NICE National Institute for Health and Care Excellence

NICE guidance

Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated

Technology appraisal guidance
Published: 27 April 2016
Last updated: 27 July 2016

www.nice.org.uk/guidance/ta387

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Abiraterone in combination with prednisone or prednisolone is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

- in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

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 current list price of abiraterone is £2,930 for 120 tablets (excluding VAT; BNF, accessed online November 2015). The company has agreed a commercial access arrangement with NHS England, the details of which are confidential. This commercial access arrangement was agreed in July 2016, after guidance publication. It presents a change to the pricing arrangement that was considered during development of this guidance. The pricing arrangement considered during guidance development was that the company would reduce the list price to £2,300 for 120 tablets at the time of publication of NICE guidance. The company had also agreed a complex patient access scheme (PAS) with the Department of Health. This would have involved the NHS paying the new list price for abiraterone for the first 10 months of treatment. After 10 months, the company would have rebated the cost of any subsequent tablets prescribed. The commercial access arrangement agreed in July 2016 replaces the PAS and therefore the list price has not been changed and the PAS no longer applies.

3 Evidence

3.1 The appraisal committee considered evidence submitted by Janssen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of all the evidence.

Clinical effectiveness

3.2 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 1,088 people; 546 people were allocated to the abiraterone arm (1,000 mg abiraterone daily plus 5 mg prednisone/prednisolone twice daily) and 542 people were allocated to placebo plus 5 mg prednisone/prednisolone 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).

3.3 The statistical plan for COU-AA-302 called for a single pre-planned analysis for radiographic progression-free survival after 378 events had occurred. 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 stated that, to be considered statistically significant, the p value for radiographic progression-free survival should be less than 0.01. 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.

3.4 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.

3.5 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.

3.6 By the final analysis, 67% of people in the abiraterone group and 80% of people in the placebo group had had subsequent treatment after stopping the study drug (see table 1). Forty-four per cent of people in the placebo group had abiraterone, of whom 17% had abiraterone before docetaxel and 27% had it after docetaxel.

Table 1 Summary of subsequent therapies taken by patients in COU-AA-302 (intention-to-treat population, final analysis)

Subsequent therapy	Abiraterone group (n=546)	Placebo group (n=542)
Docetaxel	311 (57.0%)	331 (61.1%)
Cabazitaxel	100 (18.3%)	105 (19.4%)
Abiraterone	69 (12.6%)	238 (43.9%)
Sipuleucel-T	45 (8.2%)	32 (5.9%)
Radium-223	20 (3.7%)	7 (1.3%)
Enzalutamide	87 (15.9%)	54 (10.0%)

3.7 Radiographic progression-free survival was defined as time from randomisation to 1 of the following: progression by bone, CT or MRI scan or death. An independent radiologist unaware of study group assignments determined radiographic progression, 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 (when the company did its third interim analysis of overall survival), 292 (53.5%) of people in the abiraterone group and 352 (64.9%) of people in the placebo group had had radiographic progression. The median duration of radiographic progression-free survival was 16.5 months (95% confidence interval [CI] 13.8 to 16.8 months) in the abiraterone group and 8.2 months (95% CI 8.0 to 9.4 months) in the placebo group (hazard ratio [HR] 0.52, 95% CI 0.45 to 0.62; p<0.0001).

3.8 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 group and 234 (43.2%) people in the placebo group had died. The median overall survival in the abiraterone group 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 group (HR 0.79, 95% CI 0.66 to 0.96, p=0.0151). This p value did not meet the pre-defined value for statistical significance (p=0.0034, see section 3.3). By the final data cut-off, 354 (65%) people in the abiraterone group and 387 (71%) people in the placebo group had died. The median overall survival was 34.7 months (95% CI 32.7 to 36.8 months) in the abiraterone group and 30.3 months (95% CI 28.6 to 33.3 months) in the placebo group (HR 0.81, 95% CI 0.70 to 0.93).The company

stated that adjusting for subsequent treatments would reduce the hazard ratio to 0.74 but did not describe the methods of this adjustment.

