive evidence that abiraterone offers a survival advantage in patients with castration-resistant metastatic prostate cancer. However, the ERG stated that the one prior chemotherapy subgroup differed from the COU-AA-301 trial population and, because it was smaller, it had reduced statistical power for comparison of outcomes between the treatment arms. The ERG commented that the manufacturer had submitted a relatively straightforward economic model comparing the relevant comparators following docetaxel chemotherapy, and had closely adhered to the NICE reference case requirements for economic analysis.

3.24 The ERG commented that the factors with the most influence on the cost effectiveness of abiraterone compared with prednisolone and with mitoxantrone were the differences in the EQ-5D utility values attached to the pre- and post-progression health states for all three treatments, which the manufacturer had derived from different sources. The ERG noted that the mapping function, developed and used by the manufacturer to determine pre-progression utility values, had yet to appear in a peer-reviewed publication. The ERG noted that the pre-progression utility value for patients taking abiraterone, which was estimated from a function mapping FACT-P to EQ-5D, was similar to or higher than EQ-5D utility values for men of similar age taken from a survey of the

general UK population living in the community (Kind et al. 1998).
This survey reported average EQ-5D visual analogue scores of
between 0.800 and 0.750 for men aged between 60 and 79 years.
The ERG's clinical advisers suggested that, because the COU-AA-
301 trial may have been oversubscribed, the population selected
could have been fitter than generally seen in clinical practice.

3.25   The ERG noted that because most patients in the cross-sectional
study used to derive the mapping function were receiving
chemotherapy, both their FACT-P scores and EQ-5D utilities would
probably be lower than for patients in the COU-AA-301 trial who
were not taking chemotherapy, but who received abiraterone or
prednisolone. The ERG argued that this could have resulted in the
FACT-P mapping function converting FACT-P values outside the
reliable range of the mapping function, which would increase the
uncertainty around the manufacturer's derived EQ-5D utility values.
The ERG noted that the manufacturer derived the mapping function
from a restricted set of patients who provided FACT-P scores both
at baseline and over the course of the trial, but that over time, a
declining proportion of trial participants who remained on treatment
provided FACT-P scores. The ERG further noted that the
manufacturer's regression analysis was based on changes from
baseline rather than on absolute values of the scores and that the
baseline scores among those reporting FACT-P scores after
baseline may have been higher in the prednisolone group than in
the abiraterone group. The ERG suggested that patients receiving
prednisolone who reported FACT-P scores after baseline may have
had a smaller change in their scores than patients receiving
abiraterone because they had less severe disease at baseline.

3.26   The ERG had some concerns about the manufacturer's approach
to the regression analysis used to estimate separate pre-

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progression utility values for treatment with abiraterone and prednisolone. The ERG noted that the utility values used in the manufacturer's model implied that utility dropped when a patient discontinued treatment (disease progressed) but that the manufacturer assumed a larger utility decrement for discontinuing treatment with abiraterone than for discontinuing prednisolone. The ERG considered this pre-progression utility value to be an overestimate, which, by increasing the utility decrement when moving from the pre-progression to the post-progression state, would exaggerate the benefit of remaining on abiraterone treatment. The ERG also noted that the utility decrement applied when moving from stable to progressive disease in the ongoing NICE appraisal of cabazitaxel was lower than that used in this appraisal.

3.27   The ERG explored the manufacturer's methods for extrapolating overall survival and suggested that the manufacturer's decision to extrapolate beyond a cut-off of 10% of trial participants at-risk was arbitrary. However, the ERG was aware that when the manufacturer applied a cut-off of 5% in sensitivity analyses there was little impact on the ICERs for abiraterone compared with prednisolone. In contrast, the ERG's exploratory analyses using cut-offs ranging from 0% to 20% showed that the cut-off of 10% used by the manufacturer resulted in a relatively low ICER compared with other cut-off points. The ERG noted that when extrapolating progression-free survival, the manufacturer chose different cut-off points (or none at all) depending on the treatment. The ERG noted that when data from Kaplan–Meier survival plots of the prednisolone group were used in the economic model, 2% of patients remained in the pre-progression state, which may have slightly underestimated progression-free survival for the

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mitoxantrone and prednisolone treatment groups compared with abiraterone. The ERG also noted that the Kaplan–Meier curve for treatment discontinuation had an unusual shape, with many patients discontinuing treatment over a period of a few weeks at approximately 60 days into treatment. In the ERG's view, this was unlikely to represent actual disease progression which would be better represented by fitting a parametric distribution.

3.28   The ERG noted that there was uncertainty around the most appropriate functions for extrapolating overall survival and progression-free survival in the manufacturer's model. The ERG commented that by using patient-level trial data to generate Kaplan–Meier curves for overall survival (up to the cut-off) the manufacturer considered all time points. The ERG argued that patient-level Kaplan–Meier data, although representing observed data, may be less applicable to patients outside the COU-AA-301 trial than well-fitting parametric distributions. The ERG commented that when extrapolating overall survival using a constant hazard, the manufacturer used only two time points (baseline and cut-off). The ERG considered that this approach was less reasonable than applying a parametric distribution to the data representing all time points.

