# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using abiraterone in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 8) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using abiraterone in the NHS in England.

For further details, see the Guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 15th January 2015

Fourth Appraisal Committee meeting: to be confirmed

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

# 1 Appraisal Committee's preliminary recommendations

1.1 Abiraterone is not recommended for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated.

1.2 People whose treatment with abiraterone was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

# 2 The technology

2.1 Abiraterone acetate (Zytiga, Janssen) is a selective androgen synthesis inhibitor that works by blocking cytochrome P450 17 alpha-hydroxylase. It blocks androgen production in the testes and adrenal glands, and in prostatic tumour tissue. Abiraterone is administered orally in combination with prednisolone or prednisone. It is indicated for treating 'metastatic castration resistant [hormone-relapsed] prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated'. It is also indicated for treating 'metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen'.

2.2 The summary of product characteristics lists the following adverse reactions for abiraterone as being very common (that is, occurring in 1 in 10 or more people): diarrhoea, urinary tract infection,

hypokalaemia (low blood potassium concentrations), hypertension (high blood pressure) and peripheral oedema (swelling of the limbs). The summary of product characteristics states that 'other important adverse reactions' are cardiac disorders, hepatotoxicity and fractures. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price of abiraterone is £2930 for 120 tablets (excluding VAT; British national formulary [BNF], accessed online November 2015). In its submission, the company proposed to reduce the list price to £2300 for 120 tablets if this appraisal recommended abiraterone. The company also agreed a new complex patient access scheme (PAS) with the Department of Health, which involves the NHS paying the new list price for abiraterone for the first 10 months of treatment. After 10 months, the Company will rebate the cost of any subsequent tablets prescribed. The reduced price and new complex PAS were used in the economic analyses reported in section 3. However, as this draft guidance does not recommend abiraterone, the cost of abiraterone will remain at £2930 for 120 tablets and the complex PAS will not be implemented. The simple discount PAS for abiraterone, which was agreed as part of the appraisal of abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen, still exists.

# 3 The company's submission

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

## *Clinical effectiveness*

3.1 The clinical-effectiveness evidence presented in the company's submission came from COU-AA-302, a worldwide trial in which 9%

of the trial population were from the UK. This randomised controlled trial compared abiraterone plus oral prednisone or prednisolone (referred to hereafter as abiraterone) with placebo plus prednisone/prednisolone (referred to hereafter as placebo) in 1088 people; 546 people were allocated to the abiraterone arm (1 g abiraterone daily plus 5 mg prednisone/prednisolone twice daily) and 542 people were allocated to placebo plus prednisone/prednisolone 5 mg twice daily. Patients in the trial stopped abiraterone or placebo at disease progression, if they had not already stopped for another reason (for example, because of adverse reactions). After disease progression, patients in the trial were followed up for up to 60 months after stopping treatment or until the patient was lost to follow-up, or withdrew consent; median follow-up was 27.1 months. The trial had co-primary end points of radiographic progression-free survival and death (overall survival).

3.2 The statistical plan called for a single pre-planned analysis for radiographic progression-free survival after 378 events had accumulated. This plan included 3 interim analyses and 1 final analysis for overall survival after 15%, 40%, 55% and 100% of the 773 deaths occurred that the company had determined it would need to find a difference between the 2 treatment arms. The company's statistical plan for COU-AA-302 stated that, to be considered statistically significant, the p value for radiographic progression-free survival should be less than 0.01 and the p value for the final analysis should be less than 0.04. Because of the repeated analyses of overall survival, the p values at which the results could be considered statistically significant were $p<0.0001$, 0.0005, 0.0034 and 0.040 respectively for each of the 4 analyses. COU-AA-302 was unblinded by the company between the second and third interim analyses, based on advice from the Independent Data Monitoring Committee (IDMC). The IDMC considered abiraterone to have a 'highly significant advantage' for patients,

despite the p value for overall survival not meeting the criteria for statistical significance. The company's submission presented data from the second interim analysis (December 2011; when the trial was still blinded) and the third interim analysis (May 2012; after the trial was unblinded and 3 people in the placebo group had crossed over to the abiraterone group). The company's additional evidence included data from the final analysis of overall survival (May 2014); by this time point, 93 people had crossed over from placebo to abiraterone.

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

3.4 The median treatment duration in COU-AA-302 was 13.8 months in the abiraterone arm and 8.3 months in the placebo arm, based on the third interim data cut. Treatment was continued until disease progression (defined by radiographic progression or unequivocal

clinical progression, for example, need for alternative cancer therapy), or if the patient had adverse reactions, started a new anticancer treatment, had medications prohibited by the trial or withdrew consent to take part in the trial. By 10 cycles (28 days per cycle), 70% of people were taking abiraterone and 30% were taking placebo. By 20 cycles, 38% of people were taking abiraterone and 21% were taking placebo. By 40 cycles, 15% of people were taking abiraterone and less than 1% were taking placebo.

3.5 By the final analysis, 67% of people in the abiraterone arm and 80% of people in the placebo arm had had subsequent treatment. About 57% of people in the abiraterone arm and 61% of people in the placebo arm had docetaxel. Eighteen per cent of people in the abiraterone arm and 19% of people in the placebo arm went on to have cabazitaxel. Forty four per cent of people in the placebo arm had abiraterone (of whom 17% had abiraterone before docetaxel and 27% had it as subsequent therapy) and 13% of people in the abiraterone arm had abiraterone again. Eight per cent of people in the abiraterone arm and 6% of people in the placebo arm had sipuleucel-T. Sixteen per cent of people in the abiraterone arm and 10% of people in the placebo arm had enzalutamide.

3.6 Radiographic progression-free survival was defined as time from randomisation to 1 of the following: progression by bone scan (adapted Prostate Cancer Working Group criteria), CT or MRI (modified Response Evaluation Criteria in Solid Tumor [RECIST] criteria) and death. Scans were done every 8 weeks after the first 24 weeks and every 12 weeks thereafter. An independent radiologist unaware of study group assignments determined radiographic progression-free survival, but only until unblinding, after which local radiologists determined progression. The company used intention-to-treat (ITT) analyses including all patients for efficacy analyses. By May 2012 (the point at which the company

did its third interim analysis of overall survival), 292 (53.5%) of people in the abiraterone arm and 352 (64.9%) of people in the placebo arm had had radiological progression. The median time to radiographic progression-free survival was 16.5 months (95% confidence interval [CI] 13.8 to 16.8 months) in the abiraterone arm and 8.2 months (95% CI 8.0 to 9.4 months) in the placebo arm (hazard ratio [HR] 0.52, 95% CI 0.45 to 0.62; p<0.0001).

3.7 At the third interim analysis (when 55% of the 773 deaths on which the study was powered had occurred), 200 (36.6%) people in the abiraterone arm and 234 (43.2%) people in the placebo arm had died. The median overall survival in the abiraterone arm was 35.3 months (95% CI 31.2 to 35.3 months) and 30.1 months (95% CI 27.3 to 34.1 months) in the placebo arm (HR 0.79, 95% CI 0.66 to 0.96, p=0.0151). Again, this p value did not meet the pre-defined value for statistical significance (p=0.0034, see section 3.2). By the final data cut-off, 354 (65%) people in the abiraterone arm and 387 (71%) people in the placebo arm had died. The median overall survival was 34.7 months (95% CI 32.7 to 36.8 months) in the abiraterone arm and 30.3 months (95% CI 28.6 to 33.3 months) in the placebo arm (HR 0.81, 95% CI 0.70 to 0.93).The company stated that adjusting for subsequent active treatments would reduce the hazard ratio to 0.74 but did not describe the methods of this adjustment.

