NICE National Institute for Health and Care Excellence

NICE guidance

Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen

Technology appraisal guidance
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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 Guidance

1.1 Enzalutamide is recommended within its marketing authorisation as an option for treating metastatic hormone-relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.

1.2 The use of enzalutamide for treating metastatic hormone-relapsed prostate cancer previously treated with abiraterone is not covered by this guidance.

2 The technology

2.1 Enzalutamide (Xtandi, Astellas Pharma) is an oral androgen receptor signalling inhibitor that reduces the proliferation of prostate cancer cells and therefore stops the growth of cancerous tumours. It has a UK marketing authorisation 'for the treatment of adult men with metastatic castrate-resistant prostate cancer whose disease has progressed on or after docetaxel therapy'. The recommended dosage of enzalutamide is 160 mg once daily until disease progression. The summary of product characteristics states that if severe toxicity or an intolerable adverse reaction occurs after taking enzalutamide, treatment should be stopped for 1 week or until symptoms improve, then resumed at the same or a lower dose (120 or 80 mg/day). The dose of enzalutamide should also be reduced if a drug that inhibits CYP2C8 is administered at the same time.

2.2 The summary of product characteristics lists the following common adverse reactions to enzalutamide: headache, hot flushes, falls, bone fractures, hallucinations, anxiety, dry skin, itching, hypertension, low white blood cell count, memory impairment and difficulty thinking clearly. It advises caution when administering enzalutamide to people with a history of seizures or other predisposing factors for seizures, such as underlying brain injury, stroke, brain tumours or brain metastases, or alcoholism. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Enzalutamide costs £2734.67 for 1 pack of 112 40-mg capsules, (excluding VAT; 'British national formulary' [BNF] website accessed March 2014). Assuming a daily dose of 160 mg and a mean length of treatment of 8.5 months, the manufacturer estimated that the average cost of treatment with enzalutamide, based on the list price, is £25,269. The manufacturer of enzalutamide has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the price listed above, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considers that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

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

Clinical-effectiveness evidence

3.1 The manufacturer conducted a systematic review of studies evaluating the efficacy and safety of enzalutamide and its comparators for treating metastatic hormone-relapsed prostate cancer that had progressed during or after treatment with docetaxel-containing (cytotoxic) chemotherapy. The manufacturer considered abiraterone and best supportive care to be the relevant comparators for enzalutamide. It excluded mitoxantrone as a comparator, even though mitoxantrone being listed as a comparator in the final scope issued by NICE. This was because: mitoxantrone has a small and diminishing market share in the NHS; there are several new treatments available that have displaced mitoxantrone; existing NICE guidance for prostate cancer does not include recommendations on the use of mitoxantrone; clinical evidence does not support using mitoxantrone after docetaxel therapy; and mitoxantrone does not have a marketing authorisation for metastatic hormone-refractory prostate cancer.

3.2 The key clinical evidence for enzalutamide came from 1 randomised controlled trial, AFFIRM, which compared enzalutamide plus best supportive care with placebo plus best supportive care. The manufacturer considered placebo to be equivalent to best supportive care because people in both treatment groups received best supportive care. Another randomised controlled trial, COU-AA-301, compared abiraterone plus prednisone with placebo plus prednisone, and the manufacturer used this trial to compare enzalutamide indirectly with abiraterone using placebo as a common comparator. No relevant observational or single-arm trials of enzalutamide were identified by the manufacturer.

3.3 AFFIRM was a phase III randomised double-blind placebo-controlled study that was conducted at 156 sites in 15 countries, including 12 sites in the UK. Eligible patients were adults with metastatic hormone-relapsed prostate cancer who had previously received 1 or 2 cytotoxic chemotherapy regimens, at least 1 of which contained docetaxel. The AFFIRM study excluded patients who had received abiraterone or treatment with any other investigational agents that block androgen synthesis. The study also excluded patients who had disease progression on ketoconazole, or who were using herbal products that may affect prostate-specific antigen (PSA). Randomisation was stratified by baseline Eastern Cooperative Oncology Group (ECOG) performance status and the average pain burden that patients experienced over the 7 days that preceded randomisation measured using the Brief Pain Inventory-Short Form (BPI-SF) question 3 score. Investigators randomly assigned patients in a 2:1 ratio to either enzalutamide (160 mg orally once daily) plus best supportive care (n=800) or placebo plus best supportive care (n=399). Best supportive care in AFFIRM could include radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies, corticosteroids, and radiotherapy (which the trial protocol stipulated should be reported as a skeletal-related event end point as defined in section 3.4). Treatment with the study drug continued until disease progressed and the patient was about to start further systemic therapy, or the patient experienced unacceptable adverse reactions, died or withdrew from the study.

3.4 The primary end point in AFFIRM was overall survival, defined as time from randomisation to death from any cause. In AFFIRM, secondary end points included measures of disease progression and response to treatment. Disease progression was defined as radiographic progression or the occurrence of a skeletal-related event (either radiotherapy or surgery to bone, pathological bone fracture, spinal cord compression, or change of cancer therapy to treat bone pain). Other secondary end points included:

- time to PSA progression (time to an increase in PSA of 25% or more, and an increase in absolute PSA of 2 nanograms per millilitre or more above the lowest concentration reached since treatment started)
- radiographic progression-free survival (time to the earliest objective evidence

of radiographic soft tissue or bone progression, or death)

- time to first skeletal-related event (either radiotherapy or surgery to bone, pathological bone fracture, spinal cord compression, or change of cancer therapy to treat bone pain)
- rate of pain palliation (a reduction of 2 or more points in BPI-SF question 3 score at week 13).

In addition, the manufacturer defined 2 further end points after the trial results had been compiled (see section 3.9).

3.5 Of the 1199 patients randomised in AFFIRM, the median age was 69 years (range 41–92 years), 92.7% were white, and 8.5% had an ECOG performance status of 2 (enzalutamide 8.8%, placebo 8.0%). All patients had received docetaxel therapy, and 27% of the trial population had received further cytotoxic chemotherapy, but none of the patients had received abiraterone. Most patients (91.2%) had bone metastases and 25.6% had visceral lung or liver involvement. The manufacturer considered that the 2 treatment groups were well balanced in terms of demographics, disease characteristics at baseline and medical history.

3.6 AFFIRM was designed to detect, with 90% power, a statistically significant difference in overall survival (2-sided, at the 0.05 level) with a hazard ratio of 0.76 for enzalutamide compared with placebo. A protocol-defined interim analysis was conducted when 520 patients had died (25 September 2011). Based on the results of this analysis, the data monitoring committee recommended that AFFIRM be terminated. The study remained blinded until 576 patients had died and the database was locked (16 December 2011). All the analyses presented in the manufacturer's submission are based on data at the cut-off date for the interim analysis (25 September 2011), except the analyses of overall survival and adverse events, for which the manufacturer reported results at the cut-off dates for both the interim analysis and the database lock. The manufacturer censored data for patients who had not reached the end points on the date they were last assessed.

3.7 At the cut-off date for the interim analysis (25 September 2011), the maximum follow-up time for any patient was 24.0 months and the

median follow-up time was 14.4 months. Of patients randomised to enzalutamide and placebo, 308 (38.5%) and 212 (53.1%) respectively had died. Median overall survival was 4.8 months longer for enzalutamide than placebo (enzalutamide 18.4 months, placebo 13.6 months). Treatment with enzalutamide reduced the risk of death by 36.9% compared with placebo (hazard ratio [HR] 0.631, 95% confidence interval [CI] 0.529 to 0.752, p<0.001). At the final cut-off date (16 December 2011), the median duration of follow-up was 15.0 months, by which time 344 patients (43%) randomised to enzalutamide and 232 patients (58%) randomised to placebo had died, lowering the difference in median overall survival to 4.5 months (enzalutamide 17.8 months, placebo 13.3 months). The relative risk reduction associated with enzalutamide was 38.0% (HR 0.618; 95% CI 0.523 to 0.730, p<0.001). More patients randomised to placebo (61.4%) than enzalutamide (42.0%) stopped study medication and moved to other therapies, and the manufacturer suggested that this may have caused the relative effect of enzalutamide on overall survival to be underestimated. In response to a request for clarification, the manufacturer provided estimates of mean overall survival obtained using different parametric functions, with the analysis truncated at 5 years (this assumed that all remaining patients would die at 5 years from baseline). Enzalutamide was associated with longer mean overall survival than placebo (estimates are designated as commercial in confidence by the manufacturer).

3.8 For the secondary end points, the manufacturer reported the following results:

- Time to PSA progression: of patients randomised to enzalutamide and placebo, 400 patients (50.0%) and 190 patients (47.6%) met the criteria for PSA progression respectively. Median time to PSA progression was 5.3 months longer for enzalutamide than placebo (enzalutamide 8.3 months, placebo 3.0 months), and enzalutamide delayed time to PSA progression (HR 0.248; 95% CI 0.204 to 0.303, p<0.001).
- Radiographic progression-free survival: enzalutamide prolonged median radiographic progression-free survival by 5.4 months compared with placebo (enzalutamide 8.3 months, placebo 2.9 months), and decreased the risk of radiographic disease progression (HR 0.40; 95% CI 0.35 to 0.47, p<0.001).

- Time to first skeletal-related event: 35.9% and 40.3% of patients randomised to enzalutamide and placebo, respectively, experienced a skeletal-related event. Median time to first skeletal-related event was 3.4 months longer with enzalutamide than with placebo (enzalutamide 16.7 months, placebo 13.3 months), and enzalutamide delayed time to first skeletal-related event (HR 0.688; 95% CI 0.566 to 0.835, p<0.0001).

- Rate of pain palliation at week 13: data were available for 68.1% and 58.1% of patients in the enzalutamide and placebo groups respectively. These showed that enzalutamide reduced pain in more patients than placebo (enzalutamide 25%, placebo 14.2%, p<0.001).

3.9 The manufacturer performed 2 post-hoc analyses (after the trial results had been compiled) on a modified definition of progression-free survival and on time to treatment discontinuation. Modified progression-free survival was defined as the time to radiographic progression, first skeletal-related event or death, whichever occurred first. The median modified progression-free survival was 8.11 months for enzalutamide and 2.79 months for placebo, with a hazard ratio of 0.46 (95% CI 0.40 to 0.53, p<0.001). For time to treatment discontinuation, patients in AFFIRM stopped treatment when investigators confirmed disease progression (radiographic disease progression or a skeletal-related event occurred) and the patient was about to start further systemic therapy, or if the patient experienced an adverse event. The manufacturer reported a median time on study treatment of 8.3 months for enzalutamide and 3.0 months for placebo, a difference of 5.3 months. The proportion of patients who remained on treatment for 12 months or more was higher for enzalutamide than placebo (24.8% and 4.5% respectively), consistent with a hazard ratio of 0.34 (95% CI 0.30 to 0.39, p<0.001).