3.9 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 study medication). By the third interim analysis, more people had drug-related grade 3 to 4 adverse events with abiraterone than with placebo (relative risk 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 than placebo (5.5% compared with 0.7%), increased aspartate aminotransferase (3.1% compared with 0.9%) and dyspnoea (breathing difficulty; 2.6% compared with 0.9%) but less hydronephrosis (retention of urine in the kidney causing swelling; 0.2% compared with 1.5%).

3.10 The health-related quality of life of patients in COU-AA-302 was measured using the Functional Assessment of Cancer Therapy prostate cancer subscale (FACT-P). 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), hazard ratio 0.79 (95% CI 0.67 to 0.93, p=0.0046).

3.11 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 group 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 dysfunction and interrupted social relationships. Of these, the company only reported time to an increase in pain intensity (it did not report the differences in pain intensity between the 2 treatment groups). 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 groups.

Cost effectiveness

3.12 The company submitted 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 assessed 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.

3.13 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 previous technology appraisal guidance on cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (now replaced by NICE's technology appraisal guidance on cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel), 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. It then adjusted the survival of people who had cabazitaxel after docetaxel in the abiraterone

group of COU-AA-302 to exclude this benefit. It did not adjust the survival estimates of the placebo group. The company carried out a scenario analysis in which it did not include a survival adjustment for cabazitaxel (see section 3.20). The company did not adjust for other active treatments that were used by some patients in COU-AA-302 but are not used in the NHS after abiraterone, including sipuleucel-T (the marketing authorisation has been withdrawn).

3.14 The model used 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 different times. The company constructed the equations in 3 steps:

- First, it decided whether a separate equation was needed for the abiraterone and best supportive care arms. For most equations, the company used the same equation for both arms and used 'treatment' as a predictor. However, for 'time from stopping abiraterone or best supportive care to death', the company used a separate equation for each treatment arm.
- Second, for 10 of the equations, the company chose a parametric distribution with which to extrapolate the trial data over a longer period of time. It chose the curve with the best fit to the survival curves from the ITT population from COU-AA-302.
- Third, it determined which baseline variables (such as age) should be included in the equation. The company included covariates that had a statistically significant association with the event/outcome of interest at a 10% level of statistical significance. The covariates differed between equations. Two further covariates that did not meet the 10% level of statistical significance were also included. The company justified this by stating that it was better to 'be inclusive', that analyses may not have reached statistical significance because of small patient numbers, and that the inclusion of these 2 covariates was clinically justified. To derive the prediction equations, the company used data from patients who had complete data for the baseline variables of interest (meaning that the sample size differed between equations). Out of the 1,088 patients in the ITT population, 902 patients (83%) had complete data for all baseline variables, so the minimum sample size was 902.

The company reported that all of the equations had a good fit to the trial data. In response to the second appraisal consultation document, the company provided further details of how it constructed the prediction equations, and stated that it followed a pre-specified analysis plan.

3.15 The company's base case used utility values from the company-sponsored 'UK mCRPC patient utility study'. This study was an online survey of 163 men with metastatic hormone-relapsed prostate cancer in the UK all of whom, unless they had been surgically castrated, had previously taken anti-androgen tablets for more than 1 month but had since stopped. 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 metastatic hormone-relapsed prostate cancer after androgen deprivation therapy had failed were divided into the following subgroups:

- No or mild symptoms; chemotherapy not yet clinically indicated (n=50). The mean EQ-5D utility value was 0.83.
- With symptoms; chemotherapy clinically indicated but not started (n=50). The mean EQ-5D utility value was 0.63.
- Having chemotherapy (n=17). The mean EQ-5D utility value was 0.69.
- After 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 Sandblom et al. (2004). The company did not apply a utility decrement for adverse events with different treatments.