3.8 The company presented safety data from the 'safety population' in COU-AA-302 (that is, 1082 people who had had at least 1 dose of any study medication). By the third interim analysis, no statistically significant difference in the rates of drug-related serious adverse events were reported (relative risk [RR] 1.14, 95% CI 0.81 to 1.61) but more people had drug-related grade 3–4 adverse events with abiraterone than with placebo (HR 1.30, 95% CI 1.03 to 1.65). The most frequently reported adverse events affecting 5% or more

people were fatigue, back pain, arthralgia, nausea, peripheral oedema, constipation and diarrhoea, and they were mostly grade 1 or 2. Abiraterone was associated with more grade 3 or 4 increased alanine aminotransferase (5.5% compared with 0.7%, RR 7.47, 95% CI 2.65 to 21.07), increased aspartate aminotransferase (3.1% compared with 0.9%, RR 3.39, 95% CI 1.26 to 9.12) and dyspnoea (breathing difficulty) (2.6% compared with 0.9%, RR 2.79, 95% CI 1.01 to 7.69) but less hydronephrosis (retention of urine in the kidney causing swelling) (0.2% compared with 1.5% RR 0.12, 95% CI 0.02 to 0.99) than placebo.

3.9 The health-related quality of life of patients in COU-AA-302 was measured using the Functional Assessment of Cancer Therapy (FACT prostate cancer [P] subscale). The company presented the results as the median time to a decrease of 10 or more points and the hazard ratio of abiraterone relative to placebo. People randomised to abiraterone showed a longer median time to a 10-point decrease in total FACT-P score (12.7 months, 95% CI 11.1 to 14.0) than people randomised to placebo (8.3 months, 95% CI 7.4 to 10.6), HR 0.79 (95% CI 0.67 to 0.93, p=0.0046).

3.10 The ERG had concerns about how the company used data from the FACT-P measure in its submission; it presented the results only as time-to-event data and did not provide scores by treatment arm for baseline or follow-up. The ERG commented that the company stated that the main drivers of reduced health-related quality of life reported by patients with metastatic hormone-relapsed prostate cancer are bone pain, fatigue, sexual disturbances and interrupted social relationships. Of these, the company only reported time to an increase in pain intensity (rather than the differences in pain intensity between the 2 treatment arms). The time to an increase in the worst pain intensity (an increase in baseline BPI score of 30%

or more on 2 consecutive occasions) showed no difference between the 2 treatment arms.

### *Cost effectiveness*

3.11 The company did not identify any published studies of cost effectiveness directly relevant to the decision problem, so it did a new analysis. The company produced an individual time-to-event model (discrete event simulation), tracking patients at an individual level through a sequence of treatments until they reached a maximum age of 100 years, to reflect a lifetime horizon. Costs were considered from the NHS and personal social services perspective and a 3.5% discount rate was applied. The company's base case compared 2 treatment pathways:

- abiraterone followed by docetaxel followed by best supportive care
- best supportive care followed by docetaxel followed by abiraterone.

Modelled patients passed through 3 treatment phases (pre-docetaxel, on-docetaxel and post-docetaxel). In each treatment phase, patients could have active treatment or best supportive care. Once the active treatment had stopped, patients had best supportive care until starting their next treatment or until death (if the patient did not have further treatment). The model included whether subsequent treatments were suitable after ending an active treatment. For example, if a patient's disease had progressed, the modelled patients were monitored in a phase (lasting over 6 months in the company's base case) of pre-docetaxel best supportive care to assess whether moving on to docetaxel was suitable. Patients who were too unwell to have docetaxel (people with a Karnofsky performance status of 60% or less [approximately an ECOG performance status of 2 and above])

transitioned to best supportive care and had no further treatment until death.

3.12 Some patients in COU-AA-302 had cabazitaxel after docetaxel. Because cabazitaxel has a survival benefit compared with best supportive care, but is not recommended in NICE's technology appraisal on cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen, the company adjusted post-docetaxel survival estimates from COU-AA-302 to exclude the survival benefit associated with cabazitaxel. The company made this adjustment by modelling the survival benefit of abiraterone compared with best supportive care after docetaxel (using data from the COU-AA-301 trial, which had assessed abiraterone taken after docetaxel). It then adjusted the survival of people who had cabazitaxel after docetaxel in the abiraterone arm of COU-AA-302 to exclude this benefit. It did not adjust the survival estimates of the placebo arm. The company carried out a scenario analysis in which it did not include a survival adjustment for cabazitaxel (see section 3.20). The model censored patients who had cabazitaxel before docetaxel. The company did not adjust for other active treatments that were used in the COU-AA-302 trial but are not used in the NHS after abiraterone, including sipuleucel-T (the marketing authorisation has been withdrawn) or enzalutamide. The company assumed that, after a patient with progressed disease exhausted all treatment options, best supportive care would evolve to palliative care.

3.13 The model consisted of 17 prediction equations to estimate the time to starting treatment, time to stopping treatment and time to death within the treatment phases and also to estimate the disease status of the patient at a particular position in the modelled treatment pathway (see table 1). The company constructed the equations in a series of steps, each needing a number of decisions.

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

**Table 1: prediction equations used in the company's base case**

| Prediction equation | Extrapolation |
|---|---|
| • Time from starting to stopping first treatment with abiraterone or BSC[1,2]<br>• Time from starting docetaxel to death (if patient died while on docetaxel)[2] | Log-logistic |
| • Time from stopping abiraterone or BSC to starting docetaxel[2] | Log-normal |
| • Time from starting to stopping docetaxel<br>• Time from stopping docetaxel to starting next (third) treatment<br>• Time from starting to stopping third treatment<br>• Time from stopping abiraterone to death (if patient died before starting docetaxel)<br>• Time from stopping BSC to death (if patient died before starting docetaxel)<br>• Time from stopping docetaxel to death (if patient died after stopping docetaxel but before next treatment starts)<br>• Time from stopping third treatment to death | Weibull |
| • ECOG performance status (4 equations, each for a different place in the treatment pathway)<br>• Disease progression (measured by prostate-specific antigen levels) when stopping abiraterone or BSC<br>• Radiographic progression when stopping abiraterone or BSC<br>• Opiate use when stopping abiraterone or BSC | None |
| [1]Company sensitivity analysis used Weibull; [2]ERG sensitivity analyses used Weibull<br>Abbreviations: BSC, Best supportive care; ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group | |

3.14 The company derived utility values for its base case from the company-sponsored 'UK mCRPC patient utility study'. This study was an online survey of 163 men with mCRPC in the UK who had previously taken anti-androgen tablets for more than 1 month but had since stopped (unless they had had surgical castration). The study did not compare men taking abiraterone with men not taking abiraterone and assumed that patients had the same utility

regardless of their treatment, provided that they were in the same treatment phase. Patients with mCRPC were divided into the following subgroups:

- No or mild symptoms after androgen deprivation therapy had failed; chemotherapy not yet clinically indicated (n=50). The mean EQ-5D utility value was 0.83.
- Symptoms after androgen deprivation therapy had failed; chemotherapy clinically indicated but not started (n=50). The mean EQ-5D utility value was 0.63.
- After androgen deprivation therapy had failed; having chemotherapy (n=17). The mean EQ-5D utility value was 0.69.
- After androgen deprivation therapy had failed; post chemotherapy, completed 1 or more cycles of chemotherapy (n=46). The mean EQ-5D utility value was 0.70.

The utility value for people receiving best supportive care before death was assumed to be 0.5 based on a published study (Sandblom et al. 2004). The company did not apply a utility decrement for adverse events with different treatments.

3.15 The company also presented utility values derived from mapping FACT-P to EQ-5D from the data collected in COU-AA-302 (see section 3.9). The company used data from an observational study of patients with mCRPC in 6 European countries (including the UK), in which both EQ-5D and FACT-P data were available to develop an algorithm to map FACT-P data to EQ-5D using an ordinary least squares regression model and the UK EQ-5D tariff. The company applied this mapping algorithm to map FACT-P data from patients in both treatment groups in the COU-AA-302 study to EQ-5D utility values. From this, the company calculated a utility gain of 0.021 for people while they were taking abiraterone (either pre- or post-docetaxel).

3.16 The company grouped the use of medical resources into 'scheduled' and 'unscheduled'. Scheduled resources included disease-related tests including imaging, diagnostic and clinical laboratory tests. To determine the frequency of scheduled appointments over a 3-month period during the different stages of the disease pathway, the company surveyed 53 oncologists. The company applied higher resource use for patients having abiraterone than for patients on best supportive care in both the pre- and post-docetaxel setting for the first 3 months of abiraterone treatment to account for the additional monitoring as specified in the summary of product characteristics. Thereafter, the company assumed that patients incurred the same costs in both treatment arms.