3.10 In AFFIRM, pre-specified subgroup analyses were performed by prognostic factors for prostate cancer (including patients who had received 1 compared with 2 or more courses of cytotoxic chemotherapy), demographic characteristics and region. Although it did not report interaction tests for the subgroup analyses, the manufacturer stated that the treatment effect of enzalutamide was consistent across all subgroups, with a median overall survival consistently exceeding placebo by more than 3 months. For patients who had received 1 course of cytotoxic chemotherapy (docetaxel), the median time to death for

patients randomised to enzalutamide was not reached, and for patients randomised to placebo, it was 14.2 months (HR 0.59; 95% CI 0.48 to 0.73). The difference in median overall survival for patients who had received 2 or more courses of cytotoxic chemotherapy (including docetaxel) was 3.6 months longer with enzalutamide than placebo (HR 0.74; 95% CI 0.54 to 1.03).

3.11 The manufacturer did not identify any published head-to-head trials comparing enzalutamide with abiraterone. It identified the COU-AA-301 trial, which compared abiraterone plus prednisone with placebo plus prednisone, and used it to compare enzalutamide with abiraterone indirectly, using placebo as a common comparator. COU-AA-301 was a phase III randomised controlled trial evaluating the efficacy and safety of abiraterone in patients with metastatic hormone-relapsed prostate cancer whose disease had progressed during or after treatment with up to 2 regimens of cytotoxic chemotherapy, 1 of which contained docetaxel. Patients in both groups of COU-AA-301 received best supportive care, defined as radiotherapy, bisphosphonates, analgesics and luteinising hormone-releasing hormone agonists, as needed. The primary end point of the trial was overall survival, and the secondary end points included those in AFFIRM. The hazard ratios for abiraterone compared with placebo were reported from COU-AA-301 as 0.74 (95% CI 0.64 to 0.86) for overall survival and 0.66 (95% CI 0.58 to 0.76) for radiographic progression-free survival. These were derived from data at the end of the trial when 775 deaths had occurred. At that point, the median follow-up was 20.2 months (Fizazi et al. 2012) compared with 15.0 months in AFFIRM.

3.12 In the manufacturer's opinion, the designs of AFFIRM and COU-AA-301 were comparable. However, because abiraterone is taken with corticosteroids but enzalutamide is not, different proportions of patients in the 2 placebo groups used prednisone (45.6% in AFFIRM and 100% in COU-AA-301). The manufacturer stated that because there is no evidence to suggest that corticosteroids affect overall survival or progression-free survival, it assumed that differences in corticosteroid use would not affect treatment outcomes. In addition, modified progression-free survival was defined more broadly in COU-AA-301 than in AFFIRM, but the manufacturer still considered an indirect comparison

between enzalutamide and abiraterone to be possible. The manufacturer performed the comparison using the Bucher method for the following end points: overall survival, radiographic progression-free survival, modified progression-free survival, time to first skeletal-related event, objective response rate (that is, the proportion of patients with a complete or partial radiographic response), PSA response and adverse events.

3.13 The manufacturer expressed the results of the indirect comparison as hazard ratios for overall survival, progression-free survival and time to first skeletal-related event, and as odds ratios for objective response rate and PSA response, with hazard ratios less than 1.00 and odds ratios greater than 1.00 favouring enzalutamide. The manufacturer reported a statistically significant difference ($p<0.05$) in favour of enzalutamide for radiographic progression-free survival and modified progression-free survival, with hazard ratios slightly higher than those reported for enzalutamide compared with best supportive care. The differences between enzalutamide and abiraterone for overall survival and time to first skeletal-related event were not statistically significant (hazard ratios and confidence intervals are academic in confidence). The manufacturer stated that the hazard ratio for overall survival, although not statistically significant, should be interpreted with caution because there is evidence that the hazard ratio for abiraterone compared with placebo varied over time (the treatment effect was not constant), which may have caused the relative treatment benefit of abiraterone to be overestimated. For the objective response rate and PSA response end points, enzalutamide was associated with a statistically significant difference for PSA response only (odds ratios and confidence intervals are academic in confidence).

3.14 For health-related quality of life, investigators collected data during AFFIRM using the EQ-5D and Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaires. However, EQ-5D utility data were collected only at study sites in France, Germany, Italy, Spain and the UK. In total, 179 patients provided EQ-5D data (15.8% and 13.3% of patients randomised to enzalutamide and placebo respectively). FACT-P is a 39-item questionnaire about physical, social, emotional and functional wellbeing. Each item is scaled 0 to 4 (the higher the score the better), and the FACT-P score is the sum across items. Patients achieved

a quality-of-life response in AFFIRM if their FACT-P scores improved by 10 points compared with baseline on 2 consecutive measurements, at least 3 weeks apart. Of patients evaluated using FACT-P (enzalutamide 81.5%, placebo 62.2%), 42.2% and 14.5% had a quality-of-life response in the enzalutamide and placebo groups respectively (p=0.0018).

3.15 Investigators assessed the safety and tolerability of enzalutamide throughout AFFIRM, and collected data on adverse events and serious adverse events for 30 days after the patient's last dose of study treatment or until they started another systemic cancer therapy, if sooner. The manufacturer analysed adverse events for a 'safety population', defined as patients who had taken at least 1 dose of the study drug. The rates of adverse events were similar in the 2 groups. The incidence of adverse events of grade 3 severity or above was lower in the enzalutamide group (45.3% compared with 53.1% in the placebo group), with a median time to the first grade 3 or above adverse event of 12.6 months in the enzalutamide group compared with 4.2 months in the placebo group. The incidence of all grades of fatigue, diarrhoea, hot flushes, musculoskeletal pain and headache was higher in the enzalutamide group than in the placebo group. There were no clinically significant between-group imbalances in the rates of other adverse events, such as high blood glucose concentration, glucose intolerance, weight gain or high lipid concentrations. Abnormal findings in liver function tests were reported as adverse events in 1% of patients receiving enzalutamide and in 2% of patients receiving placebo. By April 2012, 10 patients (0.9%) who received enzalutamide had had a seizure; no seizures were reported in patients who received placebo. Overall, the manufacturer considered that the safety profile of enzalutamide was acceptable and that adverse events could be managed.

3.16 In its indirect comparison between enzalutamide and abiraterone, the manufacturer compared the incidence of adverse events, skeletal-related events and tolerability. The manufacturer stated that the results of the indirect comparison showed that enzalutamide had a similar safety profile to abiraterone. Enzalutamide was associated with a decreased risk of lowering serum potassium concentrations compared with abiraterone. In contrast, the risk of bone pain was higher with

enzalutamide. No statistically significant differences were found for other adverse events, skeletal-related events or the rate of treatment discontinuation (used by the manufacturer as a proxy for tolerability) between enzalutamide and abiraterone.

3.17 In response to the second appraisal consultation document (which did not recommend for the use of enzalutamide after abiraterone), the manufacturer provided 12 retrospective studies on the effectiveness of enzalutamide in patients who had received previous treatment with abiraterone. All studies were observational record reviews or audits, and included between 23 and 150 patients who had previously received abiraterone. Outcomes varied across the studies, but in 9 studies reporting change in PSA, 10-46% of patients had a 50% or more decline in PSA from baseline after treatment with enzalutamide. In the largest study, 39% (58/150) of patients who had previously received abiraterone had a 30% or more decline in PSA from baseline after treatment with enzalutamide. This was less of a decline than that seen in patients who had not previously received abiraterone (55% [18/33] decline in PSA). The manufacturer interpreted these studies as demonstrating that a meaningful proportion of patients benefit from treatment with enzalutamide after abiraterone.

Evidence Review Group critique

3.18 The ERG considered that the manufacturer's systematic review was adequate. It noted that, although there were several randomised controlled trials that evaluated mitoxantrone in the population in the decision problem, none of these compared enzalutamide with mitoxantrone, and none allowed an indirect comparison, because the 2 treatments did not have a common comparator. The ERG therefore considered that the manufacturer was justified in excluding mitoxantrone as a comparator.

3.19 For the indirect comparison, the ERG agreed that patients in AFFIRM and COU-AA-301 were generally comparable, but noted slight differences in baseline characteristics:

- COU-AA-301 had more patients aged 75 years or older (27.7% compared with

25.3% in AFFIRM), and more patients with an ECOG performance status of 2 (10.6% compared with 8.5% in AFFIRM).

- More patients had received 1 or 3 previous regimens in AFFIRM (73.0% and 2.8% compared with 69.7% and 0.0% in COU-AA-301), whereas more patients had received 2 previous regimens in COU-AA-301 (30.3% compared with 24.3% in AFFIRM).
- More patients had previously had surgery for cancer in AFFIRM (64.6% compared with 52.1% in COU-AA-301).

In addition, the ERG questioned whether corticosteroids affect pain, quality of life and adverse events. In the manufacturer's response to a request for clarification, the manufacturer indicated that corticosteroids may lessen bone pain associated with disease metastases, improve appetite and reduce weight loss, but that they also cause debilitating adverse reactions. Because the manufacturer could not quantify the effect of corticosteroids, it assumed that their positive and negative effects cancel each other out. Overall, the ERG considered that the manufacturer's indirect comparison of enzalutamide and abiraterone was appropriate and performed correctly.

3.20 The ERG reviewed the 12 retrospective studies provided by the manufacturer in response to the second appraisal consultation document, and considered that the evidence presented was not suitable for assessing enzalutamide's effectiveness when given after abiraterone. Specifically, the ERG noted that the studies prohibited a 'robust analysis' because they all had small patient numbers, included no comparator, provided short periods of follow-up, and presented little data on overall survival or progression-free survival. Using data reported in the abstract of the largest record-review study provided by the manufacturer, the ERG noted that patients treated with enzalutamide (but who had not previously received abiraterone) were 2.3 times more likely to have at least a 50% decrease in their PSA concentration than patients treated with enzalutamide after abiraterone. Overall, the ERG considered that there was insufficient evidence to establish how clinically effective enzalutamide was after treatment with abiraterone.