3.16 The company also presented utility values derived from mapping FACT-P to EQ-5D from the data collected in COU-AA-302. The company used data from an observational study of patients with metastatic hormone-relapsed prostate cancer in 6 European countries 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).

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

3.18 The company estimated the frequency of unscheduled medical resource use (for example, adverse events while on treatment) using data from COU-AA-302 (for pre-docetaxel abiraterone or best supportive care) and COU-AA-301 (for post-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. For people being treated with 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 these events. The company also applied a one-off cost of £3,598 to account for palliative care in the last 3 months of the best supportive care phase.

3.19 The company's model used the following costs:

- £2,300.00 per 30 days for abiraterone (based on a 1,000 mg 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.
- £1,240.00 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). The company calculated the cost of docetaxel by applying a 20% discount to the BNF; edition 67 price of £1,069.50, resulting in a cost of £855.60 per 160-mg vial. In a sensitivity analysis, the company used the

electronic medicines information tool (eMIT) price for docetaxel. 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 base-case 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. In response to the second appraisal consultation document, the company submitted an analysis that included the administration costs of the complex PAS for abiraterone used both before and after docetaxel; this increased its incremental cost-effectiveness ratio (ICER) from £28,563 to £28,717 per quality-adjusted life year (QALY) gained.

3.20 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 QALYs gained compared with best supportive care. The estimated deterministic 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. A scenario in which the survival estimate in the abiraterone arm was not adjusted for cabazitaxel use (see section 3.13) resulted in an ICER of £27,738 per QALY gained.

3.21 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. Using the Weibull distribution increased the ICER to £35,789 per QALY gained. In response to the second appraisal consultation document, the company submitted data showing the duration of abiraterone treatment in clinical practice in the UK and US. The UK data are commercial-in-confidence and cannot be reported here. The US data came from the Optum database of healthcare insurance claims, which contained records for 8,326 people who had abiraterone and had not had docetaxel. The US data showed that 1,171 (14%) of people were still taking abiraterone after 53 months (4.4 years). The company stated that these data support its choice of a log-logistic curve for predicting time on first treatment.

3.22 In response to the second appraisal consultation document, the company

submitted a scenario analysis using a 'piecewise' method to predict time on first treatment. For abiraterone, the company used a log-logistic distribution for the first 2.5 years and a Weibull curve thereafter. For best supportive care, the company used a log-logistic distribution for the first 2.5 years and then it assumed that all patients stopped having best supportive care. This scenario increased the company's base-case ICER from £28,563 to £32,849 per QALY gained. The ERG stated that it was arbitrary to assume that all patients stopped best supportive care after 1,000 days.

3.23 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.

3.24 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.

3.25 The ERG commented that the model population was not the same as the entire COU-AA-302 population because the model equations used data from patients who had complete data for the baseline variables of interest. Out of the 1,088 patients in the ITT population, 902 patients (83%) had complete data for all baseline variables (the 'full covariate subgroup'), so the minimum sample size for deriving prediction equations was 902. The ERG commented that, for the abiraterone group, time on first treatment was longer in the full covariate subgroup than in the ITT population. In its response to the second appraisal consultation document, the company provided the characteristics of the full covariate subgroup. It also stated that there was no statistically significant difference between the ITT population and the full covariate subgroup in baseline characteristics, time on first treatment or overall survival.

3.26 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 to 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.

3.27 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.

3.28 The ERG stated that its preferred base case would:

- include a utility increment of 0.046 applied in the post-docetaxel phase for patients having 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 utility increment if 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.

3.29 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.

3.30 The ERG did 3 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 3.13). 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.

3.31 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

3.32 In response to the first appraisal consultation document, the company presented survival data from 2 studies that it had not included in its original submission. One was a systematic literature review by Kirby et al. (2011) stating that median survival was between 9 months and 30 months for patients with castrate-resistant prostate cancer and between 9 months 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 months and 27 months for metastatic disease.

