NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- Clinical effectiveness evidence
  - The manufacturer did not include mitoxantrone as a comparator in its decision problem despite mitoxantrone being listed as a comparator in the scope. Does the Committee accept the manufacturer's justification for not considering mitoxantrone a relevant comparator for enzalutamide?
  - The ERG highlighted differences between AFFIRM and the abiraterone trial in the baseline patient characteristics and the trial designs. Does the Committee consider the 2 trials comparable for indirectly comparing enzalutamide with abiraterone?
- Cost effectiveness evidence
  - To model overall survival for abiraterone, the manufacturer assumed that the hazard ratio for abiraterone compared with best supportive care remains at 1.39 beyond 25 months. The ERG considered that the hazard ratio of 1.39 beyond 25 months is not justified given the very low number of observations near 25 months, and that a conservative approach should be adopted by

assuming a hazard ratio of 1 beyond 25 months. What is the Committee's view on the most plausible assumption to model overall survival for abiraterone?

- To derive the progression-free survival function for abiraterone, the manufacturer estimated a hazard ratio using data related to the subgroup of patients who had received only 1 prior chemotherapy regimen. The ERG argued that a hazard ratio estimated from the overall population, which includes patients who had received more than 1 prior chemotherapy regimen, was more appropriate. Which hazard ratio does the Committee deem more appropriate?
- Utility values
  - ◊ The manufacturer used EQ-5D data collected from AFFIRM to estimate a utility value at baseline for the model. The ERG regarded this value as uncertain because the sample size from which it was estimated was small. What is the Committee's view on the appropriate utility value to use at baseline in the model?
  - ◊ To reflect the treatment benefit of enzalutamide and abiraterone in the model, the manufacturer applied utility increases to the baseline utility value. The ERG stated that the utility increase for abiraterone was not supported by evidence, and that there is no strong evidence to assume 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 the benefit of treatment. Does the Committee consider it appropriate to include an 'on-treatment' utility increase in the model, and if so, what value does the Committee deem appropriate?
  - ◊ The manufacturer derived the utility decrease for disease progression from Sandlom et al. (2004) because the time intervals of 16–8 months and 8–0 months before death in this study approximately matched the time patients in AFFIRM spent in the stable- and progressive-disease states. The ERG argued that these time intervals should match the time in stable- and progressive-disease states in Sandlom et al., not AFFIRM, and it explored the impact of applying an alternative value from Sullivan et al. (2007). Which utility value does the Committee deem more appropriate to capture the impact of disease progression?

- The manufacturer did not include hospitalisation costs in the model. Does the Committee consider this approach appropriate?
- Does the Committee consider that enzalutamide fulfils NICE's supplementary advice as an end-of-life treatment?

1 Background: clinical need and practice

1.1 The prostate is a gland in the male reproductive system. Prostate cancer accounts for approximately 25% of new diagnoses of cancer in men in England and Wales. The incidence of prostate cancer increases with age. Most men have histological evidence of prostate cancer by 80 years of age, but die of unrelated causes. The cause of prostate cancer is believed to be multi-factorial, with age, ethnic origin and family history being among the risk factors. It is estimated that 55–60% of patients with prostate cancer will eventually develop metastatic disease, most commonly in the bones. In 2005–2009, the 5-year survival from diagnosis was 81% for all patients with prostate cancer in England, and 30% if the disease was metastatic at the stage of diagnosis.

1.2 The symptoms of prostate cancer do not usually develop until the cancer has grown large enough to put pressure on the urethra and block the flow of the urine. Patients with metastatic prostate cancer may experience weight loss and lower extremity oedema, and in up to 40% of those with bone metastases, spinal cord compression or vertebral fractures may develop.

1.3 Metastatic prostate cancer usually responds to hormonal treatment which depletes or blocks male sex hormones (androgens). However, after 12 to 18 months, the cancer often stops responding to hormonal treatment and starts to grow again (that is, the cancer becomes hormone-refractory). Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (NICE technology appraisal guidance 101) recommends docetaxel as a first-line treatment option for men with hormone-refractory metastatic prostate cancer who have a Karnofsky performance-status score of 60%

or more (that is, patients who have an above-average performance). If metastatic hormone-refractory prostate cancer progresses on or after one docetaxel-containing chemotherapy regimen, Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE technology appraisal guidance 259) recommends abiraterone in combination with prednisone or prednisolone as a second-line treatment option.

2 The technology

2.1 Enzalutamide (Xtandi, Astellas Pharma) is an androgen receptor signalling inhibitor that reduces the proliferation of prostate cancer cells thereby stopping the growth of cancerous tumours. Enzalutamide 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'. Enzalutamide is taken orally. The marketing authorisation states that patients should take 160 mg of enzalutamide once daily until their disease progresses. If enzalutamide causes severe toxicity or an intolerable adverse reaction, the marketing authorisation stipulates that treatment should be stopped for 1 week or until symptoms improve, then resumed at the same or a lower dose (120 or 80 mg). The dose of enzalutamide should also be reduced if a CYP2C8 inhibitor is to be 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. The summary of product characteristics advises caution in administering enzalutamide to patients with a history of seizures or other predisposing factors such as underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The manufacturer's submission states that the acquisition cost of enzalutamide (excluding VAT) is £2734.67 per 112-capsule pack, with each capsule containing 40 mg enzalutamide. Based on 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 is £25,269. The manufacturer of enzalutamide has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of enzalutamide within its licensed indication for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen.

Table 1 Decision Problem

	Final scope issued by NICE	Decision problem addressed in the manufacturer's submission
Population	Adults with metastatic hormone relapsed prostate cancer which has been previously treated with a docetaxel-containing chemotherapy regimen	
Intervention	Enzalutamide	Enzalutamide once daily 160 mg (4 x 40 mg) capsules

Comparators	• Abiraterone in combination with prednisone or prednisolone • Mitoxantrone alone or in combination with prednisolone • Best supportive care (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).	As per the final scope, with the exception of not considering mitoxantrone as a comparator. Radiotherapy is considered as best supportive care (NB: In the AFFIRM trial administering radiotherapy was reported as a skeletal-related event).
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • prostate-specific antigen (PSA) response • adverse effects of treatment • health-related quality of life.	

3.2 Comparators

3.2.1 The manufacturer stated that, according to the 5 criteria on selecting appropriate comparators listed in NICE's Guide to the methods of technology appraisal 2013, mitoxantrone is an irrelevant comparator because it has a very small and diminishing market share in the NHS; several new alternative treatments have displaced mitoxantrone; existing NICE guidance does not support using mitoxantrone for the indication in this appraisal; the clinical evidence does not support using mitoxantrone after docetaxel therapy; and mitoxantrone is not licensed for patients with metastatic hormone-refractory prostate cancer. The ERG agreed that, although several randomised controlled trials evaluated mitoxantrone for the population in the decision problem, none of these directly compared enzalutamide with mitoxantrone, or would allow an indirect comparison between the 2 treatments because a common comparator is lacking. Whether the use of mitoxantrone forms established practice within the NHS was discussed during the scoping workshop held by NICE in 2012. It

was noted during the workshop that data published in 2010 suggested that it was used by some patients, but it was noted that the use of mitoxantrone had been decreasing since abiraterone and cabazitaxel were licensed. However, scoping workshop attendees agreed that the evidence available at that time suggested that mitoxantrone was still prescribed for this indication in the NHS and should be included as a comparator.