3.21 The ERG noted that the adverse events associated with enzalutamide were similar to those with abiraterone, and less debilitating than the

bone marrow suppression, diarrhoea, physical weakness, hair loss and other adverse events experienced with cytotoxic agents such as mitoxantrone. The ERG viewed enzalutamide as generally safe, with relatively mild adverse events.

Cost-effectiveness evidence

3.22 The manufacturer submitted a de novo economic model to estimate the cost effectiveness of enzalutamide, compared with abiraterone and with best supportive care, in patients with metastatic hormone-relapsed prostate cancer whose disease had progressed during or after docetaxel therapy. The manufacturer conducted the analysis from the perspective of the NHS and personal social services and chose a time horizon of 10 years. The cycle length of the model was 3 weeks, in line with previous models for this indication, and the manufacturer applied a half-cycle correction except for direct drug costs. Costs and health effects were discounted at an annual rate of 3.5%.

3.23 The manufacturer's model was a state-transition Markov cohort model simulating 3 states: stable disease, progressive disease and death. All patients entered the model in the stable-disease state and received enzalutamide, abiraterone or best supportive care. They could then remain in this state, move to the progressive-disease state or die. Once they moved to a different state in the model, patients could not return to their previous state. Patients who moved to the progressive-disease state stopped treatment and received palliative care. The manufacturer modelled adverse events (grade 3 and above in AFFIRM) in the stable-disease state (assuming that only patients receiving treatment could have an adverse event), and skeletal-related events (spinal cord compression, pathological non-vertebral bone fracture, radiation to the bone and bone surgery) in the progressive-disease state (assuming that skeletal-related events result only from disease progression in the bones).

3.24 The manufacturer used clinical data for enzalutamide and best supportive care from AFFIRM, and data for abiraterone from COU-AA-301 (Fizazi et al. 2012). To estimate overall survival and progression-free survival, the manufacturer chose best supportive care

as a 'reference' treatment. It then fitted alternative parametric functions (exponential, Weibull, log-logistic, log-normal and gamma) to patient-level data for the placebo group in AFFIRM (representing best supportive care) and extrapolated the curves beyond the end of the trial, using the final cut-off date (16 December 2011) for overall survival, and the interim analysis cut-off date (25 September 2011) for progression-free survival. The manufacturer chose the base-case survival functions for best supportive care based on statistical tests, visually inspecting the curves' fit to the data, and the clinical plausibility of the extrapolation as judged by its clinical experts. The survival functions for enzalutamide and abiraterone were then estimated by applying a hazard ratio derived from their respective trials to the survival function for best supportive care. The manufacturer used these survival functions to establish the transition between states in the model for each treatment.

3.25 The manufacturer chose the Weibull function to estimate overall survival for best supportive care (the 'reference' treatment) because, according to its clinical experts, the shape of its 'tail' was more realistic than other functions, even though the log-logistic function fitted the data best according to statistical tests. The Weibull function produced a median overall survival of 12.96 months for best supportive care. The manufacturer stated that, unlike the hazard ratio for abiraterone compared with placebo, the hazard ratio for enzalutamide compared with placebo remained constant over time (that is, meeting the proportional hazards assumption). Therefore, the manufacturer derived the survival function for enzalutamide by applying the hazard ratio of 0.618 from AFFIRM to the best supportive care function. In contrast, the manufacturer stated that using a constant hazard ratio may overestimate the survival benefit of abiraterone. This was because, over the course of follow-up in COU-AA-301, the hazard ratio for abiraterone compared with placebo varied and the Kaplan–Meier curves separated and then converged, implying that the benefit of abiraterone decreased over time. For this reason, the manufacturer fitted a Cox proportional hazards model including a time-dependent covariate, which it chose over piecewise modelling, to capture the changing effect of abiraterone over time. This approach resulted in hazard ratios starting at 0.52 and increasing over time (treatment effect decreasing) to 1.0 at 16.6 months

and 1.39 at 25 months. Because no data were published beyond 25 months, the manufacturer assumed that the hazard ratio beyond 25 months remained at 1.39.

3.26 To derive the curves for progression-free survival, the manufacturer did not use either radiographic progression-free survival (a secondary end point in AFFIRM) or modified progression-free survival (defined post hoc) because it considered that neither measure accurately reflected how disease progression would be defined in clinical practice. The manufacturer believed that, in clinical practice, patients would not stop treatment based on a single measure of disease progression (for example, radiographic disease progression). It therefore used time to treatment discontinuation (defined post hoc) as a proxy for progression-free survival in its base-case analysis, noting that the criteria for stopping treatment were the same in AFFIRM and COU-AA-301 (the manufacturer used the definition of modified progression-free survival instead of time to treatment discontinuation in a scenario analysis). The manufacturer chose the Weibull function for best supportive care (estimating a median time to treatment discontinuation of 3.71 months), and derived the survival function for enzalutamide by applying enzalutamide's hazard ratio for treatment discontinuation of 0.34. To estimate a hazard ratio for abiraterone, the manufacturer used data from the manufacturer's submission for abiraterone from Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE technology appraisal guidance 259). However, these data related to the subgroup of patients who had received only 1 cytotoxic chemotherapy regimen (which included docetaxel). The manufacturer estimated a hazard ratio of 0.52 (95% CI 0.44 to 0.60) for abiraterone, and used this ratio to derive the progression-free survival function for abiraterone.

3.27 Adverse events in the model (applied in the stable-disease state) comprised all grade 3, 4 or 5 adverse events that occurred in more than 1% of patients in the enzalutamide or placebo groups of AFFIRM, together with seizures. Skeletal-related events in the model (applied in the progressive-disease state) were spinal cord compression, pathological non-vertebral bone fractures, radiation to the bone or surgery to the bone. The manufacturer noted that a change in cancer

therapy to treat bone pain was a skeletal-related event in AFFIRM, but it did not consider it as such in the model.

3.28 Because a limited number of patients completed the EQ-5D questionnaire, the manufacturer used a mapping algorithm to transform the FACT-P responses into EQ-5D data. However, because mapping utility values introduces uncertainty, the manufacturer used the EQ-5D data collected from AFFIRM in the model, and applied the mapped values only when it considered the number of EQ-5D responses insufficient. The manufacturer derived the EQ-5D utility values by applying UK valuations of health states estimated using the time trade-off method. For the baseline utility value in the model, the manufacturer presented the EQ-5D value collected from the trial and the mapped value (both are academic in confidence), but used the former because it considered the sample size to be reasonable (n=209). To capture the benefit of treatment with enzalutamide or abiraterone, the manufacturer applied a value reflecting the increase in utility above the baseline utility value. For patients receiving enzalutamide, the manufacturer estimated a mapped utility increase (academic in confidence) and, for patients receiving abiraterone, it used a value of 0.04 (95% CI 0.032 to 0.048) from the manufacturer's submission for abiraterone to the Dutch Health Care Insurance Board.

3.29 For the decrease in utility associated with disease progression, the manufacturer derived a value from a published study, Sandblom et al. (2004), because no health-related quality-of-life data were collected in AFFIRM after a patient's disease had progressed. Sandblom et al. measured the health-related quality of life of patients with metastatic hormone-relapsed prostate cancer at the end of life, and reported EQ-5D utility data for 2 time intervals: 16–8 months before death and 8–0 months before death. The manufacturer stated that the duration of these intervals approximated the time patients in AFFIRM spent in the stable- and progressive-disease states. The utility decrease used by the manufacturer for the progressive-disease state was −0.085, reflecting the decrease in utility from 16–8 months before death to 8–0 months before death in the Sandblom et al. study. Although published studies show that utility decreases in the last months of life, the manufacturer did not model this and instead applied a constant utility for the

progressive-disease state. The manufacturer justified this approach because it did not identify reliable data to reflect this utility decrease, and because it believed that health would deteriorate equally among patients on different treatments. The manufacturer sourced the utility decreases associated with adverse events from the published literature, and for skeletal-related events, it mapped values from FACT-P to EQ-5D because it considered that there were insufficient EQ-5D data for skeletal-related events from AFFIRM.

3.30 The manufacturer included the following costs in the model: intervention and comparators' costs, resource use costs, and costs of adverse events and skeletal-related events. The price of enzalutamide in the model took into account the patient access scheme discount for enzalutamide, and the manufacturer assumed the patient access scheme discount for abiraterone because the discount was commercial in confidence. The manufacturer applied the resource use costs associated with monitoring patients based on the abiraterone submission for NICE technology appraisal guidance 259. It used NHS reference costs 2011/12 for diagnostic imaging and tests, palliative care, and the management of adverse events and skeletal-related events; the average monitoring cost per 3-week cycle in the model was £70.90. The frequency of concomitant medications in the model was based on AFFIRM. For drug costs, the manufacturer used the 'British national formulary' (BNF) and the Electronic Market Information Tool (EMIT). Because resource use and associated costs usually peak immediately before death, the manufacturer incorporated a terminal care cost of £3133 per patient as a transition cost to the death state. The manufacturer assumed that all hospitalisation costs would be captured by the costs of adverse events, skeletal-related events and terminal care.

3.31 The manufacturer's deterministic cost-effectiveness results estimated that enzalutamide provides additional quality-adjusted life years (QALYs) at an additional cost to abiraterone (values are commercial in confidence), resulting in an incremental cost-effectiveness ratio (ICER) of £14,795 per QALY gained for enzalutamide compared with abiraterone. Compared with best supportive care, the ICER for enzalutamide was £43,587 per QALY gained (costs and QALYs are commercial in confidence). In an incremental analysis, abiraterone was extendedly

dominated by enzalutamide (that is, a QALY is attained at a higher cost with abiraterone than with enzalutamide because the ICER for abiraterone compared with best supportive care [£102,751 per QALY gained] is higher than that for enzalutamide compared with best supportive care).

3.32 The manufacturer presented deterministic sensitivity analyses in which it varied all the parameters in the model, one at a time. Most parameters were varied to the lower and upper limits of their 95% confidence intervals. In comparing enzalutamide with abiraterone, the ICERs were most sensitive to the hazard ratio used to estimate overall survival for abiraterone. When varied, this resulted in ICERs ranging from £11,843 to £46,022 per QALY gained for enzalutamide compared with abiraterone. The manufacturer advised caution when interpreting these results because 2 parameters (the intercept and the time covariate) were correlated in the hazard ratio for abiraterone and, in the sensitivity analysis, the manufacturer varied only 1 parameter (the intercept), which it suggested may cause the ICERs to be overestimated. For the comparison of enzalutamide with best supportive care, the ICER was most sensitive to enzalutamide's hazard ratio for overall survival (0.618), with ICERs ranging from £34,692 to £58,042 per QALY gained when this was varied. The manufacturer stated that, compared with abiraterone or best supportive care, the cost effectiveness of enzalutamide was most sensitive to the hazard ratios for overall survival and treatment discontinuation, and the degree to which health-related quality of life improved while taking enzalutamide or abiraterone (that is, the degree to which utility increased 'on-treatment').