4 Committee discussion

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 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. 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 noted that abiraterone, which is taken with prednisolone, has a marketing authorisation for use before chemotherapy. It understood that patients can currently get abiraterone at this point in the treatment pathway through the Cancer Drugs Fund. 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 been recommended by NICE for use before chemotherapy. 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. The committee was

aware of responses to consultation, highlighting that it is important to patients and clinicians to have a choice of treatments. It concluded that both patients and clinicians would like to have the option of using abiraterone.

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 should be used 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 concluded that the key comparison in this appraisal was between a sequence of:

- abiraterone followed by docetaxel and subsequent treatments, and
- watchful waiting (including best supportive care) followed by docetaxel and subsequent treatments.

  The committee noted that, in current clinical practice in England, the 'subsequent treatments' in the second sequence may include abiraterone. It 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 unable 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 in terms of survival and quality of life, 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 3.4), 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 marketing authorisation for abiraterone does not include people for whom chemotherapy is indicated (that is, people with more than mild symptoms) but who are unfit for chemotherapy. 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. In line with advice from the clinical experts, the committee considered that the placebo arm reflected best supportive care in England before treatment with chemotherapy. 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 3.3). It also heard that, after unblinding, people in the trial having placebo could cross over to have abiraterone. Following a request from the committee, the company provided data on treatment switching and subsequent treatments in COU-AA-302, to clarify 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 previous technology appraisal guidance on cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (now replaced by NICE's technology appraisal guidance on cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel). 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, about 29% of patients had subsequent abiraterone or enzalutamide which would not 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. 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 or disease status, the committee noted that the company made a large number of judgements when determining which covariates to include and which parametric distribution to choose for extrapolation (see section 3.14). The committee noted that, for 2 equations, the company had not followed its own statistical plan when choosing covariates, and the committee agreed that this could introduce bias to the model. The committee 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 preferred to use data from the third interim analysis of COU-AA-302 rather than the final analysis because 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, 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 to 4.14).

4.10 The committee discussed the company's choice of parametric distribution for each of the 10 equations in the model that needed extrapolating. 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:

- A log-logistic curve had been used to extrapolate the equations to predict:
  - time from starting to stopping first treatment with abiraterone or best supportive care
  - time from starting docetaxel to death (if patient died while taking docetaxel).
- A log-normal distribution had been used to extrapolate the equation to predict:
  - time from stopping abiraterone or best supportive care to starting docetaxel.
- All other prediction equations had been extrapolated with a Weibull distribution.

  The committee heard from the ERG that using the log-logistic distribution for extrapolating is sometimes criticised because it has a 'long tail', 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. 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 while taking docetaxel) increased the ERG's exploratory base-case ICER from £35,500 to £55,600 per QALY gained. The committee was also aware of the company's analysis, submitted in response to the second appraisal consultation document, using a piecewise curve for predicting time on first treatment (see section 3.22). Using the piecewise curve increased the company's base-case ICER from £28,600 to £32,800 per QALY gained. The committee heard from the company that it preferred to use 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. After the third committee meeting, the committee asked the company to submit additional data about treatment durations with abiraterone.

4.12 The committee discussed how long people take abiraterone, noting that the company had provided 3 sets of data: the final analysis of COU-AA-302; data from clinical practice in the UK; and data from clinical practice in the US. The UK data are commercial-in-confidence and cannot be presented here.

- The committee inspected the final Kaplan–Meier curves from the COU-AA-302 trial and compared them with the extrapolation curves used in the company's model (that is, log-logistic in the base case and Weibull or piecewise in sensitivity analyses). For the abiraterone arm, for the time period for which data were available (the trial period), the committee agreed with the company that the log-logistic curve was the best fit to the trial data. 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, but the trial data did not support this prediction because the

maximum follow-up time in the trial was about 5 years. The committee noted that the Weibull curve predicted that fewer patients remain on abiraterone in the long term, and the piecewise curve gave predictions that were in-between the log-logistic and Weibull curves.