3.2.2 The manufacturer compared enzalutamide with abiraterone and with best supportive care. For the comparison of enzalutamide with best supportive care, the manufacturer provided evidence from the AFFIRM trial, which compared enzalutamide plus best supportive care with placebo plus best supportive care. The manufacturer provided a rationale that, because patients in both treatment groups received best supportive care, the placebo group can be considered equivalent to best supportive care.

4 Clinical-effectiveness evidence

4.1 The manufacturer did a systematic review of studies evaluating the efficacy and safety of enzalutamide and its comparators (abiraterone and best supportive care) for the treatment of metastatic hormone-refractory prostate cancer that had progressed on or after docetaxel therapy. It identified the AFFIRM randomised controlled trial (RCT), which compared enzalutamide plus best supportive care with placebo plus best supportive care. Another RCT, COU-AA-301, compared abiraterone plus prednisone with placebo plus prednisone, and the manufacturer used this trial to compare enzalutamide indirectly with abiraterone. No relevant observational or single-arm trials were identified by the manufacturer.

4.2 AFFIRM was a phase III randomised double-blind placebo-controlled study that was conducted at 156 sites in 15 countries, including the UK (12 sites). Eligible patients were adults with metastatic hormone-refractory prostate cancer who had previously received 1 or 2 chemotherapy regimens, at least 1 of which contained docetaxel. Randomisation in the

trial 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 (on a scale of 0 to 10). 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 comprised radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies and corticosteroids. Radiotherapy was also considered best supportive care, but the trial protocol stipulated that when radiotherapy is given, it should be reported as the end point 'skeletal-related event'. The use of prednisone or other glucocorticoids was permitted during the trial. Treatment with the study drug continued until disease progressed and the patient was about to start further systemic therapy, unacceptable toxicity occurred, or the patient died or withdrew from the study.

4.3 The primary end point in AFFIRM was overall survival, defined as time from randomisation to death from any cause. In AFFIRM, disease was deemed to have progressed if investigators confirmed radiographic progression or if a skeletal-related event occurred. Secondary end points included measures of disease progression and measures of disease response to treatment including:

- Time to prostate-specific antigen (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 absolute lowest level that the PSA had reached since treatment started, with confirmation by a second consecutive value obtained 3 or more weeks later.
- Radiographic progression-free survival: Time to the earliest objective evidence of radiographic soft tissue or bone progression, or death. To assess soft tissue progression, investigators used the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 on

computed tomography or magnetic resonance imaging scans, and for bone progression, they used the Prostate Cancer Trials Working Group 2 (PCTWG2) criteria on bone scans (that is, the appearance of 2 or more new bone lesions). Investigators assessed soft tissue and bone progression at weeks 13 and 25 of the trial, and then every 12 weeks until the patient died. If soft tissue or bone progression was documented at week 13, a confirmation 6 or more weeks later was required.

- Time to first skeletal-related event: A skeletal-related event was defined as either radiotherapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of cancer therapy to treat bone pain.
- PSA response rate: Patients could achieve 1 of 2 PSA responses – if their lowest post-baseline value was lower by 50% or more than their baseline value, or if their lowest post-baseline value was lower by 90% or more than their baseline value.
- Rate of pain palliation at week 13: Pain palliation was defined in the trial as either a reduction of 2 or more points in BPI-SF question 3 score at week 13; or a reduction of 30% or more in the average pain score at week 13 compared with baseline, and an increase of 30% or less in analgesic use.

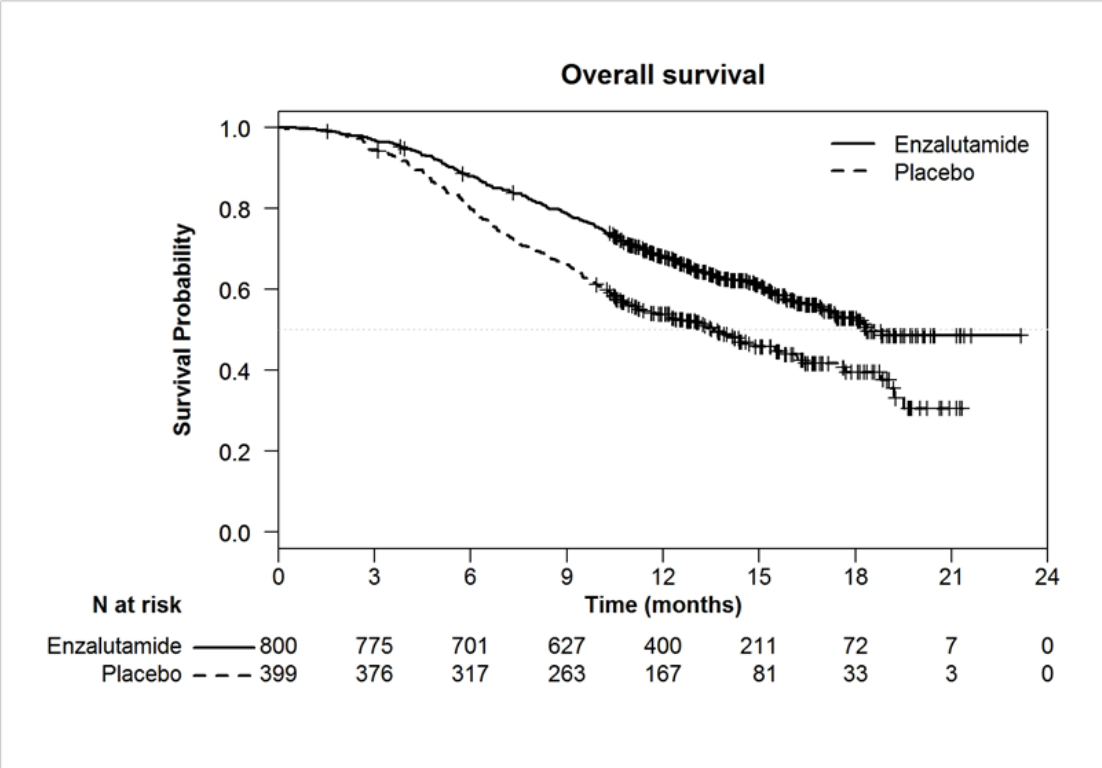
4.4 Of the 1199 patients randomised in AFFIRM, the median age was 69 years (range 41–92 years), 92.7% were white, and 8.5% had an ECOG performance status of 2 (enzalutamide 8.8%, placebo 8%). All patients had received prior docetaxel therapy; those who had received further chemotherapy accounted for 27% of the trial population. Most patients (91.2%) had bone metastases and 25.6% had visceral lung or liver involvement. At study entry, 41% of randomised patients had PSA progression only, while 59% of patients had radiographic progression. The manufacturer considered that both treatment groups were well balanced in terms of demographics, disease characteristics at baseline and medical history.