3.17 The company estimated the frequency of unscheduled medical resource use (for example, adverse events while on treatment) using data from COU-AA-301 (for post-docetaxel abiraterone or best supportive care) and COU-AA-302 (for pre-docetaxel abiraterone or best supportive care). COU-AA-301, the key clinical trial in NICE's technology appraisal on abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (hereafter referred to as TA259), compared abiraterone plus prednisone or prednisolone with placebo plus prednisone or prednisolone in people whose disease had progressed on or after docetaxel therapy and who had an ECOG performance status of 0 to 2. For people having docetaxel, the company used the rates of grade 3 and 4 adverse events reported in the literature and consulted its clinical advisors on the costs of treating such events. The unscheduled medical resource use associated with best supportive care came from the COU-AA-301 trial. The cost of unscheduled medical care per month was:

- £93.79 for abiraterone and best supportive care before docetaxel
- £380.29 while having docetaxel, best supportive care post-docetaxel, abiraterone post-docetaxel or best supportive care before death.

The company also applied a one-off cost of £3598 to account for palliative care in the last 3 months of the best supportive care phase.

3.18 The company's model used the following costs:

- £2300.00 per 30 days for abiraterone (based on a 1 g daily dose). To reflect the new complex patient access scheme (PAS), the cost of abiraterone was incurred only for the first 10 months of treatment.
- £2.63 per month for 10 mg prednisone or prednisolone taken daily (applied in both the abiraterone and best supportive care arms).
- £1240.00 per month for docetaxel (based on 1 dose every 3 weeks for a patient of average weight based on the patient characteristics in COU-AA-302). In its submission, the company used the list price for docetaxel, but the Committee was concerned that the list price might be higher than that paid by the NHS. So, in its additional evidence, the company calculated the cost of docetaxel by applying a 20% discount to the British national formulary (BNF; edition 67) price of £1069.50, resulting in a cost of £855.60 per 160-mg vial. An additional administration cost of £214.00 was applied for docetaxel.

The company estimated that some patients would not take the full licensed dose of abiraterone ('non-adherence') and so reduced the cost of abiraterone prescribed before docetaxel by 2%. The company's model did not include the training or administration

costs associated with implementing the new complex PAS. It estimated that these costs would be £388 per year per hospital or homecare provider.

3.19 In the company's deterministic base-case analysis, abiraterone was associated with an incremental cost of £16,055, 0.62 life years gained and 0.56 quality-adjusted life years (QALYs) gained compared with best supportive care. The estimated incremental cost-effectiveness ratio (ICER) was £28,563 per QALY gained. The company did not present a probabilistic ICER but presented the results of a probabilistic sensitivity analysis and cost-effectiveness acceptability curves.

3.20 The company did deterministic one-way sensitivity analyses. Increasing or decreasing the size of the treatment effect of abiraterone had the largest effect. Decreasing the treatment effect by 2 standard errors increased the ICER to £38,070 per QALY gained. Increasing the treatment effect by 2 standard errors decreased the ICER to £22,908 per QALY gained. The company carried out a scenario analysis in which it replaced the log-logistic distribution for the equation 'time from starting to stopping first treatment with abiraterone or BSC' with a Weibull distribution (see table 1). Using the Weibull distribution increased the ICER to £35,789 per QALY gained. A scenario in which the survival estimate in the abiraterone arm was not adjusted for cabazitaxel use (see section 3.12) resulted in an ICER of £27,738 per QALY gained.

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

3.22 When the ERG ran the model, the ICER for the company's deterministic base case differed slightly from that reported by the company (that is, the ICER was £28,598 per QALY gained rather than £28,563 per QALY gained).

3.23 The ERG stated that the model structure lacked face validity because it did not allow the possibility of dying during abiraterone treatment, or during best supportive care before docetaxel treatment, or during post-docetaxel treatments. It noted that, in COU-AA-302, 5 patients had died before the end of abiraterone or placebo treatment.

3.24 The ERG commented that the model population was not the same as the COU-AA-302 ITT population because the model included only the subgroup of 902 people (of the 1088 people in the ITT population) with complete baseline data for covariates. The company did not provide the characteristics of this subpopulation in its submission. In its clarification response, the company stated that there was not a statistically significant difference in the time to stopping treatment and overall survival between the ITT population and the population with complete baseline data for covariates.

3.25 The ERG agreed with the company that using the EQ-5D utility values from the UK mCRPC utility study was the preferred approach given the uncertainty about the mapped utility values based on the FACT-P responses from COU-AA-302. The ERG considered whether the utility value for the pre-docetaxel treatment phase would be expected to be different between treatment arms. In the base case, the ERG noted that the company had applied a utility increment for people taking abiraterone (see section 3.15), and that the company stated that this was based on the benefits experienced with abiraterone compared with best supportive care with respect to pain and fatigue. The ERG did not agree with this approach because, in COU-AA-302, abiraterone led to significantly

more adverse events (both overall and grade 3–4) than best supportive care. The ERG considered it more appropriate to incorporate and apply separate utility decrements for each separate adverse event in the model.

3.26 The ERG noted that the company used a different utility increment for patients taking abiraterone (before or after docetaxel) in the current appraisal (0.021) than it did for patients taking abiraterone after docetaxel in its previous submission for TA259 (0.046). The ERG also preferred to apply a utility decrement to the baseline utility values for people not taking abiraterone, rather than adding on an increment to baseline utility values for people taking abiraterone.

3.27 The ERG stated that its preferred base case would:

- include a disutility of 0.046 to be applied in the post-docetaxel phase for patients not on abiraterone
- derive prediction equations for time to stopping treatment, time to starting treatment and time to death from the full ITT population in COU-AA-302, accounting for treatment effect only, and not including other risk predictors based on baseline characteristics
- not adjust the cost of abiraterone for non-adherence because the NHS would not recover the cost of dispensed medication for people who do not take the full course of treatment.

Applying the first assumption (post-docetaxel disutility if not having abiraterone) to the company's base case resulted in an ICER of £29,498 per QALY gained. Applying new risk equations based on the ITT population resulted in an ICER of £35,191 per QALY gained. Removing the cost adjustment for non-adherence to abiraterone resulted in an ICER of £29,307 per QALY gained. The

combination of these 3 scenarios (the ERG's exploratory base case) resulted in an ICER of £35,486 per QALY gained.

3.28 The ERG noted that the post-docetaxel survival in the current model was much lower than at the same point in the care pathway in TA259, which had appraised the cost effectiveness of abiraterone taken after docetaxel compared with best supportive care. In a sensitivity analysis, the ERG modified the prediction equation so that the post-docetaxel survival was similar to that estimated in TA259. This increased the 'ERG exploratory base case' ICER from £35,486 to £39,722 per QALY gained.

3.29 The ERG did 4 additional sensitivity analyses:

- The ERG stated that it was unclear how the company had adjusted for treatment with cabazitaxel in COU-AA-302 in the model (see section 3.12). Therefore, it tested a scenario without adjusting for cabazitaxel use. This decreased the ICER from the ERG's exploratory base-case estimate of £35,486 to £34,771 per QALY gained.
- The ERG stated that a log-logistic model, as used for 2 prediction equations in the company's base case, is often criticised for its long tail, which may result in an unrealistic survival benefit. The ERG therefore used a Weibull model to extrapolate the data for time from starting to stopping treatment with abiraterone or best supportive care, and time from starting treatment with docetaxel to death while on docetaxel treatment. This increased the ICER to £55,616 per QALY gained.
- The ERG stated that its criticisms of log-logistic models also apply to log-normal models. The ERG therefore used a Weibull model rather than a log-normal distribution to extrapolate time from stopping first treatment to starting docetaxel. This

decreased the ICER from the ERG's exploratory base-case estimate from £35,486 to £34,928 per QALY gained.