- The committee discussed the UK data. It noted that the company had not presented the sample size, and the data included people treated with abiraterone both before and after chemotherapy. The committee concluded that the UK data could not be used to inform its decision.
- The committee discussed the data from healthcare insurance claims made by 8,326 patients treated with abiraterone in the US; these patients had not had previous chemotherapy. It noted that 14% of people were still taking abiraterone after 4.4 years. While the committee had concerns about whether the results were generalisable to the UK, it concluded that some patients in the UK were likely to take abiraterone for long periods of time.

Having considered all of the evidence, the committee concluded that its preferred analysis used either a log-logistic curve or a piecewise curve to predict time on abiraterone.

4.13 The committee discussed how long people remain on best supportive care before starting docetaxel, noting that the company had provided data from the final analysis of COU-AA-302. The committee was concerned that neither the log-logistic distribution (used in the base case) nor the Weibull distribution (used in sensitivity analyses) provided a good fit to the final trial data, and both distributions overestimated the time that patients would remain on best supportive care. The committee noted that the piecewise curve (used in sensitivity analyses) was a closer fit to the trial data, but in this analysis the company assumed that all patients stopped having best supportive care at about 1,000 days; the committee was concerned that this assumption may not be clinically plausible. The committee concluded that, for predicting time on best supportive care, it preferred to use the same distribution as was used for abiraterone (that is, log-logistic or piecewise, see section 4.12).

4.14 The committee discussed the predictions of overall survival in the company's model. It inspected the final Kaplan-Meier 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. The committee was aware of the company's response to the second appraisal consultation document, which stated that the model over-estimated survival times with best supportive care when compared with the placebo group of the trial after adjusting for treatment switching. The committee concluded that the model predictions of overall survival were uncertain and it was unclear whether the model over- or under-estimated survival times.

4.15 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. 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 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 3.13) 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.

4.16 The committee discussed the trial population used to inform the model. It noted that, for each prediction equation, the company used data from all the patients in the COU-AA-302 intention-to-treat (ITT) population who had complete data for the covariates in that equation. Consequently, the sample size varied between

equations; the minimum sample was the 902 people for whom complete data were available (the 'full covariate subgroup'). The company's approach is subsequently referred to as 'using the full covariate subgroup'. The committee was aware that the ERG preferred to use the ITT population for modelling, which meant that the ERG's prediction equations did not include covariates. The committee heard that, in the company's opinion, it was appropriate to use the full covariate subgroup because:

- Covariates were needed to predict patients' response to the 3 lines of treatment in the model.
- There was no statistically significant difference in baseline characteristics between the ITT and full covariate subgroup.
- The predicted survival times with abiraterone had a better fit to the trial data when using the full covariate subgroup than when using the ITT population.

The committee heard that the ERG preferred to use the ITT population because:

- The full covariate subgroup was a non-random subset of the ITT population, 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 clinical outcomes for those patients.
- The incremental survival benefit seems overestimated when using the full covariate population.

The ERG's analysis using the ITT population increased the company's base-case ICER from £28,600 to £35,200 per QALY gained. The committee agreed that, as a general principle, it preferred to use the ITT population for modelling because this reduces the risk of bias. However, in this specific case, the committee agreed with the company that using the full covariate subgroup provided a closer fit to the trial data. Accordingly, the committee concluded that, on this occasion, it was appropriate to use the full covariate subgroup rather than the ITT population.

4.17 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

NICE's technology appraisal guidance on 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 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. 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 and concluded 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.

4.18 The committee discussed the utility values in the company's 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 increase in utility experienced by people taking abiraterone before or after docetaxel, using Functional Assessment of Cancer Therapy prostate cancer subscale [FACT-P] data mapped to EQ-5D)

- the literature (1 value for quality of life at the end of life).

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.