4.5 AFFIRM was designed to detect a statistically significant hazard ratio for overall survival 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, and that patients in the placebo group receive enzalutamide (cross over). As a result, the study protocol was amended to reduce the target number of deaths needed for the final analysis of overall survival. 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, which used data at the final cut-off date (16 December 2011). To compare enzalutamide with placebo, the manufacturer used a stratified log–rank test (that is, adjusting for patients' ECOG performance status and BPI-SF question 3 score) to assess overall survival and the secondary end points, and provided supportive analyses of overall survival using an unstratified log–rank test and Cox proportional-hazards models (that is, assuming a constant treatment effect over time). For patients who did not reach the end points during the trial, the manufacturer censored the patient at the date when the tumour was last assessed.

4.6 At the cut-off date for the interim analysis (25 September 2011), the duration of follow-up (the maximum time any patient was followed) was 24 months (median duration of follow-up was 14.4 months). Of patients randomised to enzalutamide and placebo, 308 (38.5%) and 212 (53.1%) had died respectively (figure 1). The median overall survival was 4.8 months longer for enzalutamide than placebo (enzalutamide 18.4 months, placebo 13.6 months). Treatment with enzalutamide was found to reduce the risk of death by 36.9% compared with placebo, with a stratified hazard ratio of 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. Deaths had risen to 344 patients (43%) among those randomised to enzalutamide and 232 patients (58%) among those randomised to placebo, lowering the difference in median overall survival to 4.5 months (enzalutamide 17.8 months, placebo 13.3 months). The risk of death in the enzalutamide group was 38.0% lower than the placebo group (stratified hazard ratio 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. The manufacturer stated that this may have caused patients randomised to placebo to live longer than they would have otherwise, which may in turn have underestimated the relative effect of enzalutamide on overall survival. In response to a request for clarification, the manufacturer provided estimates of mean overall survival using different parametric functions with the analysis truncated at 5 years (this assumed that all patients die by 5 years from baseline). Enzalutamide was consistently associated with longer mean overall survival than placebo, with differences in mean overall survival ranging from [redacted] using the Weibull function to [redacted] using the exponential function.

Figure 1 Kaplan–Meier curves for overall survival

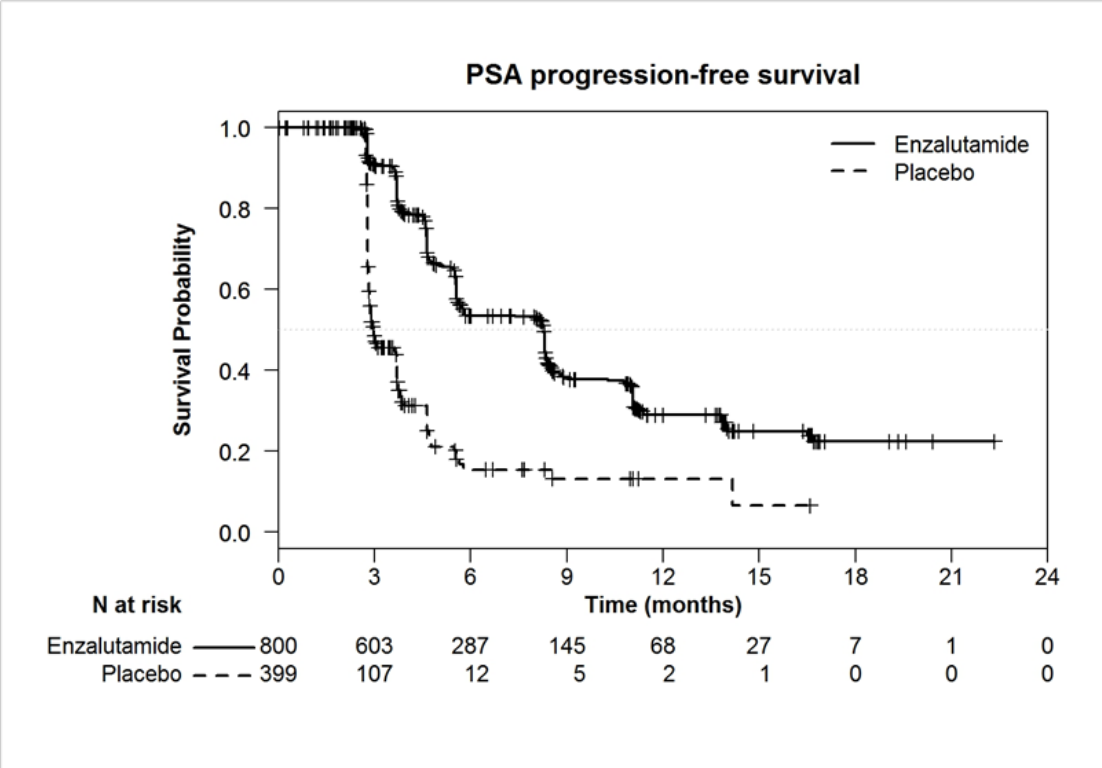


Source: Manufacturer's submission, figure 6, page 61

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

- Time to PSA progression: During AFFIRM, 400 patients randomised to enzalutamide and 190 patients randomised to placebo had PSA progression (figure 2). Median time to PSA progression was 5.3 months longer for enzalutamide than placebo (enzalutamide 8.3 months, placebo 3.0 months), and time to PSA progression was delayed by 75% with enzalutamide compared with placebo (hazard ratio 0.248 [95% CI 0.204 to 0.303, p<0.001]).

Figure 2 Kaplan–Meier curves for time to PSA progression



Source: Manufacturer's submission, figure 7, page 63

- 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 by 60% (hazard ratio 0.40 [95% CI 0.35 to 0.47, p<0.001]).
- Time to first skeletal-related event: During AFFIRM, 35.9% of patients randomised to enzalutamide, and 40.3% of those randomised to placebo experienced a skeletal-related event (most commonly radiation to bone). Median time to first skeletal-related event was 3.4 months longer with enzalutamide than placebo (enzalutamide 16.7 months, placebo 13.3 months), and time to first skeletal-related event was delayed by 31.2% for patients who received enzalutamide (hazard ratio 0.688 [95% CI 0.566 to 0.835, p<0.0001]).
- PSA response rate: A higher proportion of patients in the enzalutamide group than the placebo group experienced a decrease by 50% or more in their post-baseline PSA value compared with their baseline value

(enzalutamide 54.0%, placebo 1.5%, p<0.0001). The PSA response rate remained higher in the enzalutamide group when PSA response was defined as a decrease in post-baseline PSA value by 90% or more compared with the baseline value (enzalutamide 24.8%, placebo 0.9%, p<0.0001).

- Rate of pain palliation at week 13: For pain palliation defined as a reduction of 2 or more points in BPI-SF question 3 score 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 palliated pain in more patients than placebo (enzalutamide 25%, placebo 14.2%, p<0.001). When pain palliation was defined as a reduction of 30% or more in the average pain score at week 13 compared with baseline, and an increase of 30% or less in analgesic use, investigators could assess only 6.1% and 3.8% of patients in the enzalutamide and placebo groups respectively. Of these, enzalutamide palliated pain in 44.9%, and placebo did so in 6.7% (p=0.0079).