3.33 The manufacturer carried out a probabilistic sensitivity analysis to characterise the uncertainty in the base-case ICER, varying parameters simultaneously with values from a probability distribution. The probabilistic ICERs were £14,576 per QALY gained for enzalutamide compared with abiraterone and £43,239 per QALY gained for enzalutamide compared with best supportive care. For enzalutamide compared with abiraterone, there was an 83% probability of enzalutamide being cost effective if the maximum acceptable ICER was £20,000 per QALY gained, and a 98% probability of it being cost effective if the maximum acceptable ICER was £30,000 per QALY gained.

Compared with best supportive care, the probability of enzalutamide being cost effective at a maximum acceptable ICER of £30,000 per QALY gained was around 0% (numerical value not provided in the manufacturer's submission), and the probability of it being cost effective at a maximum acceptable ICER of £50,000 per QALY gained was 81%.

3.34 To investigate the structural uncertainty in the model, the manufacturer tested alternative assumptions related to the following in scenario analyses:

- the parametric function it used to fit the Kaplan–Meier data for overall survival and progression-free survival
- the overall survival function for abiraterone that it had estimated from time-dependent hazard ratios
- how it defined disease progression
- the utility values it derived for the model
- the potential that it had double counted the utility decreases for all adverse events and skeletal-related events
- the patient access scheme discount for abiraterone.

The key scenarios are summarised in sections 3.35–3.37.

3.35 In its base case, the manufacturer estimated overall survival for abiraterone by applying a time-dependent hazard ratio to the survival function for best supportive care (the 'reference' treatment). The manufacturer explored the sensitivity of the model to this method in 2 scenarios:

- applying the constant hazard ratio of 0.74 from COU-AA-301 (Fizazi et al. 2012) to the survival function for best supportive care
- estimating mean overall survival for abiraterone from COU-AA-301, then indirectly comparing this estimate with the mean overall survival for enzalutamide from AFFIRM to derive the model inputs.

Compared with a base-case ICER of £14,795 per QALY gained for enzalutamide

compared with abiraterone, the ICERs from these 2 scenarios were £19,972 and £18,034 per QALY gained respectively.

3.36 In the base-case model, the manufacturer applied a utility increase to the baseline utility value to reflect the treatment benefit of enzalutamide and abiraterone. The manufacturer investigated the impact of this utility increase:

- by excluding it from the model
- by assuming an equal utility increase for enzalutamide and abiraterone.

For the first scenario, the base-case ICER increased from £14,795 per QALY gained to £16,720 per QALY gained for enzalutamide compared with abiraterone, and from £43,587 per QALY gained to £51,343 per QALY gained for enzalutamide compared with best supportive care. For the second scenario, the ICERs were £15,652 and £43,587 per QALY gained for enzalutamide compared with abiraterone and best supportive care respectively.

3.37 The manufacturer investigated the effect of using modified progression-free survival instead of time to treatment discontinuation as a proxy for progression-free survival. This decreased the ICERs for enzalutamide compared with abiraterone and with best supportive care to £13,476 and £43,396 per QALY gained respectively.

3.38 The manufacturer stated that some clinical experts believed that enzalutamide and abiraterone have the same clinical effect, and that the superiority of enzalutamide demonstrated in its indirect comparison may have reflected differences in the populations of AFFIRM and COU-AA-301. Because of this, the manufacturer performed a cost-minimisation analysis, which assumed equal utility gain and equal rates of adverse events and skeletal-related events for enzalutamide and abiraterone. In this analysis, the acquisition cost of both treatments was set to be equal, but because abiraterone is taken with corticosteroids, and patients on abiraterone need more monitoring, the manufacturer concluded that enzalutamide was less costly and as effective as abiraterone (the manufacturer estimated cost savings of £1007 for enzalutamide compared with abiraterone).

3.39 In response to the first appraisal consultation document, which did not include a recommendation on the use of enzalutamide for patients who had received 2 or more courses of cytotoxic chemotherapy, the manufacturer provided a subgroup analysis comparing enzalutamide with best supportive care for these patients. The median survival in the placebo group was 12.8 months. In this analysis, the manufacturer estimated a hazard ratio for overall survival of 0.66 (95% CI 0.48 to 0.90), which differed from the hazard ratio presented in its original submission (0.74, 95% CI 0.54 to 1.03). The manufacturer stated that this was because the hazard ratio of 0.66 was based on a stratified analysis at the final cut-off date (16 December 2011) whereas the hazard ratio in the original submission was based on an unstratified analysis at the cut-off date for the interim analysis (25 September 2011). Using the increase in utility assumed in the base case for patients on enzalutamide (academic in confidence), the manufacturer estimated an ICER for enzalutamide compared with best supportive care of £45,509 per QALY gained.

Evidence Review Group critique and exploratory analyses

3.40 The ERG considered that the manufacturer's literature review of the cost-effectiveness evidence was appropriate. The ERG noted that the economic model submitted by the manufacturer was consistent with the structure of other models for the same disease area and used a lifetime time horizon.

3.41 The ERG agreed that it was appropriate for the manufacturer to have chosen the Weibull function for overall survival over the log-logistic function (which fitted the data best according to statistical tests) because the latter predicted an implausibly high proportion of patients alive at 5 and 10 years (at 5 years: log-logistic 4.2%, Weibull 0.0%; at 10 years: log-logistic 1.1%, Weibull 0.0%).

3.42 To model overall survival for abiraterone, the manufacturer estimated hazard ratios starting at 0.52 and increasing over time to 1.39 at 25 months (implying that patients receiving or who had received abiraterone have a higher risk of death than those receiving or who had received placebo), and assumed that the hazard ratio beyond 25 months remains 1.39. In the ERG's opinion, using a hazard ratio of 1.39 beyond

25 months was not justified, given the very low number of patients still in the study at 25 months. Instead, the ERG argued that a conservative approach should be adopted by assuming a hazard ratio of 1 beyond 25 months (patients receiving or having received abiraterone or placebo have the same risk of death). The ERG applied this assumption in its exploratory analyses (see section 3.47).

3.43 To derive the progression-free survival function for abiraterone, the manufacturer estimated a hazard ratio (0.52) using data related to the subgroup of patients who had received only 1 previous cytotoxic chemotherapy regimen. The ERG argued that estimating the hazard ratio from the overall population, which included patients who had received more than 1 cytotoxic chemotherapy regimen, was more appropriate and consistent with how the manufacturer estimated overall survival for abiraterone. The ERG therefore preferred a hazard ratio of 0.49 (95% CI 0.37 to 0.63), approximated from the ratio of median values for the whole population reported from COU-AA-301 (Fizazi et al. 2012) to model progression-free survival. The ERG applied this hazard ratio in its exploratory analyses (see section 3.47).

3.44 The ERG agreed that, given the uncertainty around mapping utility values, it was appropriate for the manufacturer to have chosen the baseline EQ-5D utility value collected from AFFIRM. However, the ERG regarded this value as uncertain, because only a small proportion of patients completed the EQ-5D questionnaire (209 out of 1199 patients) and of those, a considerable proportion had missing values. In addition, the ERG stated that patients in AFFIRM may have been fitter than patients seen in clinical practice, which may have caused the utility value to be overestimated. The ERG explored the uncertainty around this parameter in a threshold analysis (see section 3.49).

3.45 The ERG could not verify the internal mapping algorithm or the details of the calculations that the manufacturer used to estimate the utility increase for patients taking enzalutamide. In addition, it considered that there was no evidence to support an increase in utility with abiraterone, and so this, too, was highly uncertain. The ERG stated that the difference between the utility increases for enzalutamide and abiraterone is an important determinant of the incremental QALYs of enzalutamide and, in

its opinion, there is no strong evidence to justify assuming different utility increases for enzalutamide and abiraterone. Furthermore, the ERG considered that incorporating a utility increase for treatment in the model introduces a risk of double counting and overestimating the benefit of treatment, because the utility decreases for adverse events and skeletal-related events already capture part of this benefit. Overall, the ERG preferred taking a conservative approach and excluding the utility increases for enzalutamide and abiraterone from the model. The ERG used this assumption in its exploratory analyses (see section 3.47).

3.46 The manufacturer derived the decrease in utility associated with disease progression from Sandblom et al. (2004), because the duration of the time intervals of 16–8 months and 8–0 months before death in this study approximated the time patients in AFFIRM spent in the stable- and progressive-disease states. The ERG argued that this may bias the utility value, because some patients assessed in Sandblom et al. may have had stable disease rather than progressed disease 8–0 months before death, and others may have had progressive disease rather than stable disease 16–8 months before death. The manufacturer stated that, although Sandblom et al. does not report the time patients spent in each state, patients are likely to have progressive disease in their last 8 months of life. The ERG considered the manufacturer's utility value from Sandblom et al. (−0.085) to be appropriate. It also explored using an alternative value of −0.07 from Sullivan et al. (2007), which was favoured by the ERG for NICE technology appraisal guidance 259. This increased the base-case ICERs for enzalutamide compared with abiraterone by approximately £150 per QALY gained, and for enzalutamide compared with best supportive care by £450 per QALY gained.

3.47 To address its concerns about some of the parameters used in the manufacturer's base-case model, the ERG made the following changes, one at a time:

- Applying a hazard ratio of 1.0 for abiraterone compared with best supportive care after 25 months. This changed the ICERs for enzalutamide to £15,020 per QALY gained compared with abiraterone and to £43,398 per QALY gained compared with best supportive care.
- Applying a hazard ratio of 0.49 estimated from the whole population to model

progression-free survival for abiraterone. This changed the ICERs for enzalutamide to £12,461 per QALY gained compared with abiraterone and to £43,285 per QALY gained compared with best supportive care.

- Excluding the utility increases to patients while taking enzalutamide or abiraterone. This changed the ICERs for enzalutamide to £16,464 per QALY gained compared with abiraterone and to £51,014 per QALY gained compared with best supportive care.