3.29   The ERG and manufacturer conducted exploratory analyses to assess the impact of fitting alternative parametric functions to data reflecting overall survival and progression-free survival from the COU-AA-301 trial. In response to requests from the ERG for clarification, the manufacturer indicated that the best-fitting parametric distributions (according to Akaike and Bayesian information criteria) were: a Weibull distribution for overall survival in the abiraterone group, a log-normal distribution for overall survival in the prednisolone group, and a log-logistic distribution for

progression-free survival for both abiraterone and prednisolone. The ERG and the manufacturer agreed that the log-normal distribution should not be used to extrapolate overall survival because its long tail resulted in implausibly long survival. The ERG also noted that when the log-logistic distribution was fitted to data for time to treatment discontinuation, the resulting curve crossed the extrapolated part of the Kaplan–Meier overall survival curve from the manufacturer's base case so that some patients appeared to remain in the pre-progression state after death, which is clinically impossible. In the ERG's view, a Weibull distribution should have been used to estimate overall and progression-free survival for abiraterone and for prednisolone alone at all time points rather than using extrapolated Kaplan–Meier curves. The ERG acknowledged that both approaches were associated with uncertainty. When the ERG fitted the Weibull parametric distribution to overall survival in both the abiraterone and prednisolone groups and an extrapolated (constant hazard) Kaplan–Meier curve for progression-free survival, the ICER for abiraterone compared with prednisolone was £56,339 per QALY gained. When the ERG fitted its preferred distribution, that is, a Weibull parametric distribution to overall survival and progression-free survival in both the abiraterone and prednisolone groups, the ICER for abiraterone compared with prednisolone increased to £58,116 per QALY gained.

3.30   In addition to fitting the Weibull distribution to estimate overall survival and progression-free survival, the ERG made changes to cost and utility parameters in the economic model. The ERG revised administration costs to reflect the costs of oncology outpatient visits and of administering mitoxantrone, and varied the proportion of patients receiving bisphosphonates following progression. The ERG corrected the manufacturer's regression

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analysis of utility for progression-free survival for patients who take prednisolone only. With these changes, mitoxantrone continued to be extendedly dominated and the ERG's revised base-case ICER for abiraterone compared with prednisolone was £60,084 per QALY gained.

3.31   The ERG conducted additional one-way sensitivity analyses for its revised base-case analysis. When the ERG varied the costs for unplanned use of medical resources the ICERs for abiraterone compared with prednisolone ranged from £60,492 to £67,554 per QALY gained. When the ERG varied utility estimates (provided as academic in confidence) ICERs for abiraterone compared with prednisolone ranged from £63,281 to £72,469 per QALY gained. When the ERG extrapolated overall survival for prednisolone using the truncated log-normal distribution, the ICER for abiraterone compared with prednisolone was £70,217 per QALY gained. Mitoxantrone continued to be extendedly dominated in all sensitivity analyses.

3.32   In response to the appraisal consultation document, the manufacturer revised the confidential discount under the patient access scheme agreed with the Department of Health. The manufacturer also amended the economic model to reflect the changes to costs suggested by the ERG. These included changes to administration costs to reflect the costs of oncology outpatient visits and of administering mitoxantrone, and changes to the proportion of patients receiving bisphosphonates following disease progression. As a result of these changes and the revised discount under the patient access scheme, the manufacturer's deterministic base-case ICER for abiraterone compared with prednisolone decreased to £46,800 per QALY gained for the one prior chemotherapy subgroup and to £52,851 per QALY gained for the

whole population (incremental costs and incremental QALYs provided as commercial in confidence).

3.33 The manufacturer conducted a number of one-way sensitivity analyses (see section 3.22) using the amended model for the one prior chemotherapy subgroup, resulting in ICERs for abiraterone compared with prednisolone of £42,904 to £51,110 per QALY gained. In all analyses, ICERs were most sensitive to changes to the utility value for the pre-progression health state and to the statistical approach used to model overall survival. When a utility value of 0.715 (taken from the UK subgroup of the study by Sullivan et al. 2007) was assigned to the pre-progression state, the ICER increased to £51,110 per QALY gained for abiraterone compared with prednisolone. When a Weibull parametric distribution was used to model overall survival, the ICER increased to £49,911 per QALY gained for abiraterone compared with prednisolone. The probabilistic sensitivity analysis showed that abiraterone had a 67% probability of being cost effective at £50,000 per QALY gained.

3.34 The ERG reviewed the amended model and revised analyses provided by the manufacturer in response to the appraisal consultation document. The ERG noted that the manufacturer's amended model retained extrapolation of the Kaplan–Meier curves using a constant hazard to model overall and progression-free survival as well as the original utility values for the pre- and post-progression health states. The ERG confirmed that the manufacturer had amended administration costs in the model to reflect the costs of oncology outpatient visits as suggested by the ERG. However, the ERG had concerns about the application of a half-cycle correction to the drug costs in the model by the manufacturer. The ERG noted that amending this half-cycle

correction in the model would increase the drug costs by approximately half the monthly cost and would slightly increase the ICERs.