4.8 The manufacturer performed 2 post hoc analyses (after the trial results had been compiled) to inform its economic model; firstly, on a modified definition of progression-free survival, and secondly, 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 [redacted] for enzalutamide and [redacted] for placebo, with a hazard ratio of [redacted] ([redacted]). For time to treatment discontinuation, patients in AFFIRM did not stop treatment unless investigators documented and confirmed disease progression (that is, confirmed radiographic disease progression or a skeletal-related event occurred), and the patient was about to start further systemic therapy. The trial also allowed stopping treatment because of an adverse event. The manufacturer reported a median time on study treatment of [redacted] for enzalutamide and [redacted] for placebo. The proportion of patients who

remained on treatment for 12 months or more was higher for enzalutamide than placebo ([redacted] and [redacted] respectively), and the hazard ratio was [redacted] ([redacted]). For Kaplan–Meier curves, see pages 71–72 of the manufacturer's submission.

4.9 The manufacturer performed pre-specified subgroup analyses for patients who shared prognostic factors for prostate cancer or demographic characteristics of interest, or who reflected regional variation in clinical practice. For further details of the subgroups see pages 55–56 of the manufacturer's submission. Although it did not perform interaction tests for the subgroup analyses, the manufacturer stated that the treatment effect of enzalutamide was consistent across all subgroups, including those that reflected patients with poorer prognoses, with a median overall survival consistently exceeding placebo by more than 3 months. For full results of the subgroup analyses, see figure 11 on page 70 of the manufacturer's submission.

4.10 The manufacturer did not identify any published head-to-head trials comparing enzalutamide with abiraterone. It identified the COU-AA-301 trial (hereafter the abiraterone trial) comparing abiraterone plus prednisone with placebo plus prednisone, which it used to indirectly compare enzalutamide with abiraterone, using placebo as a common comparator. The abiraterone trial was a phase III RCT, evaluating the efficacy and safety of abiraterone in patients with metastatic hormone-refractory prostate cancer whose disease had progressed on or after up to 2 chemotherapy regimens, of which 1 had to contain docetaxel. Patients in both groups of the abiraterone trial received best supportive care defined as radiotherapy (but reported as a skeletal-related event when received), 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 prednisone were reported from the abiraterone trial 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 (Fizazi et al. 2012).

4.11 The study designs of AFFIRM and the abiraterone trial were comparable in the manufacturer's opinion. However, because abiraterone, but not enzalutamide, needs to be taken with corticosteroids, the proportion of patients randomised to placebo who received prednisone differed in the 2 trials (45.6% in AFFIRM and 100% in the abiraterone trial). The manufacturer stated that there is no evidence to suggest that corticosteroids affect overall survival or progression-free survival, and that patients whose disease progressed will have already received corticosteroids so their disease would be resistant to corticosteroids. Because of this, the manufacturer considered that corticosteroids would be unlikely to make patients live longer, and it assumed that treatment outcomes in both placebo groups would be unaffected by taking corticosteroids. In addition, the definition of modified progression-free survival was broader in the abiraterone trial than in AFFIRM, but the manufacturer considered this difference to be small, concluding that both trials were valid and permitted an indirect comparison between enzalutamide and abiraterone. The manufacturer did the indirect 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, PSA response and adverse events.

4.12 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. The analysis was framed so that hazard ratios less than 1 and odds ratios greater than 1 favour enzalutamide. The manufacturer reported a statistically significant difference in favour of enzalutamide for radiographic progression-free survival and modified progression-free survival (hazard ratios [redacted] [redacted] and [redacted] [redacted]

respectively), but not for overall survival and time to first skeletal-related event (hazard ratios [redacted] [redacted] and [redacted] [redacted] respectively). The manufacturer stated that the hazard ratio for overall survival, although not statistically significant, favoured enzalutamide given that the upper bound of the confidence interval ([redacted]) was on the boundary of statistical significance. It further stated that this hazard ratio should be interpreted with caution because there is statistical evidence that the hazard ratio for abiraterone compared with placebo varied over time (the treatment effect was not constant), which may have overestimated the relative treatment benefit of abiraterone. For the end points objective response rate and PSA response, enzalutamide was associated with a statistically significant difference for the latter only (odds ratios [redacted] [redacted] and [redacted] [redacted] respectively).

4.13 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, after an amendment to AFFIRM's study protocol, the EQ-5D questionnaire was administered to patients only at study sites in France, Germany, Italy, Spain and the UK. In total, 15.8% and 13.3% of patients randomised to enzalutamide and placebo, respectively, provided data for EQ-5D (179 patients in total). FACT-P is a 39-item questionnaire about physical, social, emotional and functional wellbeing. Each item of the questionnaire is answered on a scale of 0 to 4 (the higher the score the better), and the FACT-P score is the sum of the points on each item. A quality-of-life response was achieved in AFFIRM if patients' 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% randomised to enzalutamide and placebo, respectively, achieved a quality-of-life response (p=0.0018).

4.14 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 before the patient started another systemic cancer therapy, whichever occurred first. The manufacturer analysed adverse events for a 'safety population' defined as patients who had taken at least 1 dose of study drug. Although the median time on study treatment was longer for enzalutamide than placebo ([redacted] and [redacted] respectively), the rates of adverse events were similar in the 2 groups. The incidence of adverse events of grade 3 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 flashes, musculoskeletal pain, and headache was higher in the enzalutamide group than in the placebo group. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo (with cardiac disorders of grade 3 in 1% and 2% respectively). Increased blood pressure was observed in 6.6% of patients in the enzalutamide group and 3.3% of those in the placebo group. There were no significant between-group imbalances in the rates of other adverse events, such as high blood glucose concentration, glucose intolerance, weight gain, or high lipid levels. Liver-function abnormalities were reported as adverse events in 1% of patients receiving enzalutamide and in 2% of those receiving placebo. At the cut-off date for the interim analysis (25 September 2011), 5 of the 800 patients in the enzalutamide group (0.6%) were reported by the investigators to have had a seizure; no seizures were reported in the placebo group. Until April 2012, 10 patients (0.9%) were reported by the investigators or the manufacturer to have had a seizure. The summary of product characteristics for enzalutamide states that 'caution should be used in administering enzalutamide to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism.' The adverse events in AFFIRM are summarised in table 2. Overall, the

manufacturer considered that the safety profile of enzalutamide was acceptable and that adverse events could be managed.