The ERG then applied the changes listed above simultaneously in the manufacturer's base case model (from now on, this modification of the manufacturer's model is referred to as the ERG base case). The ICERs were £14,488 per QALY gained for enzalutamide compared with abiraterone, and £51,124 per QALY gained for enzalutamide compared with best supportive care. In an incremental analysis, abiraterone would be extendedly dominated by enzalutamide in all the ERG's exploratory analyses.

3.48 The ERG provided analyses with mitoxantrone included as a comparator to comply with the scope. Using the manufacturer's base-case model, the ICER for enzalutamide compared with mitoxantrone was £33,585 per QALY gained. Within the ERG base case, this ICER was £37,840 per QALY gained. In an incremental analysis, mitoxantrone would be extendedly dominated by enzalutamide in both the manufacturer's and the ERG's base case.

3.49 To identify the input value of the model parameter below which enzalutamide would not be cost effective at a maximum acceptable ICER of £50,000 per QALY gained, the ERG performed 2 threshold analyses of:

- how the manufacturer estimated progression-free survival in the model (that is, by using time to treatment discontinuation as a proxy)
- the value used by the manufacturer in the model to estimate utility at baseline.

The ERG considered that, although time to treatment discontinuation was the most reasonable proxy for progression-free survival given the available evidence, uncertainty existed around the hazard ratio for treatment discontinuation. The ERG found that, for the manufacturer's base case ICER for enzalutamide compared with best supportive care to exceed £50,000 per

QALY gained, the treatment discontinuation hazard ratio for enzalutamide compared with best supportive care must be 0.23 or lower (the base case value was 0.34). That is, improving the treatment effect on progression free survival (decreasing the hazard ratio) would increase total costs more than total QALYs for enzalutamide, resulting in a higher ICER. For the utility value at baseline, the ERG found that, for the ICER to exceed £50,000 per QALY gained, the utility value must be 0.58 or lower. The ERG considered that the utility value of 0.58 seemed realistic based on the range of values reported in the literature for this stage of the disease, although these values may represent an average value for patients with both stable and progressed disease, and may reflect between-study differences.

3.50 To reflect the Committee's preferred, but not previously considered analysis described in the first appraisal consultation document, the ERG modelled an overall survival hazard ratio for abiraterone compared with placebo that was constant over time, and assumed equal 'on-treatment' utility increases for enzalutamide and abiraterone of 0.04. This gave an ICER of £22,604 per QALY gained for enzalutamide compared with abiraterone and £45,898 per QALY gained for enzalutamide compared with best supportive care.

3.51 For the subgroup analysis of patients who have received 2 or more previous cytotoxic chemotherapy regimens (of which one included docetaxel) (see section 3.39), the ERG estimated values for median overall survival for the enzalutamide and placebo groups as 15.9 months and 12.3 months respectively (a difference of 3.6 months). The ERG noted that its estimate of median overall survival in the placebo group (12.3 months) differed from the manufacturer's estimate (12.8 months). To explore the uncertainty in the manufacturer's analysis, the ERG applied an alternative 'on-treatment' utility increase for enzalutamide of 0.04 (the 'on-treatment' utility increase used for abiraterone in the manufacturer's base case). This resulted in an ICER of £48,020 per QALY gained for enzalutamide compared with best supportive care.

3.52 Full details of all the evidence can be found on the NICE website.

4 Consideration of the evidence

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

4.1 The Committee discussed the clinical management of metastatic hormone-relapsed prostate cancer in people who have received docetaxel-containing chemotherapy. It understood from the clinical specialists that there are few treatment options available for patients at this stage of the disease, and that enzalutamide represents an effective treatment. The Committee heard from the clinical specialists that enzalutamide is likely to be used at the same point in the treatment pathway as abiraterone, by patients who have received at least 1 course of cytotoxic chemotherapy. The Committee heard from the patient experts that enzalutamide is an oral treatment that, unlike abiraterone, does not need to be taken on an empty stomach, making it more convenient to take. It also heard that, with abiraterone, some patients may need to reduce their dose to prevent liver toxicity, whereas enzalutamide is less likely to cause liver toxicity. The Committee understood from the patient experts that patients' quality of life is affected by whether or not the patient is receiving treatment, and appreciated that patients with the condition would value even small improvements in quality of life. The Committee agreed with the clinical specialists and patient experts that enzalutamide would be a valuable treatment option for patients with metastatic, hormone-relapsed prostate cancer after at least 1 cytotoxic chemotherapy regimen.

4.2 The Committee was aware that the Cancer Drugs Fund offers enzalutamide to patients whose disease has progressed on or after docetaxel-containing therapy, but not if patients have previously received abiraterone. The Committee noted comments received from patient organisations and members of the public in response to the second appraisal consultation document. Most of the comments opposed the preliminary recommendation restricting the use of

enzalutamide to those who have not previously received abiraterone because it was felt that this placed a significant restriction on access. The Committee acknowledged the concern of patients, in particular that more than 7000 people had signed a Prostate Cancer UK petition calling for this restriction to be removed. The Committee noted comments from the manufacturer and professional organisations acknowledging the absence of robust clinical evidence on the most effective sequencing of enzalutamide and abiraterone. The Committee noted concerns that restricting enzalutamide to patients who had not previously received abiraterone may influence the order in which clinicians offer the drugs. It also considered the small, single-arm observational studies provided by the manufacturer in response to the second appraisal consultation document (see section 3.17) that suggested that enzalutamide is less effective at reducing PSA concentration in patients who have been treated with abiraterone. The Committee heard from the clinical specialist that these results reflect clinical practice because there is usually a decreasing response to a drug the further down the treatment pathway it is received. Therefore, enzalutamide would be expected to produce a lower response rate after cytotoxic chemotherapy with docetaxel followed by abiraterone than after cytotoxic chemotherapy alone. The Committee heard from the clinical specialists that patients might stop abiraterone for a number of clinical reasons, including drug toxicity, intolerance or disease progression; it noted that these clinical circumstances are likely to influence the effectiveness of subsequent treatment with enzalutamide. The Committee further heard from the clinical specialist that, in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone (particularly to patients who experience liver toxicity on abiraterone). Acknowledging the limitations of the observational studies (see section 3.20) and the uncertainty around the evidence base for sequential treatment, the Committee agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, the Committee agreed that the observational studies were not suitable to inform a conclusion on the magnitude of the effectiveness of enzalutamide after treatment with abiraterone.

4.3 The Committee discussed the manufacturer's decision problem, noting that the manufacturer had chosen to exclude mitoxantrone as a comparator for enzalutamide even though it had been listed as a

comparator in the final scope for this appraisal. The Committee heard from the clinical specialists that mitoxantrone was standard care years ago, and that newer treatments such as abiraterone have displaced its use in clinical practice so that its use in the NHS is now negligible. It further heard that although mitoxantrone improved quality of life, it did not prolong survival. The Committee was also aware that mitoxantrone is not licensed for treating metastatic hormone-relapsed prostate cancer, and is not included in existing NICE guidance for prostate cancer. The Committee concluded that it was appropriate for the manufacturer to have excluded mitoxantrone as a comparator in its decision problem.

4.4 The Committee discussed the relevance of the 2 comparators, abiraterone and best supportive care, in relation to the population covered by the marketing authorisation for enzalutamide. The Committee was aware that Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE technology appraisal guidance 259) recommends abiraterone for treating hormone-relapsed metastatic prostate cancer only if patients' disease progressed during or after treatment with 1 course of docetaxel-containing cytotoxic chemotherapy. The Committee therefore agreed that abiraterone is a suitable comparator for enzalutamide only for the same population for which abiraterone is recommended by NICE. It also agreed that comparing enzalutamide with best supportive care would be appropriate for the subset of the population covered by the marketing authorisation for which abiraterone is not recommended (that is, patients with hormone-relapsed disease who have received 2 or more cytotoxic chemotherapy regimens). As such, the Committee concluded that both comparators specified in the manufacturer's decision problem were appropriate, but for different populations.

4.5 The Committee considered the evidence on the clinical effectiveness of enzalutamide, noting that it came mainly from AFFIRM. It agreed that AFFIRM was a good-quality trial and relevant to the decision problem. The Committee noted that, in the trial, enzalutamide was associated with a statistically significant improvement in median overall survival of 4.5 months compared with placebo (final cut-off date 16 December 2011). It also noted that there was a statistically significant difference in quality of life for patients receiving enzalutamide compared

with placebo, as measured using Functional Assessment of Cancer Therapy-Prostate (FACT-P). The Committee concluded that, compared with best supportive care, enzalutamide was a clinically effective treatment for patients with metastatic hormone-relapsed prostate cancer whose disease progressed on or after at least 1 docetaxel-containing cytotoxic chemotherapy.

4.6 The Committee considered the different definitions of progression-free survival used by the manufacturer in its submission, namely, radiographic progression-free survival, modified progression-free survival and time to treatment discontinuation. The Committee was aware that determining progression-free survival from radiographic evidence in AFFIRM was difficult because patients entered the trial with metastatic disease and could die without evidence of further radiographic progression. The Committee heard from the clinical specialists that no single measure is routinely used to determine disease progression, and that clinicians take into account each patient's clinical, radiological and biochemical results. The Committee noted that the patient experts stressed the importance of judging how well a treatment works by how well patients feel on that treatment. The Committee discussed whether stopping treatment was a reasonable proxy for disease progression. It heard from the clinical specialists that patients are regularly monitored and their treatment is stopped, and they are offered an alternative option when their disease is considered to have progressed. The Committee noted that, of those who stopped enzalutamide in AFFIRM, the primary reason for stopping treatment in about 55% of patients was disease progression. The Committee agreed that patients are likely to stop treatment in clinical practice before all the criteria applied in AFFIRM have been met. Although the Committee appreciated the uncertainty around measuring progression-free survival, it concluded that, of the measures described by the manufacturer, time to treatment discontinuation was the most reasonable.