3.35   After correcting the manufacturer's regression analysis of utility for the pre-progression health state, the ERG conducted exploratory analyses on the manufacturer's amended model to assess the impact of fitting different curves to estimate survival. For the one prior chemotherapy subgroup, the ERG's base-case ICER for abiraterone compared with prednisolone was £53,140 per QALY gained when a Weibull parametric distribution was used to estimate overall survival and progression-free survival. When the one prior chemotherapy subgroup was used with a Weibull distribution to estimate overall survival and a Kaplan–Meier curve for progression-free survival, the ERG's base-case ICER was £52,186 per QALY gained. When the whole trial population was used with a Weibull distribution to estimate overall survival and the Kaplan–Meier curve for progression-free survival, the ERG's base-case ICER was £60,038 per QALY gained. The ERG also conducted a number of sensitivity analyses in which it varied the utility values for the pre- and post-progression health states using values for metastatic prostate cancer identified by the manufacturer in a literature review plus those used in the ongoing appraisal of cabazitaxel. This resulted in ICERs ranging from £52,362 to £71,358 per QALY gained for the one prior chemotherapy subgroup. The ICERs from all of the ERG's analyses further increased when the ERG amended the half-cycle correction applied by the manufacturer to the drug costs (ICERs provided as commercial in confidence).

3.36   Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

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4   Consideration of the evidence

4.1   The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of abiraterone, having considered evidence on the nature of castration-resistant metastatic 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.

4.2   The Committee discussed the place of abiraterone in the clinical pathway of care for people with castration-resistant metastatic prostate cancer. The Committee noted that the main treatment options for patients whose disease progresses after first-line docetaxel include mitoxantrone, best supportive care, and re-treatment with docetaxel (which is not recommended by current NICE guidance). The Committee heard from clinical specialists that mitoxantrone is used rarely in UK clinical practice because there is little evidence that people who take it live longer, but the commissioning expert informed the Committee that 20%–30% of patients at this stage of the disease are treated with mitoxantrone. The Committee also heard from the clinical specialists that they would be unlikely to offer abiraterone to patients with an ECOG performance score of 2.

4.3   The Committee heard from the patient experts that the most important benefits of abiraterone were extension to life and improved quality of life, including less pain and improved mental and physical health. The Committee also heard that patient experts believed that adverse reactions to abiraterone treatment were tolerable and comparable to those associated with hormone

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treatment. The patient experts also commented that another advantage of abiraterone is that patients can take it orally at home.

Clinical effectiveness

4.4 The Committee considered the evidence submitted by the manufacturer on the clinical effectiveness of abiraterone. The Committee agreed with the manufacturer and the ERG that, although mitoxantrone was listed as a comparator in the scope, differences in the COU-AA-301 and the TROPIC trials made it difficult to indirectly compare mitoxantrone with abiraterone. The Committee heard from clinical specialists that participants in the COU-AA-301 trial were likely to be healthier than those who would receive abiraterone treatment in UK clinical practice. However, it acknowledged that, in response to the appraisal consultation document, a number of comments from clinical organisations suggested that participants in the COU-AA-301 trial would be similar to patients who would be considered for abiraterone treatment in UK clinical practice.

4.5 The Committee considered the different ways that progression-free survival had been defined in the COU-AA-301 trial: radiographic evidence of progression-free survival, 'modified' progression-free survival and time to treatment discontinuation. The Committee noted that determining progression-free survival from radiographic evidence was difficult because patients entered the study already with metastatic disease and could die of prostate cancer without any evidence of further radiological progression. The Committee heard from the clinical specialists that disease progression is not determined with a single measure and that they would also consider progression of a patient's symptoms. The Committee discussed whether discontinuing abiraterone treatment was an

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adequate proxy for progression of disease. The Committee heard from clinical specialists that in general patients stop treatment at approximately the same time as their disease progresses, but noted that some patients in the COU-AA-301 trial continued to take abiraterone after their disease had progressed. The Committee also noted that most patients in the COU-AA-301 trial discontinued abiraterone treatment for reasons other than disease progression. The Committee acknowledged uncertainty around this measure, but agreed that of the measures of disease progression in the COU-AA-301 trial, time to treatment discontinuation was the most reasonable indicator of disease progression.

4.6   The Committee discussed the results for the COU-AA-301 trial and noted that abiraterone was associated with a statistically significant improvement in median overall survival and median progression-free survival (based on time to treatment discontinuation) compared with prednisolone for both the whole (intention-to-treat) population (improvement in median overall survival for the whole population was 4.6 months in manufacturer's updated analysis) and the manufacturer's base-case population (patients who had received only one prior docetaxel-containing chemotherapy regimen; results for this subgroup are academic in confidence). The Committee also noted that patients receiving abiraterone were more likely to experience an improvement in symptoms, including pain, functional status and fatigue. The Committee therefore concluded that the evidence demonstrated that abiraterone was an effective second-line treatment for castration-resistant metastatic prostate cancer.