- The ERG noted that in the model the time between stopping first treatment (with abiraterone or best supportive care) and starting docetaxel was over 5 months, but in clinical practice this was likely to be much shorter. Fixing this time to 1.2 weeks for both the abiraterone and best supportive care arm decreased the ERG's exploratory base case ICER from £35,486 to £30,581 per QALY gained.

3.30 Most analyses from the company and the ERG applied the new complex PAS to abiraterone used before and after docetaxel. Following a request from NICE, the ERG provided an additional analysis that applied the new complex PAS to abiraterone used before docetaxel and applied the existing simple PAS to abiraterone used after docetaxel (in the best supportive care arm of the model). The new scenario increased the ERG's base-case ICER from £35,486 to £37,859 per QALY gained. The ERG's scenario using Weibull rather than log-logistic curves for 2 prediction equations, and also applying the existing simple PAS to abiraterone used after docetaxel, resulted in an ICER of £59,567 per QALY gained.

**Estimates of life expectancy for patients for whom abiraterone is indicated**

3.31 The company presented survival data from 2 studies in its response to the appraisal consultation document that it had not included in its original submission. One was a systematic literature review by Kirby et al. (2011) citing that the median survival was between 9 months and 30 months for patients with castrate-resistant prostate cancer and between 9 and 13 months for people with metastatic disease. The other study was an observational analysis of a trial population (Hussain et al. 2006) documenting an

association between prostate-specific androgen levels and mortality in people with prostate cancer. The company reiterated that the 2012 European Association of Urology guidelines stated a mean survival of between 9 and 27 months for metastatic disease.

3.32 Full details of all the evidence are in the Committee papers.

# 4 Consideration of the evidence

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

4.1 The Committee considered current treatment options in England for people with metastatic hormone-relapsed prostate cancer after failed androgen deprivation therapy who have no or only mild symptoms. The Committee heard from clinical experts that, when cytotoxic chemotherapy is indicated, most people have docetaxel. The clinical experts stated that docetaxel is normally offered to people with rapidly progressing disease who are fit enough for chemotherapy and who have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (or a World Health Organization performance status consistent with this). They added that deferring docetaxel in this group would not be appropriate because the disease rapidly progresses, and patients may not be fit enough to have it at a later date. However, when people have no or mild symptoms, clinicians may instead offer best supportive care including corticosteroids such as prednisolone or dexamethasone. The Committee heard from the clinical experts that some patients chose not to have docetaxel. The Committee heard that

abiraterone, which is taken with prednisolone, received a marketing authorisation in December 2012 for use before chemotherapy. It understood that patients can currently get abiraterone at this point in the treatment pathway through the Cancer Drugs Fund, but that the current funding arrangements within the Cancer Drugs Fund will come to an end in April 2016. It heard from the clinical experts that there is no consensus on how to decide whether to offer abiraterone to patients, but that clinicians would generally offer it, in addition to best supportive care, to people with few symptoms to delay chemotherapy, or to treat people who are unable or do not wish to have chemotherapy. The Committee also understood from the clinical experts that they switch patients from abiraterone to docetaxel within a week of disease progression if the patients are fit enough for docetaxel. The Committee was aware that, during the course of this appraisal, enzalutamide had received a marketing authorisation for use before chemotherapy. It noted that enzalutamide is currently being appraised by NICE and was available through the Cancer Drugs Fund. The Committee accepted that, when deciding whether to offer abiraterone, enzalutamide, corticosteroids or docetaxel, clinicians would take into account a person's fitness for chemotherapy, performance status, symptom severity and the patient's views on taking chemotherapy.

4.2 The Committee discussed the relevant comparators for abiraterone, noting that the scope issued by NICE in 2012 included docetaxel and best supportive care. It understood that the company did not present a comparison of abiraterone with docetaxel because the marketing authorisation states that abiraterone is indicated for people for whom chemotherapy is not yet indicated. The Committee agreed that this was appropriate. The Committee noted that enzalutamide was now available for the same indication as abiraterone, but was not included in the final scope issued by

NICE for the appraisal of abiraterone because at that time, enzalutamide was not licensed for this indication. The Committee agreed that enzalutamide should not be included as a comparator in its decision-making for abiraterone. The Committee considered that the key comparison in this appraisal was between a sequence of a) abiraterone followed by docetaxel and subsequent treatments, and b) watchful waiting (including best supportive care) followed by docetaxel and subsequent treatments (which, in current clinical practice in England, includes abiraterone for sequence b). The Committee acknowledged that some patients may not have docetaxel at any stage.

4.3 The Committee heard from the patient experts that it is important to have the option of delaying chemotherapy because chemotherapy has adverse effects that reduce people's quality of life. The patient experts advised that chemotherapy may be particularly poorly tolerated by older people or those who lack support from a partner or carer. The patient experts stated that some people may choose not to have, or to delay, chemotherapy to avoid its debilitating effects and to maximise their quality of life, even if it may mean dying sooner. However, the Committee also noted responses to consultation suggesting that disease and performance status may worsen and that this may lead to some people becoming unable to tolerate the side effects associated with chemotherapy later on or to gain the full survival advantage from the sequence of treatments now available. The Committee appreciated that abiraterone delayed the time to treatment with chemotherapy in COU-AA-302. It also understood that patients taking abiraterone switch to docetaxel when clinically indicated, so that chemotherapy is not delayed once needed. The Committee concluded that there is some uncertainty about the benefits or consequences of delaying chemotherapy, but accepted the view of patients that delaying chemotherapy is of value to them.

4.4 The Committee discussed using abiraterone in people who are not fit enough for chemotherapy. It heard from clinical experts, commentators during consultation and the company that these patients currently get abiraterone through the Cancer Drugs Fund. The Committee noted, however, that COU-AA-302 included only people with a good performance status (ECOG 0 or 1) and few comorbidities (see section 3.3), and so did not include people unfit for chemotherapy. The Committee therefore considered that there was no clinical evidence available to allow it to appraise the cost effectiveness of abiraterone in this population. The Committee was also aware that the population for whom chemotherapy is indicated (that is, people with more than mild symptoms), but who are unfit for chemotherapy, are not included in the therapeutic indication for abiraterone. The Committee was therefore unable to make a separate recommendation for people who are not fit for chemotherapy.

### *Clinical effectiveness*

4.5 The Committee considered whether the randomised placebo-controlled trial COU-AA-302 was generalisable to clinical practice in England. It noted that the trial recruited 9% of its patients from the UK and that people in both arms had prednisolone/prednisone. The Committee considered that the placebo arm reflected best supportive care in England before treatment with chemotherapy in line with advice from the clinical experts (see section 4.1). The Committee heard from the clinical experts that the average age of people in COU-AA-302 was similar to that of the people who would be offered abiraterone in clinical practice in England. It heard that the reasons for stopping abiraterone treatment in the trial broadly reflect clinical practice in England. The Committee noted that patients in the study stopped treatment with abiraterone when their disease progressed radiographically or clinically, at which point

they could have other treatments including docetaxel. The clinical experts stated that, in clinical practice in England, people would get abiraterone or best supportive care until clinical progression rather than radiographic progression. The clinical experts advised that people switch to docetaxel within a week of clinical progression if they are fit enough to tolerate chemotherapy. Despite the difference in defining progression free survival, the Committee concluded that COU-AA-302 generally reflected clinical practice in the UK and was relevant to address the decision problem.

4.6 The Committee discussed the clinical-effectiveness results from COU-AA-302, noting that abiraterone delayed the progression of disease (diagnosed radiographically) compared with placebo. The Committee was aware that the survival benefit of abiraterone compared with placebo was not statistically significant at the second and third interim analyses, but was statistically significant at the final analysis. The Committee was aware that the company unblinded COU-AA-302 early, between the second and third interim analyses, based on advice from the Independent Data Monitoring Committee (see section 3.2). It also heard that, after unblinding, people in the trial having placebo could cross over to have abiraterone. The Committee requested that the company provide data on treatment switching and subsequent treatments in COU-AA-302, in order to understand the impact of these factors on the final survival estimates.