4.7 The Committee discussed the manufacturer's indirect comparison between enzalutamide and abiraterone. It noted that the proportion of patients who received prednisone in the placebo groups of AFFIRM and COU-AA-301 differed (AFFIRM 45.6%, COU-AA-301 100%) because patients need to take abiraterone, but not enzalutamide, together with

corticosteroids. The Committee heard from the clinical specialists that, at this advanced stage of the disease, patients would have already received corticosteroids before starting docetaxel therapy, and their disease may have developed resistance to corticosteroids. The Committee discussed the possibility that corticosteroids could reduce survival, for example, if a patient developed corticosteroid-induced diabetes, but was not presented with any evidence. The Committee concluded that corticosteroids were unlikely to affect survival, and that AFFIRM and COU-AA-301 could be used to compare enzalutamide and abiraterone indirectly. The Committee noted that comments received in response to the first appraisal consultation document pointed out that follow-up in COU-AA-301 was longer than in AFFIRM (20.2 months compared with 15.0 months) at the time points at which the manufacturer compared overall survival data from the 2 trials. The comments suggested that this biased the comparison against abiraterone because the treatment effect was time-dependent (that is, the effectiveness of abiraterone tapered in the long term), so the estimated hazard ratios could not be compared in an indirect comparison. The Committee agreed that, whenever possible, the most mature datasets should be compared and that both datasets used for the indirect comparison provided this (for AFFIRM and COU-AA-301, the longest follow-up for any patient was 15.0 months and 20.2 months respectively). The Committee was aware that the manufacturer's indirect comparison showed no statistically significant difference in overall survival between enzalutamide and abiraterone. The Committee concluded that using these datasets was acceptable for the indirect comparison.

4.8 The Committee considered the adverse reactions and skeletal-related events associated with enzalutamide in relation to the economic modelling. It noted that adherence to enzalutamide in AFFIRM was generally high and adverse reactions were generally manageable and reversible. However, the Committee was aware of the increased risk of seizures with enzalutamide treatment, and noted that the summary of product characteristics advises caution when administering enzalutamide to people with a history of seizures or other predisposing factors for seizures. It was satisfied that these provisions would help minimise the risk of seizures in susceptible patients. The Committee discussed the skeletal-related events that occurred during AFFIRM. It

was concerned that the incidence of spinal cord compression appeared high in both treatment groups in the trial, but heard from the clinical specialists that, although spinal cord compression is a serious and potentially fatal complication, it is more likely to be diagnosed in a clinical trial before neurological damage occurs. Overall, the Committee concluded that no adverse events or skeletal-related events needed special consideration in the context of the economic modelling.

4.9 The Committee discussed the relevance of the manufacturer's cost-effectiveness evidence to the patient populations for which enzalutamide would be considered. It agreed that enzalutamide should be compared with abiraterone for the same population for whom abiraterone is recommended by NICE (that is, only after 1 docetaxel-containing regimen), and with best supportive care for the subset of the population covered by the marketing authorisation for whom abiraterone is not recommended (that is, patients who have received 2 or more cytotoxic chemotherapy regimens). However, the Committee was aware that the evidence presented by the manufacturer in its original submission related to the overall population (that is, patients who had received 1 or more cytotoxic chemotherapy regimens). The Committee noted that, compared with the survival benefit of enzalutamide for the overall population (hazard ratio [HR] 0.62), the trial results suggested that the survival benefit of enzalutamide was higher for patients who had received 1 previous cytotoxic chemotherapy regimen (HR 0.59), and lower for those who had received 2 or more regimens (HR 0.74). The Committee considered that patients who had received only 1 previous course of cytotoxic chemotherapy would be less likely to have advanced disease and more likely to have better outcomes than the overall trial population, which would improve the cost effectiveness of enzalutamide for this subgroup. Therefore, the Committee concluded that it could develop a recommendation only for patients who had received 1 previous docetaxel-containing cytotoxic chemotherapy based on evidence for the overall population. The Committee also agreed that to develop recommendations for enzalutamide for treating patients who had received 2 or more cytotoxic chemotherapy regimens, it is necessary to consider data on the baseline expected survival and a robustly modelled incremental cost-effectiveness ratio (ICER) for these patients.

4.10 The Committee discussed how the manufacturer modelled overall survival for abiraterone, noting that this parameter is key to the cost effectiveness of enzalutamide compared with abiraterone. It was aware that the manufacturer assumed that the survival benefit of abiraterone varied over time, such that beyond 16.6 months after starting treatment, the hazard ratio was greater than 1 (implying that, during that time, there was a higher risk of death for patients who took abiraterone than those who took placebo). The Committee discussed the most plausible way to model the life span of patients who took abiraterone, noting that in COU-AA-301 (Fizazi et al. 2012), the Kaplan–Meier curves for abiraterone and placebo initially diverged then converged (that is, the relative treatment effect of abiraterone improved then worsened), and crossed around 24 months after starting treatment. The Committee heard from the clinical specialists that they did not believe that this represented the natural history of the disease and that, in their opinion, the survival benefit of abiraterone is unlikely to vary over time in clinical practice. The clinical specialists suggested that the shape of the Kaplan–Meier curves may reflect the rigid criteria for stopping treatment in COU-AA-301, in that patients who would have stopped abiraterone in clinical practice (and received other therapy) instead continued taking abiraterone in the trial despite their disease having progressed under normal clinical criteria. The Committee agreed that this may have biased the overall survival end point against abiraterone and introduced uncertainty. Because of this, the Committee did not agree with how the manufacturer modelled overall survival for abiraterone, preferring to take a conservative approach. The Committee was aware that the Evidence Review Group (ERG) explored a more conservative approach than the manufacturer by assuming a hazard ratio of 1.0 beyond 25 months after starting treatment. However, the Committee considered that the ERG's scenario may not be conservative enough because it applied a hazard ratio that varied up to 25 months. The Committee concluded that, given the clinical experience with abiraterone, assuming a constant hazard ratio over the entire time horizon would be the most plausible scenario to model overall survival for abiraterone. However, it appreciated that all the modelling scenarios would be associated with some degree of uncertainty.

4.11 The Committee considered how the manufacturer modelled progression-

free survival in its base-case analysis, noting that the manufacturer used time to treatment discontinuation as a proxy for disease progression. It agreed that the manufacturer's approach was acceptable because of concerns about using radiographic imaging to monitor disease in patients with prostate cancer. The Committee was aware that in AFFIRM, some patients' disease had progressed before they stopped treatment. The Committee noted that when the manufacturer applied modified progression-free survival instead of time to treatment discontinuation as a proxy for progression-free survival in a scenario analysis, the manufacturer's base-case ICER for enzalutamide compared with abiraterone decreased from £14,800 to £13,500 per QALY gained. The Committee concluded that using an alternative definition of progression-free survival did not significantly change the ICER for enzalutamide compared with abiraterone.

4.12 The Committee considered the EQ-5D utility value chosen by the manufacturer to model health-related quality of life for patients at baseline. It noted that EQ-5D data were collected only at study sites in certain European countries (n=209). Although the Committee appreciated that a larger sample would have reduced uncertainty around this estimate, it agreed that the sample size was adequate compared with those used in previous appraisals for the same indication. It also noted that the manufacturer's utility value was lower than those used in other appraisals for the same stage of the disease. The Committee concluded that it was appropriate for the manufacturer to have used the EQ-5D utility value from AFFIRM at baseline.

4.13 The Committee discussed the increase in utility attributed to being 'on-treatment' with enzalutamide or abiraterone, noting that the manufacturer applied different values for the 2 treatments. It was aware that, to estimate the utility increase for enzalutamide, the manufacturer mapped FACT-P data onto EQ-5D using a mapping algorithm that it had not externally validated, and that the ERG could not verify. The Committee noted that the ERG considered that there was no evidence to assume different utility increases for enzalutamide and abiraterone, and that the ERG preferred excluding these estimates from the model. The Committee, noting the patient experts' experience, agreed that including 'on-treatment' utility increases reflected patient experience, but that

there is no evidence to assume different values for enzalutamide and abiraterone. The Committee concluded that the modelling should incorporate the same utility increase for both treatments.

4.14 The Committee discussed the decrease in utility that occurs with disease progression (−0.085). It was aware that the manufacturer estimated this value from Sandblom et al. (2004) as the decrease in utility from 16–8 months before death to 8–0 months before death in this study. The Committee noted that the ERG argued that these time intervals should match the time in the stable- and progressive-disease states in Sandblom et al., not in AFFIRM, because the time patients spent in each state may have differed in Sandblom et al. and AFFIRM. The Committee agreed that the utility decrease for disease progression applied by the manufacturer in the model did not represent the decrease in utility experienced by patients whose disease had progressed in AFFIRM. The Committee noted that when the ERG explored an alternative utility value of −0.07, as used in NICE technology appraisal 259, there was little impact on the ICERs. Without another more robust value of the utility decrease for disease progression, the Committee concluded that the value used by the manufacturer was acceptable for its decision-making in this appraisal.

4.15 The Committee discussed the estimates of costs and resource use chosen by the manufacturer. It noted that the manufacturer had to assume the patient access scheme discount for abiraterone in the model because the discount is commercial in confidence, and was not provided by the manufacturer of abiraterone for this appraisal. The Committee would have preferred a situation in which the manufacturer of enzalutamide could have applied the actual discount for abiraterone in its economic model. The Committee acknowledged that both the manufacturer and the ERG provided sensitivity analyses varying the discount in the model. The Committee initially expressed concern that the manufacturer assumed no hospitalisation costs in the model, which the Committee considered did not reflect 'real life'. It heard from the manufacturer that these costs were not included because AFFIRM did not collect data on hospitalisation and because hospitalisation costs were marked as confidential in the manufacturer's submission for abiraterone from NICE technology appraisal 259. On this basis, the

Committee considered that, if hospitalisation costs had been included, the incremental costs for enzalutamide compared with abiraterone may have changed, and concluded that the analysis should account for costs of hospitalisation. However, in response to consultation, the manufacturer noted that it had assumed in the model that the costs of adverse events, skeletal-related events and terminal care would capture all hospitalisation costs. The Committee concluded that this approach could be considered appropriate and that it did not need to consider hospitalisation costs further.

4.16 The Committee was concerned that the costs and QALYs for abiraterone produced by the manufacturer's model were not in line with those reported in NICE technology appraisal 259. It noted that neither the manufacturer nor the ERG could compare the 2 analyses because of the confidential information in the manufacturer's submission for abiraterone. The Committee was aware that, in NICE technology appraisal 259, the base-case analysis modelled a subset of the population covered by the marketing authorisation. It was also aware that assumptions and model inputs differed, notably the underlying survival curves estimated from patient-level data, how overall survival was modelled for abiraterone, and hospitalisation costs. The Committee appreciated the difficulty in comparing the 2 analyses and that there would remain some uncertainty around the ICERs, concluding that this issue could not be resolved within the remit of a single technology appraisal.