4.7   The Committee considered the manufacturer's base-case population of patients who had received one prior chemotherapy in the COU-AA-301 trial. The Committee noted that this subgroup did not match the population for which abiraterone is licensed (the

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therapeutic indication in the marketing authorisation does not stipulate only one prior chemotherapy) but probably reflected the population in England and Wales for whom abiraterone would be considered. The Committee noted that in the COU-AA-301 trial the relative median overall survival benefit for abiraterone was higher in the subgroup with one prior chemotherapy than in the subgroup with more than one prior chemotherapy, but tests for interaction showed that the difference between these two groups was not statistically significant. The Committee heard that the manufacturer considered the number of prior chemotherapies sufficiently important as a prognostic factor (in that more than one chemotherapy would imply a later stage of disease, more previous adverse reactions and more treatment-resistant tumours) to include it as a stratification factor for randomisation. The Committee also heard from the manufacturer that the difference in relative median overall survival benefit for abiraterone between the one prior chemotherapy subgroup and the subgroup who received more than one prior chemotherapy was supported by results for progression-free survival and other related outcomes from the COU-AA-301 trial. The difference was also supported by overall survival results from published studies of other second-line treatments for castration-resistant metastatic prostate cancer. The Committee accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease. Therefore, the Committee concluded that it was reasonable based on biological plausibility and the pre-specification of this group in the COU-AA-301 trial (as a stratification factor) to accept this patient subgroup and its associated effectiveness data as the base-case for the analysis.

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4.8 The Committee considered the evidence on adverse reactions associated with abiraterone. The Committee was aware that abiraterone may cause hypertension, hypokalaemia and fluid retention as a consequence of an increased mineralocorticoid concentration. The Committee noted that adherence to abiraterone in the COU-AA-301 trial was generally high and reflective of abiraterone use in clinical practice, and that adverse reactions were generally manageable and reversible. The Committee also noted that abiraterone is not associated with the more severe adverse reactions that can occur with cytotoxic drugs such as mitoxantrone. The Committee heard from the clinical specialists that abiraterone is a well tolerated oral medication. The Committee concluded that abiraterone is generally safe and that any associated adverse reactions are tolerable.

Cost effectiveness

4.9 The Committee considered the manufacturer's economic model, the assumptions on which the parameters were based, and the critique and exploratory analyses conducted by the ERG. The Committee concluded that the model closely adhered to the NICE reference case for economic analysis.

4.10 The Committee considered the comparator treatments (placebo plus prednisolone and mitoxantrone with or without prednisolone) and the population included in the economic model. The Committee noted that in the base-case analysis the manufacturer assumed that overall survival and progression-free survival were the same for patients taking mitoxantrone and patients taking prednisolone. The Committee agreed that, in the absence of any direct or indirect comparative data and the absence of published evidence showing

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any survival benefit for mitoxantrone in a population without prior chemotherapy, this assumption was reasonable.

4.11 The Committee considered the overall survival curve used in the manufacturer's economic model. The Committee noted that estimates related to overall survival were taken from the 'updated' analyses, which the Committee preferred to the 'primary' analyses. The Committee also noted that the manufacturer had modelled overall survival using Kaplan–Meier survival analysis of patient-level data from the COU-AA-301 trial up to a cut-off point at which a small proportion (10%) of patients were still alive. Beyond this, the manufacturer had extrapolated overall survival using a constant hazard. The Committee considered that the Kaplan–Meier survival curves specifically reflected the COU-AA-301 trial population and whether a well-fitting parametric distribution would be more applicable to all patients for whom abiraterone may be a potential therapy in clinical practice. The Committee noted that the 10% cut-off chosen by the manufacturer for overall survival produced a relatively favourable ICER compared with other possible cut-off points. The Committee heard from the manufacturer that fitting a specific parametric distribution to the overall survival curve was not necessary because survival data in the COU-AA-301 trial were almost complete and because additional analyses suggested that no single parametric function provides a better fit to the data than others. The Committee accepted that it may have been more appropriate to use a well-fitting parametric curve to extrapolate overall survival, but was also sympathetic to the manufacturer's argument that it is appropriate to use the observed Kaplan–Meier data when trial data were almost complete.

4.12 The Committee considered the modelling of progression-free survival in the manufacturer's base-case analysis. The Committee

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noted that time to treatment discontinuation was used as a proxy for disease progression in the economic model. The Committee was aware that the manufacturer was unable to determine the proportion of patients among those who discontinued therapy who met criteria for disease progression. The Committee agreed with the ERG that using time to treatment discontinuation as a proxy for disease progression was acceptable because of concerns about using radiographic imaging to monitor disease progression in prostate cancer. However, the Committee considered that, although time to treatment discontinuation may provide a reliable estimate of treatment costs in the model, it was less clear whether it provided a reliable estimate of the QALY gains associated with being in the pre-progression state. The Committee was also aware that disease is likely to progress before patients stop abiraterone. However, the Committee concluded that changing the duration of progression-free survival did not significantly alter the ICERs associated with treatment with abiraterone relative to treatment with prednisolone.