Table 2 Summary of adverse events in AFFIRM

Number of patients with 1 or more:	Enzalutamide (n=800)	Placebo (n=399)
Adverse event	785 (98.1%)	390 (97.7%)
Adverse event associated with study drug discontinuation	128 (16.0%)	73 (18.3%)
Adverse event as primary reason for study drug discontinuation	61 (7.6%)	39 (9.8%)
Adverse event leading to dose reduction of study drug	17 (2.1%)	11 (2.8%)
Adverse event leading to temporary interruption of study drug dosing	102 (12.8%)	61 (15.3%)
Adverse event leading to death	23 (2.9%)	14 (3.5%)
Serious adverse event	268 (33.5%)	154 (38.6%)
Grade 3 or higher adverse event	362 (45.3%)	212 (53.1%)

Source: Manufacturer's submission, table 30, page 93

4.15 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 as abiraterone. Enzalutamide was associated with a decreased risk of lowering serum potassium levels compared with abiraterone (odds ratio [redacted] [redacted]). In contrast, the risk of bone pain increased with enzalutamide (odds ratio [redacted] [redacted]). No statistically significant differences were found for other adverse events, skeletal-related events or rate of treatment discontinuation (used by the manufacturer as a proxy for tolerability) between enzalutamide and abiraterone.

ERG critique

4.16 The ERG considered that the manufacturer's systematic review was adequate and included all relevant clinical evidence for enzalutamide.

4.17 For the purpose of an indirect comparison, the ERG agreed that patients in AFFIRM and the abiraterone trial were comparable in terms of demographic characteristics and disease status assessed at baseline. However, the ERG noted slight differences in the baseline patient characteristics of the populations in the 2 trials with respect to the following:

- The abiraterone trial had more patients aged 75 years or older (27.7% compared with 25.3% in AFFIRM), and more patients with 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 the abiraterone trial respectively) but more patients had received 2 previous regimens in the abiraterone trial (30.3% compared with 24.3% in AFFIRM).
- More patients had previously had surgery for their cancer in AFFIRM (64.6% compared with 52.1% in the abiraterone trial).

In addition, the ERG questioned whether corticosteroids affect patient-reported outcomes such as pain, quality of life and adverse events. In the manufacturer's response to clarification from the ERG, the manufacturer explained that the impact of corticosteroids on patient-reported outcomes is affected by their benefits on symptoms and their adverse reactions. The manufacturer indicated that corticosteroids may lessen bone pain associated with disease metastases, and may improve appetite and reduce weight loss. Conversely, the adverse reactions of corticosteroids can be debilitating. Because it was difficult to quantify the effect of corticosteroids on patient-reported outcomes, the manufacturer assumed that their positive and negative effects cancel each other out.

4.18 The ERG stated that the manufacturer's method to compare enzalutamide with abiraterone indirectly was appropriate and performed correctly.

4.19 The ERG noted that the adverse events with enzalutamide were similar to those with abiraterone, and less debilitating than bone marrow suppression, diarrhoea, physical weakness, hair loss and others experienced with cytotoxic agents such as mitoxantrone. The ERG viewed enzalutamide as generally safe with relatively mild adverse events that can be easily managed.

4.20 The ERG agreed that no head-to-head trials compared enzalutamide with mitoxantrone, and that the available evidence would not allow for an indirect comparison between the 2 treatments. However, because mitoxantrone was listed as a comparator in the scope, the ERG presented the results of the pivotal study of cabazitaxel, TROPIC, which compared cabazitaxel plus prednisone with mitoxantrone plus prednisone for patients with metastatic hormone-refractory prostate cancer whose disease had progressed during or after docetaxel therapy. For the results of this study alongside those of AFFIRM and the abiraterone trial, see table 4.27 on page 86 of the ERG report.

5 Comments from other consultees

5.1 Comments from professional groups noted that licensed treatment options for patients whose disease progressed on or after docetaxel therapy include abiraterone (recommended by NICE), cabazitaxel (not recommended by NICE) and radium-223 (undergoing NICE appraisal). Clinical specialists indicated that mitoxantrone is used less commonly than other available treatments, and that a recent survey of 63 specialists in urological oncology showed that 13 (20%) would prescribe mitoxantrone for patients with metastatic prostate cancer after docetaxel therapy. Clinical specialists noted that the Cancer Drugs Fund (in England, but not in Wales) provides enzalutamide to patients who have not received abiraterone.

5.2 According to clinical specialists, treatment options for patients after docetaxel therapy is evolving rapidly, with enzalutamide adding

significantly because it demonstrated an overall survival benefit and improved both bone and soft tissue disease. In addition, clinical specialists considered that enzalutamide had a very favourable safety profile with no requirement to monitor patients routinely. Compared with abiraterone, specialists noted that patients do not need to take enzalutamide on an empty stomach and avoid food for the following 2 hours, nor do they need to take corticosteroids concurrently.

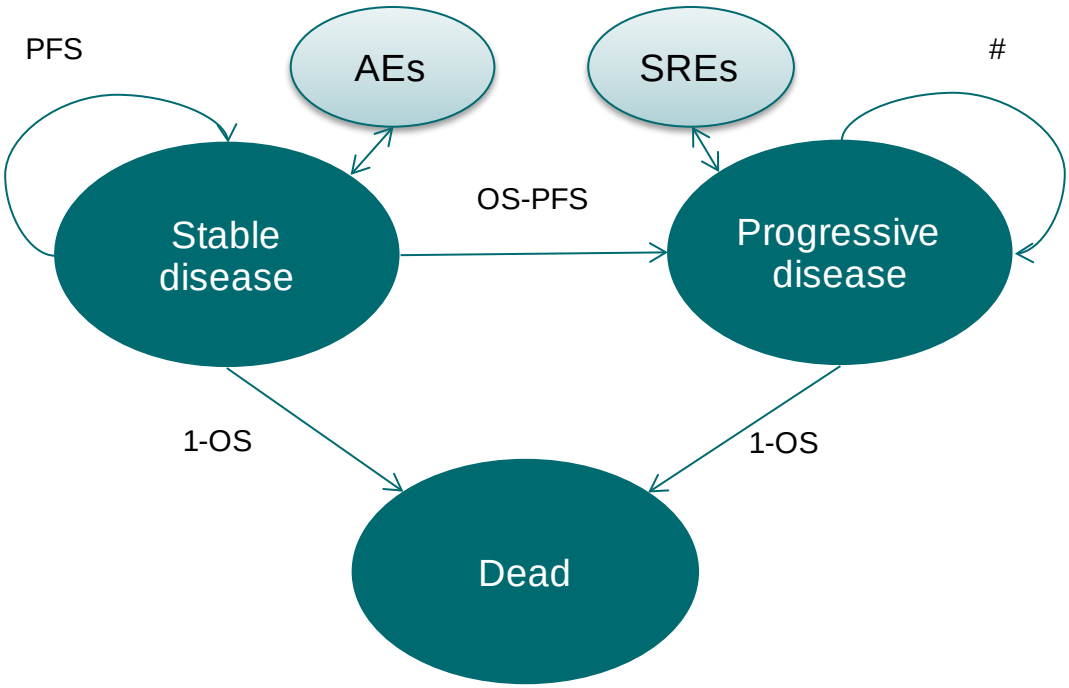
5.3 Patients experts stated that enzalutamide, being an oral medication, is easy to take, and is well tolerated by the majority of patients. Patient experts expect that enzalutamide would offer patients a ‘huge’ increase in quality of life by increasing life expectancy, lessening bone pain, reducing disability, and allowing them to enjoy activities and socialise with family and friends. Patient experts noted that currently abiraterone is the only active treatment available for patients with this type of cancer, and that abiraterone affects the liver in some patients, whereas enzalutamide does not. They considered that, if NICE were to recommend enzalutamide, this would standardise access to the drug, increase the range of clinically effective treatment options, provide patients with a greater choice and hope, and possibly give them more time with their family and improve their quality of life.