4.7 The Committee discussed the company's additional evidence about treatment switching and subsequent treatments in COU-AA-302. It noted that patients had treatments that prolong survival but are not routinely available in the NHS, specifically:

- About 42% of patients in the placebo group had cabazitaxel, sipuleucel-T or abiraterone before docetaxel. The Committee noted that, although currently offered via the Cancer Drugs

Fund, cabazitaxel is not recommended for prostate cancer in NICE's technology appraisal on cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Sipuleucel-T no longer has a UK marketing authorisation.

- About 27% of patients in the abiraterone group had cabazitaxel or sipuleucel T.

In the abiraterone group, 29% of patients had subsequent abiraterone or enzalutamide. However, such subsequent treatments would not currently be offered in the NHS. The Committee noted that the company provided evidence about selected additional therapies including docetaxel (which is part of established NHS treatment) and ketoconazole (which has not been proven to extend life); the Committee concluded it was not necessary to control for the effects of docetaxel and ketoconazole in analyses. The Committee agreed that treatment switching and subsequent treatments that are not available in the NHS probably extended survival in both groups of COU-AA-302, but the effect was probably greater for the placebo group because more people took these treatments. It was aware that the company's analysis controlling for treatment switching improved the hazard ratio for overall survival from 0.81 (unadjusted estimate) to 0.74, although it recognised that hazard ratios were not used in the modelling. Overall, the Committee concluded that abiraterone delayed disease progression and improved overall survival compared with placebo, but that there was uncertainty about the extent of the survival benefit.

### *Cost effectiveness*

4.8 The Committee understood that the company had developed a discrete event simulation model, rather than the more commonly used Markov model, because it allowed more flexibility to reflect a

sequence of treatments, and to model response to treatments that depend on previous treatments. In addition, the company had suitable patient-level data from COU-AA-302 to develop this type of model. The Committee agreed that using a discrete event simulation model was not unreasonable, but that the company's model was particularly complex. In particular, for each of the model's 17 equations predicting time to events, the Committee noted that the company made a large number of judgements when determining which covariates to include in the prediction equations and which parametric distributions to choose for extrapolation (see section 3.13 for how the company built the prediction equations). The Committee noted that some prediction equations included covariates that had not met the company's pre-specified statistical criteria for inclusion. The Committee concluded that the company had not fully justified the approach it used for choosing the different covariates to include in each prediction equation, and so questioned the model's validity. The Committee further concluded that the company's model was complex and lacked transparency, which made it difficult for the Evidence Review Group (ERG) to validate and critique, and for the Committee to determine the plausibility of the model outcomes.

4.9 The Committee discussed the clinical data used to inform the company's model. It noted that the company stated it preferred to use data from the third interim analysis of COU-AA-302 rather than the final analysis. This was because the company considered that the interim data needed less adjustment for patients who crossed over from the placebo group to the abiraterone group. The Committee concluded that it was reasonable to use data from the third interim analysis in the model, but it requested that the company provide further evidence comparing the modelled estimates with the final trial data for time on first treatment and overall survival (see sections 4.12 and 4.13).

4.10 The Committee discussed the company's choice of parametric distribution for each of the 10 equations in the model that needed extrapolating (see table 1). The Committee was aware that the company considered several functions and selected the best fitting distribution using statistical criteria and visual inspection. The Committee noted that:

- the equations to predict **'time from starting to stopping first treatment with abiraterone or best supportive care'** and **'time from starting docetaxel to death (if patient died while taking docetaxel)'** had been extrapolated with a log-logistic distribution
- the equation to predict **'time from stopping abiraterone or best supportive care to starting docetaxel'** had been extrapolated with a log-normal distribution
- all other prediction equations had been extrapolated with a Weibull distribution.

The Committee heard from the ERG that using log-logistic and log-normal distributions for extrapolating is sometimes criticised because these distributions have 'long tails', unlike the Weibull distribution. A 'long tail' means that some patients continue for a long time without having the relevant event (such as stopping treatment). The Committee, noting NICE's Guide to the methods of technology appraisal 2013, concluded that it was appropriate to explore the impact of using different parametric distributions on the model results.

4.11 The Committee discussed the sensitivity analyses that used different parametric distributions. It noted that using a Weibull instead of a log-normal distribution in both arms for the equation 'time from stopping abiraterone or best supportive care to starting docetaxel' had a minimal impact on the results of the model. Using

a Weibull instead of a log-logistic distribution for 1 equation (time from starting to stopping first treatment) increased the company's base-case incremental cost-effectiveness ratio (ICER) from £28,600 to £35,800 per quality-adjusted life year (QALY) gained. Similarly, using Weibull instead of log-logistic distributions for 2 equations (time from starting to stopping first treatment and time from starting docetaxel to death whilst taking docetaxel) increased the ERG's exploratory base-case ICER from £35,500 to £55,600 per QALY gained. The Committee heard from the company that data from the final analysis of COU-AA-302 supported using the log-logistic distribution to predict time on first treatment because, if people's disease responds to abiraterone, they tend to stay on it for a long time. The Committee asked the company to submit these data to help the Committee reach a decision about which parametric distribution was more appropriate for modelling.

4.12 The Committee discussed the new data from the final analysis of COU-AA-302 showing how long people took their first treatment (abiraterone or best supportive care). It inspected the Kaplan-Meier curves from the trial and compared them with the extrapolation curves used in the company's model (that is, log-logistic in the base case and Weibull in sensitivity analyses).

- For the abiraterone arm, for the time period (the trial period) for which data were available, the Committee agreed with the company that the log-logistic curve fitted the trial data better than the Weibull curve. However, it noted that the log-logistic curve predicted that some patients remained on abiraterone for a long time and about 4% took abiraterone for at least 8 years. The Committee heard from the company that there was anecdotal evidence that a few patients take abiraterone for several years. However, the Committee agreed that it had not seen data to support the extrapolation in the company's model because the

maximum follow-up time in the trial was about 5 years. The Committee noted that the patient access scheme for abiraterone meant the NHS would only pay for the first 10 months of abiraterone, and that the Weibull and log-logistic curves were similar during this period. The Committee recognised therefore that if time on first treatment was overestimated this would not be expected to have a large impact on the cost of abiraterone incurred, but would over-estimate the QALYs gained.

- For the best supportive care arm, the Committee was concerned that neither parametric distribution provided a good fit to the final trial data. It noted that both distributions overestimated the time that patients would remain on best supportive care.

Having considered the evidence carefully, the Committee did not agree with the company's statement that the final data supported the company's choice of a log-logistic distribution for predicting time on first treatment. The Committee could not choose a preferred parametric distribution for predicting time on first treatment because no data were available to validate predictions beyond about 5 years. Accordingly, it considered both the log-logistic curve and the Weibull curve in its decision-making (see section 4.21).

4.13 The Committee discussed the predictions of overall survival in the company's model. During the third committee meeting, it heard from the company that the final COU-AA-302 data supported the predictions in its model. The Committee had not seen these data, so it asked the company to submit these results. The Committee then inspected the final Kaplan-Meier overall survival curves from the trial and compared them with the survival curves predicted by the company's base-case model, which extrapolated beyond the trial data. The Committee noted that, beyond about 3 years of follow-up, for both treatment groups the trial data showed longer survival times than predicted by the model. The Committee

acknowledged that this may be because of treatment switching and the use of subsequent treatments in the trial that are not available on the NHS (see section 4.7). It was also aware that, because of these potential confounders, the company had used data from the third interim analysis for modelling rather than the final analysis. Nonetheless, the Committee did not agree with the company's statement that the final trial data supported its model predictions of overall survival. It concluded that the model predictions of overall survival were uncertain.

4.14 The Committee discussed the company's method for adjusting modelled survival times to remove the benefit of treatments that were used in the COU-AA-302 trial but are not used in the NHS. Based on the company's new evidence submission, the Committee understood that the survival times of patients in the abiraterone arm of the model were reduced to remove the benefit of cabazitaxel, enzalutamide and re-treatment with abiraterone. The Committee noted that cabazitaxel is not recommended by NICE and is currently available on the Cancer Drugs Fund. The Committee accepted that it was appropriate to adjust for treatments that have a survival benefit and which are not available in the NHS. However, it noted that the company's method (see section 3.12) was an approach that neither the ERG nor the Committee had seen before. The Committee noted that adjusting for subsequent treatments had a modest impact on the ICER (the company's base case with adjustment was £28,600 per QALY gained; a scenario without adjustment was £27,700 per QALY gained). The Committee also noted that the company did not adjust for treatment switching and subsequent treatments in the best supportive care arm of the model. Overall, the Committee concluded that adjustment for subsequent treatments in the abiraterone arm should be included in the analyses used for decision-making, recognising that such an

adjustment was included in the company's base case and scenario analyses, and the ERG's exploratory base case.