4.13   The Committee noted the manufacturer's inconsistent approach to extrapolating progression-free survival beyond the data observed in the trial, with extrapolation beyond the time at which 5% of the population remained for abiraterone, and no extrapolation for prednisolone. The Committee also considered the ERG's concerns that the shape of the Kaplan–Meier survival curve for treatment discontinuation in the prednisolone group was unusual, with a high proportion of patients discontinuing treatment over a narrow time period after approximately 60 days of treatment. The Committee agreed that this was unlikely to represent actual disease progression and that a well-fitting parametric distribution should have been used. The Committee noted that when the manufacturer

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used a Weibull parametric distribution to extrapolate progression-free survival beyond the 5% cut-off for abiraterone, the base-case ICER increased slightly from £46,800 to £47,200 per QALY gained. The Committee accepted that, although it would have been more appropriate to use a well-fitting parametric curve to extrapolate progression-free survival, data for time to treatment discontinuation in the COU-AA-301 trial were virtually complete and thus the impact on the ICER of using alternative assumptions was minimal.

4.14   The Committee considered the utility values used in the economic model for the pre-progression and the post-progression health states. The Committee was aware that the manufacturer had not provided EQ-5D values for health states obtained directly from patients, which would have been in line with the preferred methods recommended by NICE, but had derived utility values for the pre-progression state from an algorithm that mapped FACT-P scores to EQ-5D utility values from a separate cross-sectional dataset of patients with castration-resistant metastatic prostate cancer. The Committee also noted that this mapping algorithm produced utility values that differed according to treatment. The Committee was aware that patients contributing to the cross-sectional dataset may have differed from the population in the COU-AA-301 trial and from patients who might receive abiraterone in the UK. The Committee also heard from the manufacturer that its mapping algorithm had not been externally validated. The Committee noted that the mapping algorithm resulted in pre-progression utility values which were similar to or higher than utility values observed in the age-matched general population. In the Committee's view this might not be reasonable because people with metastatic prostate cancer would be expected to have a poorer quality of life than people without prostate cancer. However, it heard from the manufacturer

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and consultees that, because patients in the COU-AA-301 trial had few comorbidities and had been fit enough to receive chemotherapy, it was not implausible that they would have a similar health-related quality of life to people of the same age in the general UK population. The Committee also noted that the utility values for the pre-progression state were slightly higher than those used in the ongoing technology appraisal of cabazitaxel for metastatic hormone-refractory prostate cancer (derived from interim analysis of a small study). The Committee acknowledged a sensitivity analysis from the manufacturer which showed that when a published utility value of 0.715 (from the UK subgroup of Sullivan et al. 2007) was assigned to the pre-progression state, the ICER increased to £51,110 per QALY gained for abiraterone compared with prednisolone. However, the Committee was aware that the utility value taken from Sullivan et al. was based on a small patient subgroup and that this study may have included patients at different stages of prostate cancer. Additionally, the Committee also heard from one clinical specialist that the estimated utility gain for abiraterone compared with prednisolone may have been underestimated and, as a result, the ICER may have been overestimated. The Committee concluded that there was uncertainty about the validity of the utility values for the pre-progression health state derived from the manufacturer's FACT-P mapping algorithm, but that no other robust utility value for the pre-progression health state was currently available.

4.15   The Committee noted that the COU-AA-310 trial did not collect FACT-P data after patients stopped treatment and therefore the manufacturer identified a utility value for the post-progression state from the literature (see section 3.18). This value was lower than that estimated by the ERG from the manufacturer's FACT-P

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mapping algorithm for patients at the end of treatment. The Committee acknowledged that the utility value estimated from patients at the end of treatment in the COU-AA-301 trial was based on a small group of patients healthy enough to complete the questionnaire after treatment discontinuation. The Committee also heard from the manufacturer that this utility value was measured at the start of progression and would not reflect the mean utility experienced by a patient throughout progression up to the time of death. The Committee acknowledged that although patients were considered to be in the pre-progression state for the purposes of the model, they already had metastatic disease and would be unlikely to have the decrease in utility modelled by the manufacturer when progressing further to the post-progression state (defined only by stopping treatment). However, the Committee noted that a patient's health related quality of life could be very poor in the last months of life and that the post-progression utility value should also reflect this. Additionally, the Committee heard from the manufacturer that the utility difference between the pre-progression and post-progression health states was within the range used in recent technology appraisals of treatments for metastatic and advanced solid tumours. The Committee noted that a smaller utility difference between the pre-progression and post-progression health states would increase the ICER. The Committee concluded that uncertainty remained about the true difference in utility values between the pre-progression and post-progression states in the economic model, but that no other robust utility values that correctly capture the changes in health related quality of life in progressed disease were currently available.

4.16   The Committee considered the assumptions related to resource use in the manufacturer's economic model. The Committee noted

that the ERG was generally satisfied with these assumptions. The Committee also noted that, in response to the appraisal consultation document, the manufacturer had made corrections to resource use suggested by the ERG (see section 3.32). The Committee was informed by the ERG that the manufacturer had incorrectly applied a half-cycle correction to the drug costs in the model, and that changing this increased the drug costs by approximately half the monthly cost. The Committee was satisfied that the change to the half-cycle correction to drug costs would probably result in only small increases in the ICER.