6 Cost-effectiveness evidence

6.1 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-refractory prostate cancer whose disease progressed on 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. It used a 3-week cycle length, in line with previous models for this indication, and applied a half-cycle correction except for direct drug costs. Costs and health effects were discounted at an annual rate of 3.5%.

6.2 The manufacturer's model was a state-transition Markov cohort model simulating 3 states: stable disease, progressive disease and death (figure 3). 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, or move to the progressive-disease or death state; once transitioned 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 the AFFIRM trial) in the stable-disease state (assuming that only patients receiving treatment could experience an adverse event), and skeletal-related events (spinal cord compression, pathologic non-vertebral bone fracture, radiation to the bone and bone surgery) in the progressive-disease state because skeletal-related events normally result from disease progression in the bones.

Figure 3 The manufacturer's model structure



Source: Manufacturer's submission, figure 17, page 121

6.3 The manufacturer obtained the clinical data for enzalutamide and best supportive care from AFFIRM, and for abiraterone, it obtained the data from the abiraterone trial. 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 trial follow-up period. The manufacturer chose the base-case survival functions for best supportive care based on the results of 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 the respective trials to the survival function for best supportive care. The manufacturer used these survival functions to govern the transition between states in the model for each treatment.

6.4 To estimate overall survival for best supportive care, the reference treatment, the manufacturer chose the Weibull function because, according to experts, the shape of its ‘tail’ was more realistic than other functions, even though the log-logistic function fit the data best according to statistical tests. The Weibull function produced a mean overall survival of [redacted] and a median of 12.96 months for best supportive care.The manufacturer stated that, unlike the hazard ratio for abiraterone compared with placebo, there was no statistical evidence that the hazard ratio for enzalutamide compared with placebo varied over time (that is, the proportional hazards assumption was met). So, the manufacturer derived the survival function for enzalutamide by directly applying the hazard ratio (stratified on randomisation variables) of 0.618 from AFFIRM to the best supportive care function. For abiraterone, the manufacturer stated that using a constant hazard ratio may overestimate the survival benefit of abiraterone given that, over the course of follow-up in the abiraterone trial, the hazard ratio varied and the Kaplan–Meier curves for abiraterone and prednisone separated then converged, implying that the benefit of abiraterone decreased over time. Because of this, the manufacturer fitted a Cox proportional hazards model, including a time-dependent covariate,

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 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 remains 1.39.

6.5 To derive the model inputs for progression-free survival, the manufacturer did not use the end points radiographic progression-free survival (predefined secondary end point in AFFIRM) or modified progression-free survival (estimated post hoc) to derive the curves. It stated that radiographic progression-free survival was measured in AFFIRM every 3 months only, and that neither radiographic progression-free survival nor modified progression free survival accurately reflect 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), and that they are likely to stop treatment based on the same criteria in the trial. It therefore used the end point time to treatment discontinuation (estimated post hoc) as a proxy for progression-free survival, noting that the criteria for stopping treatment were the same in AFFIRM and the abiraterone trial (the manufacturer used the end point modified progression-free survival as a proxy for progression-free survival in a scenario analysis). The manufacturer chose the Weibull function for best supportive care (estimating a mean time to treatment discontinuation of [redacted] and a median of 3.71 months), and derived the survival function for enzalutamide by directly applying the stratified hazard ratio of [redacted]. To estimate a hazard ratio for abiraterone, the manufacturer used data from the submission of the manufacturer of abiraterone for NICE technology appraisal 259. These data, however, related to the subgroup of patients who had received only 1 prior chemotherapy regimen (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.

6.6 Adverse events in the model (applied in the stable-disease state) comprised all grade 3 or above 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, pathologic non-vertebral bone fractures, radiation to the bone, or surgery to the bone. The manufacturer noted that this definition differs from that in AFFIRM in that change in cancer therapy to treat bone pain was considered a skeletal-related event in AFFIRM but not in the model. The manufacturer derived the probability of each adverse event and skeletal-related event occurring in the model from the rates in the individual trials.

6.7 Because a limited number of patients completed the EQ-5D questionnaire, the manufacturer used a mapping algorithm to transform the Functional Assessment of Cancer Therapy-Prostate (FACT-P) responses to EQ-5D data. However, because mapping utility values introduces uncertainty, the manufacturer used the EQ-5D data collected from the trial in the model, and applied the mapped values only when the number of EQ-5D responses was insufficient. The manufacturer derived the EQ-5D utility values by applying UK valuation of health states estimated using the time trade-off method. At baseline, the EQ-5D utility value from the trial was [redacted] (n=209) and the mapped value was [redacted] (n=1008); the manufacturer chose the EQ-5D value from the trial for the model because it considered the sample size reasonable. To reflect the treatment benefit of enzalutamide and abiraterone, the manufacturer applied a utility increase to the baseline utility value. For patients receiving enzalutamide, the manufacturer estimated a mapped utility increase of [redacted] ([redacted]), and for those receiving abiraterone, it used a value of 0.04 (95% CI 0.032 to 0.048) from the submission of the manufacturer of abiraterone to the Dutch Health Care Insurance Board. For more information on how the utility increase for enzalutamide was estimated, see page 147 of the manufacturer's submission.

6.8 For the utility decrease associated with disease progression, the manufacturer derived a value from a published utility study, Sandblom et al. (2004), because no health-related quality of life data were collected during AFFIRM beyond disease progression. Sandblom et al. measured health-related quality of life of patients with metastatic hormone-refractory prostate cancer at the end of life, and reported EQ-5D utility data for 2 time intervals before death: 16–8 months and 8–0 months. The manufacturer stated that these intervals approximately matched the time patients in AFFIRM spent in the stable- and progressive-disease states. The utility decrease used by the manufacturer in the model 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 found 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 because it did not identify reliable data to reflect this effect and because, as the manufacturer advised, the deterioration in health at the end of life would not influence incremental results (that is, would affect patients on different treatments equally). The manufacturer sourced the utility decreases associated with adverse events from the published literature, and mapped those associated with skeletal-related events from FACT-P to EQ-5D, noting insufficient EQ-5D data for skeletal-related events from AFFIRM. For further details on the utility values applied in the model, see table 58 on page 152 and table 59 on page 154 of the manufacturer's submission. A summary of the QALY gain in each health stated estimated by the model is provided in table 3.

Table 3 Summary of QALY gain by health state

Health state	QALYs enzalutamide	QALYs abiraterone	QALYs BSC[a]	% absolute increment (vs. abiraterone)	% absolute increment (vs. BSC[a])
Stable disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SREs[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]BSC, best supportive care; [b]SREs, skeletal-related events

Source: Manufacturer's submission, tables 76–78, page178

6.9 The manufacturer included the following cost categories 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 was [redacted] per pack (112 tablets of 40 mg) after applying the patient access scheme discount of [redacted].