4.15 The Committee discussed the trial population used to inform the model. It noted that the company used results from the subgroup of 902 people in COU-AA-302 for whom complete data were available on baseline characteristics. The Committee heard that, in the company's opinion, it was necessary to use this 'full covariate subgroup' because covariates were needed to predict patients' response to the 3 lines of treatment in the model. The Committee heard from the ERG that the full covariate subgroup was a non-random subset of the overall intention-to-treat (ITT) population of 1088 people, and using the subgroup could bias the results of the model. That is, the reasons patients did not have complete data may have been related to the outcomes of the model. The Committee was aware that, in response to this concern, the company presented baseline characteristics for the full covariate subgroup. However, the Committee noted that the company had not tested whether this subgroup differed from the ITT population. The Committee further noted that survival curves from the ITT population in the trial showed little difference in death rates between the abiraterone and placebo groups within the first 18 months of follow-up. In contrast, the company's model (using data from the full covariate subgroup) showed that people having abiraterone lived longer than people having best supportive care within the first 18 months of follow-up. The ERG's approach of using the ITT population in the model increased the company's base-case ICER from £28,600 to £35,200 per QALY gained. The Committee was aware of the company's opinion that using the ITT population rather than the full covariate subgroup meant that the model outputs would be less similar to the trial results, but the Committee noted that it had not seen data to support this. The Committee concluded that the company's analysis based on the

subgroup with full covariate data may have overestimated the survival benefit of abiraterone. The Committee concluded that the ITT population represented all patients, was less likely to bias the results, and provided more data, and, for these reasons, preferred it.

4.16 The Committee discussed the survival estimates for the post-docetaxel phase of the model. It noted that abiraterone taken after docetaxel had been appraised in abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (hereafter referred to as TA259), but that the company had not used data from TA259 to check the validity of its model in the current appraisal. It also noted that the modelled post-docetaxel survival times were shorter in the current appraisal (based on data from COU-AA-302) than in TA259 (based on data from COU-AA-301). The Committee was aware that the ERG carried out a scenario analysis in which it fixed post-docetaxel survival to be the same as in COU-AA-301, and this increased the ICER. The Committee heard from the company that, although the estimates from COU-AA-301 came from a larger sample of patients, it did not consider these data to be relevant for modelling the current appraisal because the population in COU-AA-301 was different from that in COU-AA-302. In particular, the company stated that people in COU-AA-301 started docetaxel earlier in their treatment pathway than in COU-AA-302 and therefore people in COU-AA-301 were also fitter at the point they started post-docetaxel treatments. The Committee requested data to support this statement. The company's response stated that 70% of patients in COU-AA-301 had received only 1 course of treatment whereas a 'significant proportion' of patients in COU-AA-302 had received both abiraterone and docetaxel. The company advised that data on characteristics for the 2 trial populations, at the time when patients started post-docetaxel treatment, were not available

for patients in COU-AA-302. During the Committee meeting, the company stated that the model was designed to follow individual patients through several stages of treatment. In the company's opinion, it was not appropriate to use the COU-AA-301 data in the model because doing so would 'break randomisation' and it would not be possible to adjust the data to reflect differences in baseline characteristics between the COU-AA-301 trial and the modelled population. On balance, and because of the complex model chosen by the company, the Committee agreed with the company that it was appropriate to use COU-AA-302 to estimate post-docetaxel survival times. Nonetheless, it concluded that uncertainty about the modelled survival times persisted because only a small number of patients from COU-AA-302 contributed data to this phase of the model.

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

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

The Committee considered that, when a trial includes quality-of-life data (as in COU-AA-302), in line with its Guide to the methods of technology appraisal 2013, NICE prefers that these data are used to derive utility values in the model. However, the Committee had concerns about the study that the company used to map FACT-P data from COU-AA-302 to EQ-5D. Specifically, the Committee was

concerned about how the mapping function had been validated, whether uncertainty around the assumptions in the mapping function had been tested in sensitivity analyses, and how the company had chosen when to apply the mapped utility values rather than using values from other sources. The Committee questioned whether it was appropriate for the company to include an increment in utility associated with taking abiraterone, given that patients on abiraterone have more adverse events than patients on best supportive care. However, it heard from clinical experts that the adverse events people had on abiraterone were mild and tolerable, and the Committee noted that the utility increment associated with taking abiraterone came from trial data. It was also aware of the company's opinion that the adverse events that were more common with abiraterone did not impact on quality of life. The Committee accepted that it was appropriate to include a utility increment associated with taking abiraterone in the model. Overall, the Committee concluded that the company's modelled utility values were plausible.

4.18 The Committee discussed the costs used in the model.

- It understood that, in the COU-AA-302 trial, patients took 98% of the licensed dose on average and so the company's base-case model used 98% of the cost of the licensed dose of abiraterone. The Committee considered that the cost of unused tablets was unlikely to be recovered by the NHS, so the full cost of the licensed dose of abiraterone should be included in the model.
- The Committee noted that the administration costs of administering the PAS, although low, had not been included in the modelling and considered that these costs should have been included.
- The Committee noted that generic versions of docetaxel have become available during the course of the appraisal. To account

for this, the company had reduced the cost of docetaxel by 20% from the British national formulary cost (£856 for a 160-mg vial), and the ERG presented a scenario using the electronic market information tool (eMIT) cost (£35 for a 160-mg vial). It noted that using the eMIT cost increased the ERG's exploratory base case ICER from £35,500 to £37,500 per QALY gained, but recognised that other costs (for drugs or NHS care) which may have also changed during the course of the appraisal had not been amended. The Committee agreed that the cost of docetaxel may vary across the NHS, but it was likely to be closer to the eMIT cost than that modelled by the company.

The Committee noted that the Company's assumptions relating to these costs favoured abiraterone, but that including the Committee's preferred assumptions increased the ICER for abiraterone compared with best supportive care only slightly.

4.19 The Committee discussed how the company incorporated the abiraterone PAS in its model. It was aware of an existing simple discount PAS for abiraterone, which was agreed as part of TA259 (the appraisal of abiraterone after docetaxel). The Committee was also aware that, if the current appraisal recommended abiraterone, then the new complex PAS would apply to abiraterone used either before or after docetaxel, but if the current appraisal did not recommend abiraterone before docetaxel, then the old PAS would exist for abiraterone after docetaxel. The Committee noted that the company's model applied the new complex PAS to abiraterone used before but also after docetaxel. The Committee noted that an alternative approach was to apply the new complex PAS to abiraterone used before docetaxel (in the abiraterone arm of the model) and the existing simple PAS to abiraterone used after docetaxel (in the best supportive care arm of the model). It noted that the ERG's exploratory analyses applied the existing simple

PAS to abiraterone used after docetaxel and that this increased the ICER. The Committee heard that, although the company accepted that it was technically correct to apply the existing PAS to abiraterone used after docetaxel, it did not think that this approach was reasonable because the 2 PAS's would never exist at the same time. The Committee acknowledged that the 2 PAS's would not and could not exist at the same time, but nonetheless it agreed that it was appropriate to include the existing PAS in the best supportive care arm of the model and the new complex PAS in the abiraterone arm for the purposes of decision-making. This was because the existing PAS represented the current cost to the NHS of providing abiraterone after docetaxel, but also the future cost of providing abiraterone after docetaxel if the current appraisal did not recommend abiraterone before docetaxel. Overall, the Committee agreed that it preferred to apply the existing PAS in the best supportive care arm of the model, but acknowledged that a scenario analysis using this approach had a modest impact on the ICER.