4.17   The Committee considered the most plausible ICERs presented by the manufacturer and also by the ERG in its exploratory analyses. The Committee agreed that, for nearly all analyses presented, mitoxantrone was extendedly dominated by abiraterone. In the Committee's view, a reasonable starting point for its decision was the manufacturer's base-case ICER for abiraterone plus prednsiolone compared with prednisolone alone of £46,800 per QALY gained for the one prior chemotherapy subgroup (when the discount agreed in the patient access scheme was included). The Committee agreed that the ICER would increase by a small amount if the model correctly accounted for the half-cycle correction to drug costs. The Committee noted that use of a lower utility value for the pre-progression health state or the assumption of a smaller difference in utility between the pre-progression and post-progression health states would further increase the ICER. However, the Committee agreed that more reliable utility values for the pre-progression and post-progression health states were not available. The Committee also noted that the ICER would increase slightly if a parametric curve were used to model overall and progression-free survival. However, the Committee agreed that it

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was acceptable to use the observed Kaplan–Meier data given the completeness of the survival data in the COU-AA-301 trial. The Committee therefore agreed that once these factors had been taken into account, the most plausible ICER was likely to be higher than the manufacturer's base-case estimate for the one prior chemotherapy subgroup, but would be under £50,000 per QALY gained.

4.18   The Committee was mindful that the NICE 'Guide to the methods of technology appraisal' states that there should be a strong case for accepting an ICER above £30,000 per QALY gained and judgements should specifically take account of:

- the degree of certainty around the ICER
- any strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured
- whether the innovative nature of the technology adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure.

4.19   The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. The Committee considered that abiraterone may offer a step change in treatment because it is life-extending rather than only palliative but that this element of innovation would already be accounted for when moving from an ICER of £20,000 to £30,000 per QALY gained. The Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions. The benefit related to being an oral drug was not

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captured in the analysis because the model applied the same utility benefit to abiraterone as to mitoxantrone. The Committee therefore acknowledged that abiraterone provides health-related quality of life benefits other than those captured in the QALY calculation for patients currently receiving mitoxantrone, and that the ICER would decrease when these benefits were taken into consideration. The Committee heard that a portion of the profits from sales of abiraterone would contribute to publically funded medical research within the UK. However, the Committee concluded that although health benefits were likely to accrue from this research, these did not contribute to health-related quality of life as defined within the 'Guide to the methods of technology appraisal'.

4.20   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 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.

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

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4.21   The Committee discussed whether abiraterone fulfilled the criteria for consideration as a life-extending, end-of-life treatment. For castration-resistant metastatic prostate cancer that has progressed after first-line chemotherapy, the Committee agreed that the first criterion related to life expectancy was fulfilled, because life expectancy from trials including patients randomised to best supportive care were less than 15 months. The Committee considered by how much abiraterone extended life. It noted that in the manufacturer's base-case economic analysis the estimated mean overall survival gain for abiraterone was greater than 3 months (median overall survival gain 4.6 months; mean overall survival gain commercial in confidence). The Committee concluded that an improvement of more than 3 months in mean overall survival had been robustly demonstrated. The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently

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eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. The Committee concluded that the additional weight to be assigned to the original QALY benefits in this patient group fell within the range considered acceptable for an end-of-life treatment. The Committee therefore recommended abiraterone in combination with prednisolone or prednisone as an option for the treatment of castration-resistant metastatic prostate cancer that has progressed after one docetaxel-containing chemotherapy regimen.

4.22　　The Committee discussed whether any equality issues required consideration in this appraisal. The Committee was aware that people who are undergoing or have completed male to female gender reassignment can develop prostate cancer. The Committee therefore concluded that this appraisal should refer to 'people' rather than to men. Furthermore, the Committee had been made aware that these patients may find it uncomfortable to attend male urology clinics; however, the Committee agreed that the treatment of prostate cancer would be likely to be provided in oncology clinics.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen	Section
Key conclusion		
Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if: • their disease has progressed after one docetaxel-containing chemotherapy regimen, and • the manufacturer provides abiraterone with the discount agreed in the patient access scheme.		1.1
The Committee concluded that the available evidence demonstrated that abiraterone was a clinically effective second-line treatment for castration-resistant metastatic prostate cancer.		4.6
The Committee agreed that, although the most plausible ICER was likely to be higher than the manufacturer's base-case estimate of £46,800 per QALY gained for the one prior chemotherapy subgroup, it was likely to be less than £50,000 per QALY gained.		4.17
The Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions.		4.19
The Committee concluded that abiraterone fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee also concluded that the additional weight that would need to be assigned to the original QALY benefits in this patient group was within the range considered acceptable for an end-of-life treatment.		4.21
Current practice		
Clinical need of patients, including the availability of alternative treatments	The main treatment options for patients whose disease progresses after first-line docetaxel include mitoxantrone, best supportive care, and re-treatment with docetaxel (which is not recommended by current NICE guidance). The Committee heard from clinical specialists that mitoxantrone is used rarely in UK clinical practice. The Committee also heard from the clinical specialists that they would be unlikely to offer abiraterone to patients with an ECOG performance score of 2.	4.2
The technology		