4.17 The Committee discussed the most plausible ICER for enzalutamide compared with abiraterone for patients who had received 1 previous cytotoxic chemotherapy regimen. It agreed that modelling overall survival for abiraterone should assume a constant hazard ratio over time, and that the analysis should incorporate the same 'on-treatment' utility increase for enzalutamide and abiraterone, and the actual patient access scheme discount for abiraterone. The Committee noted that, after consultation, the ERG provided analyses assuming a constant overall survival hazard ratio over time for abiraterone and equal 'on-treatment' utility increases for enzalutamide and abiraterone of 0.04, but not reflecting the actual patient access scheme discount for abiraterone. This analysis gave an ICER of £22,600 per QALY gained for enzalutamide compared with abiraterone. The Committee was aware that the ICERs for

enzalutamide would be lower for patients who had received only 1 course of cytotoxic chemotherapy. The Committee accepted that the available ICER was associated with some degree of uncertainty but, on balance, it was satisfied that the ICER for enzalutamide compared with abiraterone would remain below £30,000 per QALY gained. The Committee agreed that taking into account the correct patient access scheme for abiraterone would not change its conclusion. It therefore concluded that enzalutamide could be recommended as an option for treating hormone-relapsed metastatic prostate cancer in adults whose disease has progressed during or after 1 docetaxel-containing cytotoxic chemotherapy regimen, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.

4.18 The Committee acknowledged that, in response to the first appraisal consultation document, the manufacturer provided additional evidence for the subgroup of patients who had received 2 or more previous courses of cytotoxic chemotherapy, and for whom the Committee determined that best supportive care would be the appropriate comparator. The Committee was aware that this subgroup was pre-specified in AFFIRM's study protocol, represented around 27% of the total trial population, and did not include any patients who had received abiraterone. The Committee was aware that, although the hazard ratio presented by the manufacturer (0.66) suggested that enzalutamide was somewhat less effective in the subgroup than in the overall population, the manufacturer did not provide statistical tests to establish whether the treatment effect varied according to the number of courses of cytotoxic chemotherapy patients had received. Therefore, it could not conclude that enzalutamide was less effective in the subgroup than in the overall population. The Committee noted that the ICER estimated by the manufacturer for the subgroup was £45,500 per QALY gained and that, using an 'on-treatment' utility increase of 0.04 for enzalutamide, the ERG estimated an ICER of £48,000 per QALY gained. The Committee recognised that these ICERs were higher than the ICER range of £20,000–30,000 per QALY gained normally considered to represent a cost-effective use of NHS resources. It therefore agreed to consider this subgroup in the context of the supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are

licensed for indications that affect small numbers of people with incurable illnesses. To apply this advice, normally all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

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

4.19 The Committee considered the criterion for short life expectancy. It noted that the manufacturer and the ERG estimates of median survival for the subgroup patients receiving best supportive care were 12.8 months and 12.3 months respectively. The Committee concluded that enzalutamide fulfilled the criterion for short life expectancy.

4.20 The Committee considered the criterion that treatment offers an extension to life of normally at least an additional 3 months. It noted that, over a 10-year time horizon, the economic model predicted that enzalutamide would extend mean overall survival in the subgroup by 3.8 months compared with best supportive care. The Committee discussed whether this estimate was robust. Firstly, it was concerned that the 95% confidence interval around it was wide (0.9 months to 7.4 months), indicating that this was an imprecise and uncertain estimate. However, the Committee noted that the manufacturer's estimated extension to mean survival for the overall population reflected a more certain estimate (value and confidence interval are commercial in confidence). It also noted that the evidence presented by the manufacturer suggested that the baseline expected survival and the relative treatment effect of enzalutamide were similar in the subgroup and the overall population, with the confidence intervals around the

hazard ratios for overall survival overlapping substantially (0.48 to 0.90 in the subgroup and 0.52 to 0.73 in the overall population). Given the evidence on the survival benefit of enzalutamide for the overall population and the comparability of this benefit to the subgroup, the Committee agreed that enzalutamide was likely to extend life by more than 3 months in the subgroup. It also agreed that the wide confidence interval around the subgroup estimate was likely to be because of the small patient numbers in the subgroup. Secondly, to further explore the uncertainty around the estimate of life extension for the subgroup, the Committee considered estimates resulting from modelling the life span of patients over time horizons shorter than 10 years. It noted that, when the time horizon was shortened to 5 years, the mean survival benefit of enzalutamide remained longer than 3 months. Thirdly, the Committee noted that the estimated difference in median overall survival of 3.6 months was close to the estimated difference in the mean, suggesting that the probability distribution underlying the mean estimate was unlikely to be skewed and that the mean estimate was likely to be valid. The Committee agreed that the remaining uncertainty around the true value of the extension to mean survival could be accepted because NICE recommends abiraterone as a treatment option after docetaxel therapy, so a decreasing number of patients would be offered, or choose, a second course of cytotoxic chemotherapy instead of abiraterone. Balancing all these factors with the uncertainty around the estimate of the extension to life, the Committee was satisfied that the evidence supported that enzalutamide would extend life by at least an additional 3 months on average. It therefore concluded that enzalutamide fulfilled the criterion for life extension.

4.21 The Committee considered the criterion that the treatment is licensed or otherwise indicated for small patient populations. It noted the manufacturer's suggestion that the overall population that would be eligible for enzalutamide in England and Wales in 2013 was around 3000 patients. The Committee noted that this estimate was in line with those accepted by committees that appraised other technologies for the same indication. The Committee concluded that enzalutamide fulfilled the criterion for small patient populations and would be considered an end-of-life treatment as defined by NICE for patients who have previously received 2 or more cytotoxic chemotherapy regimens. The Committee

agreed that the magnitude of the additional weight that would need to be assigned to the QALY benefits for the subgroup who received 2 or more previous cytotoxic chemotherapy regimens would justify enzalutamide being recommended as a cost-effective use of NHS resources for these patients, if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.

4.22 The Committee discussed whether enzalutamide represents an innovative treatment. It noted that enzalutamide has a different mechanism of action from other anti-androgens, including other androgen receptor antagonists, such as flutamide and bicalutamide; it blocks binding of androgens to androgen receptors, prevents activated androgen receptors from migrating to the nucleus, and blocks the interaction of the activated androgen receptor with DNA in the nucleus. The Committee agreed that this mechanism of action is a 'step-change' compared with other androgen receptor antagonists. However, it concluded that this element of innovation would already be accounted for when moving from a maximum acceptable ICER of £20,000 per QALY gained to £30,000 per QALY gained.

4.23 The Committee considered if it could make a decision on the cost effectiveness of enzalutamide after treatment with abiraterone, noting that it had not been presented with sufficient evidence to inform a decision on the clinical effectiveness of the sequential use of enzalutamide after abiraterone (see section 4.2). The Committee noted comments received in response to the second appraisal consultation document expressing concerns about singling out abiraterone as prior treatment amongst others that were excluded from the trial. However, because the Committee also has to take cost effectiveness into consideration, and both enzalutamide and abiraterone are costly treatments, it is prudent for the Committee to establish the cost effectiveness of sequential treatment before recommending it for routine care. The Committee agreed that the comparator for enzalutamide given after treatment with abiraterone would be best supportive care, and that the ICER for enzalutamide compared with best supportive care was at the top end of the ICER range that has previously been considered to represent cost-effective treatments when the end-of-life criteria were fulfilled. The Committee noted that some of the observational studies

provided by the manufacturer in response to the second ACD consultation suggested that enzalutamide had a lower effect on reducing PSA concentration when given after abiraterone than when given to patients who have not received abiraterone before, which was in line with the natural history of the disease described by the clinical specialists (see section 4.2). In the absence of other robust evidence, the Committee agreed that it was unclear how the cost effectiveness of enzalutamide would change in the post-abiraterone setting. The Committee therefore concluded that it was not possible to make a conclusion on the clinical and cost-effectiveness of enzalutamide when given after abiraterone on the basis of the evidence it had considered. The Committee acknowledged the manufacturer's current efforts to collect data on the efficacy of enzalutamide after abiraterone as part of the pharmacovigilance plan and concluded that, until these data or results from other robust studies are available, it could not make any recommendations on the sequential use of enzalutamide and abiraterone.

Summary of Appraisal Committee's key conclusions

TA316	Appraisal title: Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen	Section
Key conclusion		
Enzalutamide is recommended within its marketing authorisation as an option for treating hormone-relapsed metastatic prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.		1.1, 4.17, 4.21
The Committee agreed that enzalutamide should be compared with abiraterone for patients who had received 1 course of docetaxel-containing cytotoxic chemotherapy and with best supportive care for patients who had received 2 or more cytotoxic chemotherapy regimens.		4.4

For patients who had received 1 course of cytotoxic chemotherapy, the Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an incremental cost effectiveness ratio (ICER) of £22,600 per quality-adjusted life year (QALY) gained for enzalutamide compared with abiraterone. The Committee accepted that this ICER was associated with uncertainty but, on balance, it was satisfied that it would remain below £30,000 per QALY gained. The Committee noted that taking into account the correct patient access scheme for abiraterone would not change its conclusion.		4.17
For patients who had received 2 or more courses of chemotherapy, the Committee noted that the ICERs for enzalutamide compared with best supportive care were between £45,500 and £48,000 per QALY gained. The Committee agreed that enzalutamide would be considered an end-of-life treatment as defined by NICE for this subgroup and that the magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of NHS resources.		4.21
The Committee did not see sufficient evidence to make any recommendations on the clinical- and cost-effectiveness of sequential use of enzalutamide and abiraterone.		1.2, 4.2, 4.23
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee understood from the clinical specialists that there are few treatment options available for patients with metastatic hormone-relapsed prostate cancer after docetaxel therapy.	4.1
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard that enzalutamide is an oral treatment that, unlike abiraterone, does not need to be taken on an empty stomach, making it more convenient to take. It also heard that, with abiraterone, some patients may need to reduce their dose to prevent liver toxicity, whereas enzalutamide is less likely to cause liver toxicity.	4.1
	The Committee agreed that the mechanism of action of enzalutamide is a 'step-change' compared with other androgen receptor antagonists. However, it concluded that this element of innovation would already be accounted for when moving from a maximum acceptable ICER of £20,000 per QALY gained to £30,000 per QALY gained.	4.22
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical specialists that enzalutamide is likely to be used at the same point in the treatment pathway as abiraterone, by patients who have received at least 1 course of cytotoxic chemotherapy.	4.1
	The Committee heard that, in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone (particularly to patients who experience liver toxicity on abiraterone).	4.2
Adverse reactions	The Committee noted that adherence to enzalutamide in AFFIRM was generally high and adverse reactions were generally manageable and reversible. However, it was concerned that the incidence of spinal cord compression appeared high in both treatment groups in AFFIRM. The Committee concluded that no adverse events or skeletal-related events needed special consideration in the context of the economic modelling.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee concluded that both comparators specified in the manufacturer's decision problem (abiraterone and best supportive care) were appropriate, but for different populations.	4.4