4.20 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising abiraterone. It noted that the company had not made a case for the relevance of the PPRS in this appraisal. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. After asking the company, the Committee heard nothing to suggest that there is any basis for taking a different view on the PPRS in this appraisal of abiraterone. It therefore concluded that the PPRS payment mechanism was not applicable when considering the cost effectiveness of abiraterone.

4.21 The Committee discussed whether abiraterone could be considered a cost-effective use of NHS resources, noting that the company's base-case ICER was £28,600 per QALY gained. The Committee agreed that this ICER was not plausible because:

- The company's modelling approach using the subgroup with complete covariate data likely overestimated the difference between abiraterone and best supportive care, both in the duration of first treatment and in overall survival (see section 4.15).
- The company's model used a log-logistic curve to predict the duration of first treatment in both the abiraterone and best supportive care arms, and this resulted in some patients remaining on abiraterone for at least 8 years. The Committee did not see evidence to support such a long duration of treatment (see sections 4.11–4.12).
- The model survival curves did not provide a good fit to the final trial data and this increased the uncertainty around the ICER (see section 4.13).
- The company's model was complex and the ERG found it difficult to validate and critique. The Committee agreed that the lack of transparency in the model increased the uncertainty around the ICER (see section 4.8).

To address some of these concerns, the Committee discussed analyses making alternative assumptions. It noted that these analyses produced ICERs ranging from £35,500 per QALY gained (ERG's base case using data from the ITT population in COU-AA-302, see section 3.27) to £59,600 per QALY gained (ERG's analysis using a Weibull curve for duration of first treatment and applying the existing simple PAS to abiraterone used after docetaxel using data from the ITT population in COU-AA-302, see section 3.30). The Committee concluded that the ICER was likely to lie between £35,500 and £59,600 per QALY gained and was

therefore above the range normally considered a cost-effective use of NHS resources.

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

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

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

4.23 To address whether metastatic hormone-resistant prostate cancer at this stage of therapy is associated with a mean life expectancy of less than 24 months, the Committee considered the median overall survival in the control arm of COU-AA-302, noting that it was about 30 months. The Committee heard from the company in the first meeting that it had estimated the mean survival for the best supportive care arm as 32 months. The Committee considered the company's and stakeholder comments received during consultation suggesting that people treated in the NHS would have a lower life

expectancy than people in the best supportive care arm of COU-AA-302. These comments included:

- In the trial, people had active treatments after docetaxel that are not available in the NHS including 'sipuleucel-T, cabazitaxel, ketoconazole and retreatment with abiraterone'**.** The committee agreed that it was appropriate to adjust survival estimates for active treatments that are not used in the NHS but the company had not done this for the survival estimate for people receiving best supportive care. The Committee noted that ketoconazole has not been proven to improve survival in patients with metastatic hormone-resistant prostate cancer, and therefore would not affect survival outcomes.
- COU-AA-302 excluded patients with significant comorbidities and a life expectancy of less than 6 months (see section 3.3), which would make the life expectancy in the control arm longer than in the real-world population. The Committee noted that both the clinical experts and the company had stated that COU-AA-302 was generalisable to clinical practice in England and reflected patients who would be offered abiraterone in England.

The Committee concluded that COU-AA-302 provides a reasonable estimate of the median life expectancy for people with metastatic hormone-resistant prostate cancer for whom abiraterone is indicated, but the impact of active treatments used in the trial that are not used in the NHS was unclear. The Committee further concluded that adjusting for these was unlikely to reduce the mean life expectancy from 32 months to below 24 months.

4.24 The Committee considered the company's review of the published literature on alternative estimates of survival for people with metastatic hormone-resistant prostate cancer. It noted that this

included estimates from the 2012 European Association of Urology guidelines, an observational analysis from a clinical trial of androgen deprivation therapy, and a systematic review of observational studies of people with castrate-resistant prostate cancer. In addition, the Committee considered a clinical trial of docetaxel compared with best supportive care cited by a professional consultee organisation. The Committee noted that the median survival estimates across these publications ranged from 9 months to 30 months (see section 3.31). However, it was concerned about the reliability of the estimates. Firstly, it had not been presented with evidence that the guidelines included a systematic review. Secondly, the estimate from the 2012 European Association of Urology guidelines had not been included in the 2013 and 2014 updates of this guideline. Instead, these updates referred to the median survival estimates from the docetaxel trials and trials of other technologies such as cabazitaxel, enzalutamide, sipuleucel-T and abiraterone. Thirdly, the primary finding from an observational analysis of a clinical trial of androgen deprivation therapy showed how prostate-specific antigen levels are associated with mortality, but did not provide life expectancy data for the population. Fourthly, it was unclear whether the populations included in the systematic review of observational studies were generalisable to the population in the UK for whom abiraterone is indicated. Finally, the trial comparing docetaxel and mitoxantrone mainly included people at a later stage of treatment, who would be expected to have a shorter life expectancy than the population for whom abiraterone is considered in this appraisal. The Committee also noted that no data had been presented suggesting that the life expectancy of people with metastatic hormone relapsed prostate cancer is less than 24 months in an ongoing appraisal of enzalutamide for this population. Overall, the Committee concluded that current mean life expectancy for people with metastatic

hormone-relapsed prostate cancer for whom chemotherapy is not yet indicated was unlikely to be less than 24 months.

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

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

treatment pathway when people had higher quality of life, or delaying the need for cytotoxic chemotherapy, such as docetaxel. The Committee agreed that the model predicted that people in the abiraterone arm have more time with better utility before docetaxel than people on best supportive care, but that the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling. The Committee agreed that, even if the benefit of delaying chemotherapy had been included in the model, this would not have lowered the ICER for abiraterone to within the range usually considered a cost-effective use of NHS resources.

4.27 The Committee concluded that abiraterone was likely to be effective and increase quality of life, but could not be considered a cost-effective use of NHS resources. Therefore, the Committee could not recommend abiraterone for people with metastatic hormone-relapsed prostate cancer who have no or mild symptoms and who have not previously been treated with chemotherapy.

## *Summary of Appraisal Committee's key conclusions*

| **TAXXX** | **Appraisal title: Abiraterone for metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy** | **Section** |
|---|---|---|
| **Key conclusion** | | |
| Abiraterone is not recommended for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated | | 1.1 |
| The Committee concluded that the incremental cost-effectiveness ratio (ICER) was likely to lie between £35,500 and £59,600 per quality-adjusted life year (QALY) gained and was above the range normally considered a cost-effective use of NHS resources. This range was due to uncertainty in how long people would receive abirterone for and uncertainty in overall survival. | | 4.21 |
| The Committee concluded that current mean life expectancy for | | 4.23–25 |

| | | |
|---|---|---|
| people with metastatic hormone-relapsed prostate cancer for whom chemotherapy is not yet indicated was unlikely to be less than 24 months, and abiraterone at this stage in the treatment pathway did not meet the end-of-life criterion for short life expectancy. Because of this abiraterone did not meet end-of-life criteria when taken at this position in the treatment pathway.<br>The Committee considered that abiraterone is innovative compared with best supportive care because it was the first active treatment available for this position in the treatment pathway and that the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling. The Committee agreed that, even if the benefit of delaying chemotherapy had been included in the model, this would not have lowered the ICER for abiraterone to within the range usually considered a cost-effective use of NHS resources. | | 4.26 |
| **Current practice** | | |
| Clinical need of patients, including the availability of alternative treatments | The Committee understood from the patient experts that chemotherapy can reduce a person's quality of life and that treatments delaying the need for chemotherapy are highly valued by patients. | 4.3 |
| **The technology** | | |
| Proposed benefits of the technology<br>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | Although abiraterone is not a new technology, it was the first active treatment available for this position in the treatment pathway and, in this regard, is innovative.<br>There is some uncertainty about the benefits and consequences of delaying chemotherapy, but patients value delaying chemotherapy. | 4.26<br>4.3 |
| What is the position of the treatment in the pathway of care for the condition? | There is no consensus on how to decide whether to offer abiraterone to patients, but clinicians generally offer it, in addition to best supportive care, to people with few symptoms to delay chemotherapy, or to treat people who are unable or do not wish to have chemotherapy. Enzalutamide, taken at the same position in the treatment pathway as abiraterone, is currently being appraised by NICE and is available through the Cancer Drugs Fund at present. | 4.1 |