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Proposed benefits of the technology	The Committee heard from the patient experts that the most important benefits of abiraterone were extension to life and improved quality of life, including less pain and improved mental and physical health. The Committee also heard that patient experts believed that adverse reactions to abiraterone treatment were tolerable and comparable to those associated with hormone treatment.	4.3
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions.	4.19
What is the position of the treatment in the pathway of care for the condition?	Abiraterone has a UK marketing authorisation for use 'with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen'.	2.1
Adverse reactions	The Committee was aware that abiraterone may cause hypertension, hypokalaemia and fluid retention as a consequence of an increased mineralocorticoid effect. The Committee noted that adverse reactions were generally manageable and reversible. The Committee concluded that abiraterone is generally safe and that any associated adverse reactions are tolerable.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The manufacturer's clinical-effectiveness evidence was derived solely from the COU-AA-301 trial (a phase III, placebo-controlled, randomised, double-blind, multicentre trial carried out across 130 sites in 13 countries, including the UK).	3.1

Relevance to general clinical practice in the NHS	The Committee heard from clinical specialists that participants in the COU-AA-301 trial were likely to be healthier than those who would receive abiraterone treatment in UK clinical practice. However, it acknowledged that, in response to the appraisal consultation document, a number of comments from clinical organisations suggested that participants in the COU-AA-301 trial would be similar to patients who would be considered for abiraterone treatment in UK clinical practice.	4.4
Uncertainties generated by the evidence	The Committee acknowledged uncertainty around the measure used for determining disease progression in the COU-AA-301 trial. However, it agreed that of the different ways of defining disease progression in the COU-AA-301 trial, time to treatment discontinuation was the most reasonable indicator of disease progression.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The manufacturer's base case analysis included a subgroup of the COU-AA-301 trial who had received one prior chemotherapy. The Committee accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease. Therefore, the Committee concluded that it was reasonable based on biological plausibility and the pre-specification of this group in the COU-AA-301 trial (as a stratification factor) to accept this patient subgroup and its associated effectiveness data as the base-case for the analysis	4.7
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Abiraterone was associated with a statistically significant improvement in median overall survival and median progression-free survival (based on time to treatment discontinuation) compared with prednisolone for both the whole (intention-to-treat) population and the one prior chemotherapy subgroup.	4.6
	The primary analysis of the whole (intention-to-treat) population of the COU-AA-301 trial reported that median overall survival was	3.3

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	statistically significantly longer in the abiraterone group than the prednisolone group (14.8 months compared with 10.9 months, hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.54 to 0.77).	
	Median progression free survival (measured by time to treatment discontinuation) in the primary analysis of the whole population for the abiraterone group was statistically significantly longer than in the prednisiolone group (8 months compared with 4 months), with similar results in the updated analysis.	3.5
	The Committee concluded that the evidence demonstrated that abiraterone was an effective second-line treatment for castration-resistant metastatic prostate cancer.	4.6
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer submitted an economic model comparing three treatments: abiraterone (plus prednisolone), prednisolone alone, and mitoxantrone (plus prednisolone).	3.9, 3.10
	The manufacturer developed a survival-based decision model with three health states: pre-progression, post-progression and dead. The model used a lifetime horizon of 10 years. The Committee concluded that the model closely adhered to the NICE reference case for economic analysis.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee accepted that, although it may have been more appropriate to use a well-fitting parametric curve to extrapolate overall and progression-free survival, it was acceptable to use the observed Kaplan–Meier data from the COU-AA-301 trial to estimate survival because survival data in the trial were almost complete.	4.11, 4.13
Incorporation of health-related quality-of-life benefits and utility values. Have any potential significant and substantial	The Committee concluded that there was uncertainty about the validity of the utility values for the pre-progression health state derived from the manufacturer's FACT-P mapping algorithm, but that no other robust utility value for the pre-progression health state was currently available.	4.14

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health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that uncertainty remained about the true difference in utility values between the pre-progression and post-progression states in the economic model. model, but that no other robust utility values that correctly capture the changes in health related quality of life in progressed disease were currently available.	4.15
	The benefit related to being an oral drug was not captured in the analysis because the model applied the same utility benefit to abiraterone as to mitoxantrone. The Committee therefore acknowledged that abiraterone provides health-related quality of life benefits other than those captured in the QALY calculation for patients currently receiving mitoxantrone, and that the ICER would decrease when these benefits were taken into consideration.	4.19
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	-
What are the key drivers of cost effectiveness?	The Committee noted that use of a lower utility value for the pre-progression health state or the assumption of a smaller difference in utility between the pre-progression and post-progression health states would further increase the ICER. The Committee also noted that the ICER would increase slightly if a parametric curve were used to model overall and progression-free survival.	4.17
Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that, for nearly all analyses presented, mitoxantrone was extendedly dominated by abiraterone. In the Committee's view, a reasonable starting point was the manufacturer's base-case ICER for abiraterone plus prednisolone compared with prednisolone alone of £46,800 per QALY gained for the one prior chemotherapy subgroup. The Committee agreed that the ICER would increase by a small amount if the model correctly accounted for the half-cycle	4.17