	The Committee noted that the evidence on the clinical effectiveness of enzalutamide came mainly from AFFIRM. It agreed that AFFIRM was a good-quality trial and relevant to the decision problem.	4.5
	The Committee concluded that AFFIRM and COU-AA-301 could be used to compare enzalutamide and abiraterone indirectly.	4.7
	The Committee acknowledged the manufacturer's current efforts to collect data on the efficacy of enzalutamide after abiraterone as part of the pharmacovigilance plan and concluded that, until these data or results from other robust studies are available, it could not make recommendations on the sequential use of enzalutamide and abiraterone.	4.23
Relevance to general clinical practice in the NHS	There are no specific Committee considerations on the relevance to general clinical practice in the NHS.	-
Uncertainties generated by the evidence	The Committee appreciated the uncertainty around measuring progression-free survival; however, it concluded that, of the measures described by the manufacturer, time to treatment discontinuation was the most reasonable.	4.6
	The Committee acknowledged the limitations of the observational studies on the effectiveness of enzalutamide after abiraterone, and agreed that although a proportion of patients may benefit from treatment with enzalutamide after abiraterone, the available evidence was not suitable to inform a conclusion on the magnitude of the effectiveness of enzalutamide after treatment with abiraterone.	4.2

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered enzalutamide for patients who had received 1 course of cytotoxic chemotherapy separately from patients who had received 2 or more courses of cytotoxic chemotherapy.	4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that, in AFFIRM, enzalutamide was associated with a statistically significant improvement in median overall survival of 4.5 months compared with placebo. It also noted that there was a statistically significant difference in quality of life for patients receiving enzalutamide compared with placebo, as measured using Functional Assessment of Cancer Therapy-Prostate. The Committee concluded that, compared with best supportive care, enzalutamide was a clinically-effective treatment.	4.5
	The Committee noted that, compared with the survival benefit of enzalutamide for the overall population (hazard ratio [HR] 0.62), the trial results suggested that the survival benefit of enzalutamide was higher for patients who had received 1 previous cytotoxic chemotherapy regimen (HR 0.59), and lower for those who had received 2 or more regimens (HR 0.74).	4.9
	The Committee noted that the observational studies on the effectiveness of enzalutamide after abiraterone suggested that enzalutamide is less effective at reducing PSA concentration in patients who have been treated with abiraterone, and heard that this reflected clinical practice because there is usually a decreasing response to a drug the further down the treatment pathway it is received.	4.2
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee was aware that the evidence presented by the manufacturer in its original submission related to the overall population (that is, patients who had received 1 or more cytotoxic chemotherapy regimens). The Committee concluded that it could make a recommendation for patients who had received 1 cytotoxic chemotherapy regimen based on the evidence for the overall population. However, for patients who had received 2 or more cytotoxic chemotherapy regimens, it concluded that it could not make a recommendation without data on the baseline expected survival and a robustly modelled ICER for these patients.	4.9
	The Committee acknowledged the additional evidence provided by the manufacturer for the subgroup of patients who had received 2 or more previous courses of cytotoxic chemotherapy. It was aware that this subgroup was pre-specified in AFFIRM's study protocol and represented around 27% of the total trial population. The Committee was aware that patients in AFFIRM had not received previous treatment with abiraterone.	4.18
	The Committee had not been presented with sufficient evidence to inform a decision on the clinical- or cost-effectiveness of the sequential use of enzalutamide after abiraterone.	4.2, 4.23
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee agreed that the rigid criteria for stopping treatment in COU-AA-301 may have biased the overall survival end point against abiraterone and introduced uncertainty. The Committee concluded that, given that the survival benefit of abiraterone is unlikely to vary in clinical practice, assuming a constant hazard ratio over the entire time horizon would be the most plausible scenario to model overall survival for abiraterone.	4.10

Incorporation of health-related quality-of-life benefits and utility values	The Committee appreciated that a larger sample would have reduced uncertainty around the EQ-5D utility value used in the model at baseline; however, it agreed that the sample was adequate compared with those used in previous appraisals in the same disease area.	4.12
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 Committee noted that the manufacturer applied different 'on-treatment' increases in utility for enzalutamide and abiraterone. The Committee, noting the patient experts' experience, agreed that including 'on-treatment' utility increases reflected patient experience, but that there was no evidence to assume different values for enzalutamide and abiraterone. The Committee concluded that the modelling should incorporate equal utility increases for both treatments.	4.13
	The Committee agreed that the utility decrease for disease progression applied by the manufacturer in the model did not represent the decrease in utility experienced by patients whose disease had progressed in AFFIRM. Without another more robust value of the utility decrease for disease progression, it concluded that the value used by the manufacturer could be considered appropriate.	4.14
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee considered enzalutamide for patients who had received 1 course of cytotoxic chemotherapy separately from patients who had received 2 or more courses of cytotoxic chemotherapy.	4.9
What are the key drivers of cost effectiveness?	The Committee noted that the method used to model overall survival for abiraterone is key to the cost effectiveness of enzalutamide compared with abiraterone.	4.10

Most likely cost-effectiveness estimate (given as an ICER)	For patients who had received 1 previous cytotoxic chemotherapy regimen, the Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an ICER of £22,600 per QALY gained for enzalutamide compared with abiraterone. The Committee agreed that enzalutamide would remain cost effective when the correct patient access scheme for abiraterone is taken into account.	4.17
	For patients who had received 2 or more previous courses of cytotoxic chemotherapy, the Committee noted that the ICER estimated by the manufacturer for enzalutamide compared with best supportive care was £45,500 per QALY gained and that the ERG's ICER was £48,000 per QALY gained.	4.18
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer of enzalutamide has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the price listed above, with the discount applied at the point of purchase or invoice.	2.3
End-of-life considerations	The Committee considered the subgroup of patients who had received 2 or more courses of cytotoxic chemotherapy under the 'end-of-life' criteria.	4.18
	The Committee concluded that enzalutamide fulfilled the criterion for short life expectancy.	4.19

	It was concerned that the 95% confidence interval around the estimate of the extension to mean survival was wide, indicating that this was an imprecise and uncertain estimate. However, considering evidence on survival for the overall population, the extension to mean survival in the subgroup at shorter time horizons, and the extension to median survival in the subgroup, the Committee was satisfied that enzalutamide was likely to extend life by more than 3 months in the subgroup. It therefore concluded that enzalutamide fulfilled the criterion for life extension.	4.20
	The Committee concluded that enzalutamide fulfilled the criterion for small patient populations and would be considered an end-of-life treatment as defined by NICE for patients who have previously received 2 or more cytotoxic chemotherapy regimens.	4.21
Equalities considerations and social value judgements	The potential for a subpopulation comprised of transgendered people was raised during the scoping workshop. NICE clarified that this population is included in the overall population of adults with metastatic hormone-relapsed prostate cancer who have previously received treatment with a docetaxel-containing chemotherapy regimen. Patient experts considered it important to ensure that access to enzalutamide is equitable, and that patients are not denied treatment because of their age, ethnicity or socioeconomic background. Because the Committee does not make recommendations based on these factors, this was not considered a relevant equality issue.	-

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has metastatic hormone-relapsed prostate cancer and the doctor responsible for their care thinks that enzalutamide is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 The Department of Health and the manufacturer have agreed that enzalutamide will be available to the NHS with a patient access scheme which makes enzalutamide available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Commercial Manager at the manufacturer directly on 0203 379 8773 or email – commercial@astellas.com

5.4 NICE has developed a costing statement explaining the resource impact of this guidance, to help organisations put this guidance into practice.

6 Recommendations for further research

6.1 The Committee supports the manufacturer's ongoing commitment to collect data on the effectiveness of enzalutamide after previous treatment with abiraterone.

6.2 The Committee considered that if enzalutamide is used in routine clinical practice for treating hormone relapsed metastatic prostate cancer that has been previously treated with abiraterone, data should be collected on resource use and overall survival.

7 Review of guidance

7.1 The guidance on this technology will be considered for review, together with NICE technology appraisal guidance 259 (Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen), in April 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
July 2014

8 Appraisal Committee members and NICE project team

8.1 Appraisal Committee members

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

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

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

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

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

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

Professor John Cairns

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

Mr Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Mr Robert Hinchliffe
HEFCE Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant Vascular Surgeon, St George's Vascular Institute

Dr Neil Iosson
Locum GP

Mrs Anne Joshua
Associate Director of Pharmacy, NHS Direct

Dr Rebecca Kearney
Clinical Lecturer, University of Warwick

Dr Miriam McCarthy
Consultant, Public Health, Public Health Agency

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, University of Southampton

Dr Elizabeth Murray
Reader in Primary Care, University College London

Mr Christopher O'Regan
Head of Health Technology Assessment and Outcomes Research, Merck Sharp & Dohme

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

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

Dr Danielle Preedy
Lay Member

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

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

Mr Cliff Snelling
Lay Member

Mr David Thomson
Lay member

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

8.2 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.

Ahmed Elsada
Technical Lead

Fiona Pearce
Technical Adviser

Jeremy Powell
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews:

- Riemsma R, Joore M, Tomini F et al., Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen, August 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the 2 appraisal consultation documents. Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Astellas Pharma

II. Professional/specialist and patient/carer groups:

- Prostate Cancer UK
- Royal College of Nursing
- Royal College of Physicians
- Right Angle

III. Other consultees:

- Department of Health
- 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
- Medicines and Healthcare products Regulatory Agency

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on enzalutamide by attending the Committee meetings and providing written evidence to the Committee. They were also invited to comment on both appraisal consultation documents.

- Dr Amit Bahl, Consultant Clinical Oncologist, Bristol Haematology and Oncology Centre, nominated by NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Dr Simon Russell, Consultant Medical Oncologist, Guys and St Thomas' Hospital, nominated by Astellas – clinical specialist
- Hugh Gunn, nominated by Prostate Cancer Support Federation – patient expert
- Stuart Watson, nominated by Prostate Cancer UK – patient expert

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

- Astellas Pharma

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE single technology appraisal process.

It has been incorporated into the NICE pathway on prostate cancer along with other related guidance and products.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility
This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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