4.19 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 costs of administering the PAS, although low, had not been included in the modelling and considered that these costs should have been included. It noted that, in response to the second appraisal consultation document, the company submitted an analysis including these costs.

- 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 BNF 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). The committee noted that, in response to the second appraisal consultation document, the company submitted an analysis using the eMIT cost for docetaxel; this increased the company's base-case ICER from £28,600 to £29,600 per QALY gained. However, the committee recognised that other costs (for drugs or NHS care), which may have also changed during the course of the appraisal, had not been amended and the impact on the ICER of amending these costs was unknown. 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.

4.20 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
- 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 existing simple PAS to abiraterone used after docetaxel (in the best supportive care arm of the model); it agreed that this would represent 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. 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 simple 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. Nonetheless it concluded 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, and it acknowledged that using this approach in a scenario analysis had a modest impact on the ICER.

4.21 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.

4.22 The committee discussed whether abiraterone could be considered a cost-effective use of NHS resources. It had concluded that its preferred approach was:

- to use the full covariate subgroup (as per the company's base case)
- to use either a log-logistic curve (as per the company's base case) or a piecewise curve (as per the company's sensitivity analysis provided after the second consultation) to predict time on first treatment.

The committee noted that the company's base-case ICER was £28,600 per QALY gained and the company's ICER using a piecewise curve was £32,800 per QALY gained. The committee agreed that including its preferred assumptions for costs would increase these ICERs, but only slightly (see sections 4.19 and 4.20). The committee remained concerned that the company's model was complex and lacked transparency (see section 4.8).

Nonetheless, the committee concluded that the ICER was likely to lie between £28,600 and £32,800 per QALY gained.

4.23 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 7,000 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.

4.24 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 3.4), 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.

4.25 The committee considered carefully the company's review of the published literature on alternative estimates of survival for people with prostate cancer. 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.

4.26 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 6,782 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 7,000 and that abiraterone therefore met the end-of-life criterion for a small patient population. The committee noted that the final analysis of COU-AA-302 showed a median survival benefit of 4.4 months and the

modelled mean survival benefit was longer than this. It concluded that the extension-to-life criterion was met. 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.

4.27 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 noted that the model predicted that people in the abiraterone arm have more time with better utility before docetaxel than people on best supportive care. However, the committee agreed that the benefit of delaying chemotherapy perceived by patients may not have been fully captured by the utility values included in the modelling and that accounting for this would have reduced the ICER. The committee concluded that abiraterone was innovative and this should be considered in its decision-making.

4.28 The committee noted that NICE's Guide to the methods of technology appraisal states that, if a technology has a most plausible ICER above £30,000 per QALY gained, the committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources. The committee noted that:

- The most plausible ICER for abiraterone compared with best supportive care was between £28,600 and £32,800 per QALY gained.
- Abiraterone was the first active treatment available for this position in the treatment pathway and, in this regard, was innovative.
- The utility values in the model may not fully capture the benefit to patients of delaying cytotoxic chemotherapy.

Taking all of these factors into account, the committee agreed that the ICER

for abiraterone compared with best supportive care would likely fall below £30,000 per QALY gained, and it considered abiraterone to be a cost-effective use of NHS resources. The committee concluded that abiraterone in combination with prednisone or prednisolone should be recommended within its marketing authorisation, for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has metastatic hormone-relapsed prostate cancer (and has no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated), and the healthcare professional responsible for their care thinks that abiraterone is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal committee members, guideline representatives and NICE project team

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 and 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 and 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

7 Sources of evidence considered by the committee

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 naive metastatic castration-resistant prostate cancer.

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.

Companies or sponsors:

- Janssen

Professional or specialist and patient or 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

Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

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

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

Update information

July 2016: This guidance was re-issued after a change to the commercial arrangements in July 2016. It was verified that this change did not impact cost effectiveness. Recommendation 1.1, sections 2.3 and 5.4, and the summary of appraisal committee key conclusions table have been updated.

- ISBN: 978-1-4731-1816-4