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	correction to drug costs. The Committee noted the uncertainty about the utility values, but agreed that more reliable utility values for the pre-progression and post-progression health states were not available. The Committee also noted that the ICER would increase slightly if a parametric curve were used to model overall and progression-free survival, but that it was acceptable to use the observed Kaplan–Meier data given the completeness of the survival data in the COU-AA-301 trial.	
	The benefit related to abiraterone being an oral drug was not captured in the analysis because the model applied the same utility benefit to abiraterone as to mitoxantrone. The Committee therefore acknowledged that abiraterone provides health-related quality of life benefits other than those captured in the QALY calculation for patients currently receiving mitoxantrone.	4.19
	The Committee therefore agreed that once these factors had been taken into account, the most plausible ICER was likely to be higher than the manufacturer's base-case estimate for the one prior chemotherapy subgroup, but would be less than £50,000 per QALY gained.	4.17
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer of abiraterone has agreed a patient access scheme with the Department of Health. This involves a single confidential discount applied to the list price of abiraterone.	2.3
End-of-life considerations	The Committee agreed that the criteria related to short life expectancy (less than 24 months) without treatment, extension to life (at least 3 months) with treatment and small patient population were met. Therefore, the Committee concluded that abiraterone meets the criteria for an end-of-life treatment.	4.21
Equalities considerations and social value judgements	The Committee was aware that people who are undergoing or have completed male to female gender reassignment can develop prostate cancer. The Committee therefore	4.22

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concluded that this appraisal should refer to 'people' rather than to men.	

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [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.

5.3 The Department of Health and the manufacturer have agreed that abiraterone will be offered to the NHS under a patient access

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scheme which makes abiraterone available with a discount on the list price. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Janssen [NICE to add details at time of publication].

6 Related NICE guidance

Published

- Prostate cancer: diagnosis and treatment. NICE clinical guideline 58 (2008). Available from www.nice.org.uk/guidance/CG58

- Docetaxel for the treatment of hormone refractory prostate cancer. NICE technology appraisal guidance 101 (2006). Available from www.nice.org.uk/guidance/TA101

- Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. NICE technology appraisal guidance 255 (2012). Available from www.nice.org.uk/guidance/TA255

- Improving outcomes in urogenital cancers: the manual. NICE cancer service guidance (2002). Available from www.nice.org.uk/guidance/CSGUC

7 Review of guidance

7.1 The guidance on this technology will be considered for review in April 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

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Amanda Adler

Chair, Appraisal Committee

May 2012

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Appendix A: Appraisal Committee members, and NICE project team

A   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 four 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, Cambridge

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

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Dr Jeff Aronson

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

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Cairns

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

Dr Mark Chakravarty

External Relations Director - Pharmaceuticals and Personal Health, Oral Care Europe

Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Eleanor Grey

Lay member

Dr Neil Iosson

General Practitioner

Terence Lewis

Lay member

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 Rubin Minhas

General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Elizabeth Murray

Reader in Primary Care, University College London

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Dr Peter Norrie

Principal Lecturer in Nursing, De Montfort University

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

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

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Alun Roebuck

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

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

Dr Florian Alexander Ruths

Consultant Psychiatrist and Cognitive Therapist at the Maudsley Hospital, London

Navin Sewak

Primary Care Pharmacist, NHS Hammersmith and Fulham

Roderick Smith

Finance Director, West Kent Primary Care Trust

Cliff Snelling

Lay member

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

Tom Wilson

Director of Contracting and Performance, NHS Tameside and Glossop

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Dr Nerys Woolacott

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

B   NICE project team

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

Matthew Dyer
Technical Lead

Fiona Rinaldi
Technical Adviser

Jeremy Powell
Project Manager

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Appendix B: Sources of evidence considered by the Committee

A   The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Connock M, Cummins E, Shyangdan D et al. Abiraterone acetate for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy. Warwick Evidence, University of Warwick (December 2011)

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

I   Manufacturer/sponsor:

- Janssen

II   Professional/specialist and patient/carer groups:

- British Association of Urological Surgeons
- British Uro-Oncology Group
- Cancer Research UK
- Macmillan Cancer Support
- PCaSO – Prostate Cancer Network
- Prostate Cancer Charity
- Prostate Cancer Support Federation
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

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- United Kingdom Oncology Nursing Society

III   Other consultees:

- Department of Health
- NHS Hertfordshire
- NHS Bradford and Airedale
- Welsh Government

IV   Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- MRC Clinical Trials Unit
- Prostate Action

C   The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on abiraterone by attending the initial Committee discussion and providing written evidence to the Committee. They were invited to comment on the ACD.

- Dr John Staffurth, , nominated by the RCP on behalf of the NCRI/RCP/RCR/ACP/JCCO and the British Uro-Oncology Group – clinical specialist
- Dr Isabel Syndikus clinical expert, nominated by the RCP on behalf of the NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Mr Hugh Gunn, nominated by the Prostate Cancer Federation – patient expert
- Mr Stuart Watson, nominated by the Prostate Cancer Charity – patient expert

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D   The following individuals were nominated as NHS Commissioning experts by the selected NHS trust allocated to this appraisal. They gave their expert/NHS commissioning personal view on abiraterone by attending the initial Committee discussion and providing written evidence to the Committee. They were invited to comment on the ACD.

- Mrs Rasila Shah, nominated by NHS Hertfordshire - NHS Commissioning expert

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

- Janssen

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