| | | |
|---|---|---|
| Adverse reactions | Abiraterone plus prednisolone increases the risk of adverse events compared with prednisolone alone, but patients can tolerate the adverse effects associated with abiraterone. | 4.17 |
| **Evidence for clinical effectiveness** | | |
| Availability, nature and quality of evidence | The clinical-effectiveness evidence came from a randomised placebo-controlled trial, COU-AA-302 that recruited 9% of its patients from the UK. | 4.5 |
| Relevance to general clinical practice in the NHS | The Committee concluded that COU-AA-302 generally reflected clinical practice in the UK and was relevant to address the decision problem. | 4.5 |
| Uncertainties generated by the evidence | The survival benefit of abiraterone compared with placebo was not statistically significant at the third interim analyses of COU-AA-302 (the data cut-off used in the modelling), but was statistically significant at the final analysis.<br>There was uncertainty around the extent of benefit with abiraterone at the final analysis because the trial was unblinded and people could cross over to abiraterone from the placebo arm. Furthermore, people in both treatment arms could have subsequent treatments that are not available in the NHS. | 4.6–7 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | None were identified. | |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee concluded that abiraterone delayed disease progression and improved overall survival compared with placebo, but that there was uncertainty about the extent of the survival benefit. | 4.7 |
| **Evidence for cost effectiveness** | | |

| | | |
|---|---|---|
| Availability and nature of evidence | The company developed a discrete event simulation model, because it allowed more flexibility to reflect a sequence of treatments, and to model response to treatments that depend on previous treatments. | 4.8 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The company's model was complex and lacked transparency which made it difficult for the Evidence Review Group (ERG) to validate and critique it.<br>In the model, data needed to be extrapolated beyond the period of the follow-up from COU-AA-302. The choice of extrapolation distribution affected the estimated time a person would have their first treatment and the overall survival estimates. Both of these estimates were a driver of the ICER for abiraterone compared with best supportive care. There was uncertainty about the choice of extrapolation distributions used in the model and the company had not provided data to validate the plausibility of its preferred extrapolation distributions. | 4.8<br>4.11-4.13 |
| Incorporation of health-related quality-of-life benefits and utility values<br>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? | The company's model used utility values from the trial (Functional Assessment of Cancer Therapy [prostate cancer subscale] mapped to EQ-5D), a survey and the literature. The model included a utility increment associated with taking abiraterone. Overall, the Committee concluded that the company's modelled utility values were plausible.<br>It was unclear whether the utility benefit of delaying cytotoxic chemotherapy had been fully taken into account in the modelling. However, the Committee agreed that fully taking into account the utility benefit of delaying chemotherapy would not have lowered the ICER for abiraterone to within the range usually considered a cost-effective use of NHS resources. | 4.17<br>4.26 |
| Are there specific groups of people for whom the technology is particularly cost effective? | None were identified. | |

| | | |
|---|---|---|
| What are the key drivers of cost effectiveness? | Using a Weibull distribution instead of a log-logistic distribution for predicting time on first treatment increased the ICER.<br><br>The choice of trial population used to inform the model. The company's model used results from the subgroup of 902 people in COU-AA-302 for whom complete data were available on baseline characteristics. The ERG's exploratory base case used the intention-to-treat population instead, and this increased the ICER. The Committee concluded that the intention-to-treat population represented all randomised patients and provided more data, and for this reason preferred it. | 4.11–4.12<br><br>4.15 |
| Most likely cost-effectiveness estimate (given as an ICER) | The Committee agreed that the company's base-case ICER (£28,600 per QALY gained) was not plausible. Analyses making alternative assumptions produced ICERs ranging from £35,500 to £59,600 per QALY gained. | 4.21 |
| **Additional factors taken into account** | | |
| Patient access schemes (PPRS) | The company proposed to reduce the list price of abiraterone. It also agreed a patient access scheme with the Department of Health, which involve the NHS paying the new list price for abiraterone for the first 10 months of treatment. After 10 months, the Company will rebate the cost of subsequent tablets. The reduced price and patient access scheme were used in the economic analyses reported in section 3. However, as this draft guidance does not recommend abiraterone, the cost of abiraterone will remain at £2930 for 120 tablets and the new patient access scheme will not be implemented. | 2.3 |

| | | |
|---|---|---|
| End-of-life considerations | The Committee concluded that abiraterone was licensed for a small patient population, and it is likely that abiraterone when given before docetaxel leads to a life extension of 3 months.<br>The Committee concluded that current mean life expectancy for people with metastatic hormone-relapsed prostate cancer for whom chemotherapy is not yet indicated was unlikely to be less than 24 months, and abiraterone at this stage in the treatment pathway did not meet the end-of-life criterion for short life expectancy. | 4.22–4.25 |
| Equalities considerations and social value judgements | No equality issues were raised during the appraisal committee meetings. | n/a |

# 5 Implementation

5.1 The Department of Health and Janssen have agreed that abiraterone will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company 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 [NICE to add details at time of publication]

5.2 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

Slides highlighting key messages for local discussion.

Costing template and report to estimate the national and local savings and costs associated with implementation.

Implementation advice on how to put the guidance into practice and national initiatives that support this locally.

A costing statement explaining the resource impact of this guidance.

- Audit support for monitoring local practice.

# 6 Related NICE guidance

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

**Published**

- Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen NICE technology appraisal guidance 316 (2014)
- Prostate cancer: diagnosis and treatment NICE clinical guideline 175 (2014)
- Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours NICE technology appraisal guidance 265 (2012)
- Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen NICE technology appraisal guidance 259 (2012)
- Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen NICE technology appraisal guidance 255 (2012)
- Docetaxel for the treatment of metastatic prostate cancer NICE technology appraisal guidance 101 (2006)

**Under development**

- Radium-223 dichloride for treating metastatic hormone-relapsed prostate cancer with bone metastases. NICE technology appraisal guidance, publication expected January 2016.
- Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. NICE technology appraisal guidance, expected date of publication to be confirmed.
- Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255). NICE technology appraisal guidance, publication expected May 2016.

# 7 Proposed date for review of guidance

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

Amanda Adler
Chair, Appraisal Committee
November 2015

# 8 Appraisal Committee members, guideline representatives and NICE project team

## *8.1 Appraisal Committee members*

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

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

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

**Dr Amanda Adler (Chair)**
Consultant Physician, Addenbrooke's Hospital Cambridge

**Professor Ken Stein (Vice Chair)**
Professor of Public Health, University of Exeter Medical School

**Dr Ray Armstrong**
Consultant Rheumatologist, Southampton General Hospital

**Dr Jeff Aronson**
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

**Professor John Cairns**

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

**Dr Lisa Cooper**

Echocardiographer, Stockport NHS Foundation Trust

**Mr Robert Hinchliffe**

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

**Mrs Anne Joshua**

Pharmaceutical Advisor NHS 111/NHS Pathways

**Dr Miriam McCarthy**

Consultant, Public Health, Public Health Agency, Northern Ireland

**Professor Ruairidh Milne**

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

**Dr Peter Norrie**

Principal Lecturer in Nursing, DeMontfort University

**Mr Christopher O'Regan**

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

**Dr Sanjeev Patel**

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

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Dr Danielle Preedy**

Lay member

**Mr Alun Roebuck**

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

**Mr Cliff Snelling**

Lay member

**Professor Andrew Stevens**

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

**Mr David Thomson**

Lay member

**Dr Nicky Welton**

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

**Dr Nerys Woolacott**

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

## *NICE project team*

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

**Mary Hughes**
Technical Lead

**Zoe Charles and Rosie Lovett**
Technical Advisers

**Jeremy Powell**
Project Manager

# 9 Sources of evidence considered by the Committee

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

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

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

I. Companies/sponsors:

- Janssen

II. Professional/specialist and patient/carer groups:

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

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

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

C. The following individuals were selected from clinical and patient expert nominations from the consultees and commentators. They gave their expert personal view on abiraterone by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the appraisal consultation document.

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

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

- Janssen