[redacted]. The manufacturer applied the resource use costs associated with monitoring patients based on the abiraterone submission for NICE technology appraisal 259. It used the NHS reference costs 2011-2012 to cost 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. For further details, see tables 61 and 62 on page 163 of the manufacturer's submission, and for the costs associated with adverse events, see table 68 on page 167. The concomitant medications used by patients in the model were based on AFFIRM. For drug costs, the manufacturer used the British National Formulary and the Electronic Market Information Tool. Because resource use and associated costs usually peak immediately before death, the manufacturer incorporated a cost for terminal care of £3133 per patient as a transition cost to the death state. For further details

on how the terminal care cost was estimated, see page 166 of the manufacturer's submission. No costs for hospitalisation were assumed in the model.

6.10 The manufacturer's deterministic cost-effectiveness results (table 4) estimated that enzalutamide compared with abiraterone provides an additional [redacted] quality-adjusted life years (QALYs). This benefit is achieved at an additional cost of [redacted], resulting in an incremental cost-effectiveness ratio (ICER) of £14,795 per QALY gained for enzalutamide compared with abiraterone. In comparison with best supportive care, enzalutamide offers an additional [redacted] QALYs at an additional cost of [redacted]; this gives an ICER of £43,587 per QALY gained. In an incremental analysis, abiraterone is 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 despite enzalutamide having a higher total cost and QALYs than abiraterone).

Table 4 Manufacturer's deterministic cost-effectiveness results

Technology	Total costs (£)	Total QALYs	Inc.[a] costs (£)	Inc.[a] QALYs	ICER versus baseline (£/QALY)	Inc.[a] ICER (£/QALY)
BSC[b]	[redacted]	[redacted]	-	-	-	-
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	102,751	102,751
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	43,587	14,795

[a]Inc., incremental; [b]BSC, best supportive care

Source: Manufacturer's submission, tables 86 and 87, page 186

6.11 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 bound of the 95% confidence intervals of each variable. In comparing enzalutamide with abiraterone, the key driver of the ICERs was the hazard ratio used to estimate overall survival for abiraterone, resulting 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 are correlated in the hazard ratio for abiraterone (the intercept and the time covariate), and in the sensitivity analysis, only 1 parameter (the intercept) was varied, which the manufacturer suggests overestimated the ICERs. 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. The manufacturer stated that the key drivers of the cost-effectiveness results against abiraterone and best supportive care were the hazard ratios for overall survival and time to treatment discontinuation, and the degree to which health-related quality of life improves while taking enzalutamide or abiraterone (the on-treatment utility increase). For the full results and tornado diagrams see pages 180–182 of the manufacturer's submission.

6.12 The manufacturer carried out a probabilistic sensitivity analysis to characterise the uncertainty in the base-case ICER, varying parameters simulaneously 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 (table 5). 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. In comparison 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 £50,000 per QALY gained was 81%.

Table 5 Manufacturer's probabilistic cost-effectiveness results

Technology	Total costs (£)	Total QALYs	Inc.[a] costs (£)	Inc.[a] QALYs	ICER versus baseline (£/QALY)	Inc.[a] ICER (£/QALY)
BSC[b]	[redacted]	[redacted]	-	-	-	-
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	102,324	102,324
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	43,172	14,576

[a]Inc., incremental; [b]BSC, best supportive care

Source: Manufacturer's submission, tables 86 and 87, page 186

6.13 To investigate the structural uncertainty in the model, the manufacturer tested in scenario analyses alternative assumptions related to: the parametric function it chose to fit the Kaplan–Meier data for overall survival and progression-free-survival; the overall survival function for abiraterone which it estimated from time-dependent hazard ratios; how it defined disease progression; the utility values it derived for the model; the potential for it having double counted the utility decreases for adverse events and skeletal-related events, and the abiraterone patient access scheme discount. For more details on the scenarios the manufacturer explored, see table 70 on page 170 of the manufacturer's submission. A description and the results of the key scenario analyses are summarised below; for full results, see table 88 on page 187 of the manufacturer's submission:

- 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:
  - by applying the constant hazard ratio of 0.74 from the abiraterone trial (Fizazi et al. 2012) to the survival function for best supportive care, and
  - by estimating mean overall survival for abiraterone from the abiraterone trial, 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.

- 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, and
  - assuming an equal utility increase for enzalutamide and abiraterone.

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

6.14 The manufacturer stated that some clinical experts believe 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 the abiraterone trial. Because of this, the manufacturer performed a cost-minimization analysis, which assumed equal utility gain, and equal rates of adverse events and skeletal-related events for enzalutamide and abiraterone. In this, the acquisition cost of both treatments was set to be equal, but because treatment with abiraterone requires taking 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).

ERG critique and exploratory analyses

6.15 The ERG considered that the manufacturer's literature review of 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.

6.16 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%).

6.17 To model overall survival for abiraterone, the manufacturer used 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 prednisone), 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 is not justified given the very low number of patients still in the study near 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 prednisone have the same risk of death); the ERG applied this assumption in its exploratory analyses (section 6.22).

6.18 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 prior chemotherapy regimen. The ERG argued that estimating the hazard ratio from the

overall population, which includes patients who had received more than 1 prior 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 to model progression-free survival; the ERG applied this hazard ratio in its exploratory analyses (section 6.22).

6.19 The ERG agreed that, given the uncertainty around mapping utility values, it was appropriate for the manufacturer to have chosen the EQ-5D utility value at baseline ([redacted]) estimated from AFFIRM. However, the ERG regarded this value as uncertain because only a small proportion of patients completed the EQ-5D questionnaire (179 patients in total) and, of those, a considerable proportion of patients had missing items in their questionnaire. In addition, the ERG stated that patients in AFFIRM may have been fitter than those seen in clinical practice, which may have overestimated the utility value. The ERG explored the uncertainty around this parameter in a threshold analysis (section 6.23).

6.20 The ERG could not verify the internal mapping algorithm or the details of the calculations that the manufacturer used to estimate the utility increase to patients while taking enzalutamide. In addition, it considered that no evidence supports a utility increase with abiraterone, and so this, too, was highly uncertain. The ERG stated that the difference between the utility increases to patients while taking either enzalutamide or abiraterone is an important determinant of the incremental QALYs of enzalutamide, and in its opinion, there is no strong evidence to assume 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 (section 6.22).

6.21 The manufacturer derived the utility decrease for disease progression from Sandlom et al. (2004) because the time intervals of 16–8 months and 8–0 months before death in this study approximately matched the time patients in AFFIRM spent in the stable- and progressive-disease states. The ERG argued that these time intervals should match the time in stable- and progressive-disease states in Sandlom et al., not AFFIRM, because some patients assessed in Sandlom et al. may have had stable disease 8–0 months before death and progressive disease 16–8 months before death. In response to a clarification request by the ERG, the manufacturer stated that, although Sandlom et al. does not report the time that patients spent in each state, patients are likely to have progressive disease in their last 8 months of life. The ERG considered that the utility decrease used from Sandlom et al. (−0.085) could be considered appropriate. However, it explored the impact of using an alternative value of 0.07 from Sullivan et al. (2007). 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.

6.22 In all its exploratory analyses, the ERG added mitoxantrone 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, but mitoxantrone was extendedly dominated by enzalutamide.

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

- Applying a hazard ratio of 1.0 for abiraterone compared with best supportive care after 25 months

- Applying a hazard ratio of 0.49 relating to the whole population to model progression-free survival for abiraterone
- Excluding the utility increases to patients while taking enzalutamide or abiraterone

The ERG then applied the above-listed changes simultaneously in the manufacturer's base-case model. The results of these analyses are presented in table 6.

Table 6 Results of the ERG's exploratory analyses

	Inc.[a] costs (£)	Inc.[a] QALYs	ICER (£/QALY)
Manufacturer's base case			
Enzalutamide compared with:			
Abiraterone	[redacted]	[redacted]	14,576 (ED[b])
BSC[c]	[redacted]	[redacted]	43,239
a. Overall survival HR[d] of 1 for abiraterone versus BSC[d] after 25 months			
Enzalutamide compared with:			
Abiraterone	[redacted]	[redacted]	15,020 (ED[b])
Mitoxantrone	[redacted]	[redacted]	33,582 (ED[b])
BSC[c]	[redacted]	[redacted]	43,398
b. Whole population PFS[e] HR[d] of 0.49 for abiraterone			
Enzalutamide compared with:			
Abiraterone	[redacted]	[redacted]	12,461 (ED[b])
Mitoxantrone	[redacted]	[redacted]	33,510 (ED[b])
BSC[c]	[redacted]	[redacted]	43,285
c. Excluding the 'on treatment utility gain'			
Enzalutamide compared with:			
Abiraterone	[redacted]	[redacted]	16,464 (ED[b])
Mitoxantrone	[redacted]	[redacted]	37,703 (ED[b])
BSC[c]	[redacted]	[redacted]	51,014
a, b and c applied simultaneously			
Enzalutamide compared with:			
Abiraterone	[redacted]	[redacted]	14,488 (ED[b])
Mitoxantrone	[redacted]	[redacted]	37,840 (ED[b])
BSC[c]	[redacted]	[redacted]	51,124

[a]Inc., incremental; [b]ED, extendedly dominated; [c]BSC, best supportive care; [d]HR, hazard ratio; [e]PFS, progression-free survival

Source: ERG report, table 6.1, page 129

6.24 The ERG performed 2 threshold analyses to explore the uncertainty around:

- how the manufacturer estimated progression-free survival in the model (that is, by using time to treatment discontinuation as a proxy), and
- 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 resulting estimates. 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 time to treatment discontinuation hazard ratio for enzalutamide compared with best supportive care must be 0.23 or lower (the base-case value was [redacted]). That is, improving the treatment effect with regard to progression-free survival (decreasing the hazard ratio) would make enzalutamide both more effective (in terms of QALY gain) and more expensive, but the increase in costs would outweigh the increase in QALYs, resulting in a higher ICER. For the utility value at baseline, the ERG found that, for the ICER to be higher than £50,000 per QALY gained, the utility value must be 0.58 or lower (the base-case value was [redacted]). 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 both patients with stable and progressed disease, and may reflect in-between study differences.

7 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The manufacturer stated that in the control groups of AFFIRM and the abiraterone trial, patients had a life expectancy of approximately 1 year. In NICE technology appraisal guidance 259, the Committee agreed that the first criterion was fulfilled because life expectancy from trials including patients randomised to best supportive care was less than 15 months.

<table>
<tr>
<td>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</td>
<td>The manufacturer provided estimates of mean overall survival using different parametric functions with the analysis truncated at 5 years (this assumed that all patients die by 5 years). The estimates were as follows:
<table>
<tr><th>Distribution</th><th>Difference in mean overall survival (in favour of enzalutamide)</th></tr>
<tr><td>Exponential</td><td>[redacted]</td></tr>
<tr><td>Weibull*</td><td>[redacted]</td></tr>
<tr><td>Log-Normal</td><td>[redacted]</td></tr>
<tr><td>Log-Logistic</td><td>[redacted]</td></tr>
<tr><td>Gamma</td><td>[redacted]</td></tr>
</table>
*Distribution used in the base-case analysis

Restricted mean overall survival (without any extrapolation, assuming all remaining patients die immediately at the end of the trial): enzalutamide [redacted], best supportive care [redacted] (difference [redacted]) (Kaplan–Meier curves truncated at 19.5 months)

Model estimates (using a lifetime horizon)
<table>
<tr><th></th><th>Life years gained</th><th>Difference</th></tr>
<tr><td>Enzalutamide</td><td>[redacted]</td><td>-</td></tr>
<tr><td>Abiraterone*</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BSC[b]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
[a]m, months; [b]BSC, best supportive care
*The difference of [redacted] is obtained when the time-dependent hazard ratio is used to model overall survival for abiraterone. When the constant hazard ratio of 0.74 is used instead, the difference is [redacted].</td>
</tr>
</table>

The treatment is licensed or otherwise indicated for small patient populations	The manufacturer stated that the potential patient population for enzalutamide in 2013 is estimated at 2977 patients. In NICE technology appraisal guidance 259, the Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n=2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation.

8 Equalities issues

8.1 The potential for a subpopulation of people who have proposed, started or completed male to female gender reassignment and have prostate cancer was raised during the scoping workshop. However, NICE representatives clarified that this population is already included in the overall population of 'adults with metastatic hormone refractory prostate cancer which has been previously treated with a docetaxel-containing chemotherapy regimen'. For the purpose of clarity, this appraisal refers to people rather than men.

8.2 Patient experts noted that prostate cancer is more common among men aged over 60 years, and that African-Caribbean men are 3 times more likely to develop prostate cancer than White men of the same age in the UK. They further noted that men from lower socioeconomic backgrounds are less likely to survive prostate cancer. Patient experts considered it important to ensure that access to this technology is equitable, and that patients are not denied treatment because of their age, ethnicity or socioeconomic background. They also stressed the importance of information, communication strategies, and consulting patients to ensure that access to treatment is as equitable as possible.

9 Innovation

9.1 The manufacturer considers enzalutamide to be an innovative technology. It stated that enzalutamide is the first androgen receptor signalling inhibitor that inhibits 3 steps in the signalling pathway, making it a pure androgen receptor antagonist compared with other treatments that do not inhibit nuclear translocation or DNA binding.

9.2 The manufacturer stated that, unlike abiraterone, enzalutamide does not need to be administered with corticosteroids and can be administered with food, which makes administering it safer and simpler. It also stated that monitoring liver function, blood pressure, serum potassium and fluid retention is required with abiraterone but not with enzalutamide.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. NICE technology appraisal guidance 259 (2012).
- Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. NICE technology appraisal guidance 255 (2012).
- Prostate cancer. NICE clinical guideline 58 (2008).
- Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. NICE technology appraisal guidance 101 (2006).
- Improving outcomes in urological cancers. NICE cancer service guidance CSGUC (2002)

NICE pathways

- There is a NICE pathway on prostate cancer, which is available from http://pathways.nice.org.uk/pathways/prostate-cancer.

Hyperlink to the published European Public Assessment Report