NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Determination

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

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

1 Guidance

1.1 Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

- in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- and only when the company provides it with the discount agreed in the patient access scheme.

2 The technology

2.1 Enzalutamide (Xtandi, Astellas) is an androgen receptor antagonist that acts on the androgen receptor signalling pathway to decrease the proliferation of cancer cells and induce cancer cell death. It is administered orally. Enzalutamide is indicated for the treatment of 'adult men with metastatic castration-resistant prostate cancer who

are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated'.

2.2 The most common adverse reactions with enzalutamide are tiredness, headache, hot flushes and high blood pressure. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost (list price) of enzalutamide is £2734.67 for a 112-capsule pack of 40 mg enzalutamide. The daily dose of enzalutamide is 160 mg and costs £97.67 per day. The company has agreed a patient access scheme with the Department of Health. This is a simple discount to the list price of enzalutamide. The level of the discount is commercial in confidence, and has been changed from that used in technology appraisal 316: enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. The same level of discount is applicable to both this indication and that of technology appraisal 316 The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 The company's submission

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

3.1 PREVAIL was a randomised, double-blind, placebo-controlled trial comparing enzalutamide 160 mg once daily with placebo in adults with asymptomatic or mildly symptomatic metastatic hormone-refractory prostate cancer in whom immediate chemotherapy was

not yet clinically indicated. In total, 1717 people were randomised ('intention to treat population'); 872 to enzalutamide and 845 to placebo. A total of 1715 patients had at least 1 dose of the study drug ('safety population'); 871 had enzalutamide and 844 had placebo. The study was done at 207 sites in 22 countries; 153 patients were from the UK. People were eligible to participate if they were asymptomatic or mildly symptomatic (that is, had a score of less than 4 on the Brief Pain Inventory [BPI] question 3), had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and had an estimated life expectancy of 6 months or more. The mean age of the study population was 71 years (range 42–93). Most people in both arms had an ECOG status of 0 (enzalutamide 67%; placebo 69%).

3.2 The co-primary endpoints in PREVAIL were overall survival (OS) and radiographic progression-free survival (PFS). Radiographic PFS (rPFS) was defined as time from randomisation to the first objective evidence of radiographic disease progression, based on imaging review by central (trial) radiologists, or death due to any cause within 168 days of stopping treatment, whichever was first. It was planned that, to show a statistically significant treatment effect, the probability (p) value for OS should be less than 0.049 and the p value for rPFS should be less than 0.001 at their final analyses. The study was powered on target hazard ratios of 0.83 for OS (equal to 80% power, based on 765 deaths), and 0.57 for PFS (>99% power). The company planned 1 ('final') analysis for PFS when 410 patients had evidence of radiographic progression; this was done on 6 May 2012, at which point the disease had progressed in 439 people. The company planned 2 analyses of OS; 1 interim analysis at 516 deaths (two-thirds of deaths used in sample size calculations) and 1 final analysis (at 765 deaths). The interim analysis for OS was done on 16 September 2013 at which

point there had been 540 deaths. To account for the increased risk of false positive results, the statistical plan stipulated that the p value should not exceed 0.012 to be considered statistically significant at the interim analysis for OS. The company did another (post-'final', post hoc) analysis of rPFS at the same time as the interim OS analysis. After this, the Independent Data Monitoring Committee recommended unblinding the study and allowing people in the placebo arm to switch to enzalutamide. The study was unblinded on 3 December 2013. However, the company continued to follow the patients and presented an analysis of OS done on 30 June 2014.

3.3 Patients remained on the study drug until their disease progressed, which was radiographically confirmed or a skeletal-related event, and then began either cytotoxic chemotherapy or an investigational agent for prostate cancer. After stopping the study drug, people could have docetaxel, hormonal treatments, abiraterone, enzalutamide, cabazitaxel or sipuleucel-T. The company stated that, in current practice, after disease progression, clinicians would offer cytotoxic chemotherapy. However, more than 25% of patients in the placebo arm and more than 15% of patients in the enzalutamide arm had treatments that would not normally be given to patients at this stage of the treatment pathway in the UK. The company has stated that the number of patients having treatments that are not available at this stage in the UK treatment pathway is academic in confidence and cannot be reported here.

3.4 The company stated that at the first planned analysis for OS in September 2013, 241 people (27.6%) in the enzalutamide arm and 299 people (35.4%) in the placebo arm had died. OS with enzalutamide was longer than with placebo (median 32.4 months and 30.2 months respectively; hazard ratio [HR] 0.706; 95%

confidence interval [CI] 0.596 to 0.837; log-rank test p<0.001). OS was also longer with enzalutamide compared with placebo in the data analysis done in June 2014 after study unblinding (the company has stated that the results of this analysis are academic in confidence and so cannot be published here). The company applied 2 statistical methods to adjust the OS estimates for people switching after their study drug to an active drug that would not be given at this position in the treatment pathway in clinical practice in the UK and which can prolong survival (see section 3.3). These were the inverse probability of censoring weights (IPCW) and a 'two-stage method'. Applying these adjustments was associated with a larger OS benefit with enzalutamide relative to placebo than seen with the unadjusted estimates; of the 2 methods, the IPCW was associated with the greatest benefits. The company stated that the data are academic in confidence and cannot be reproduced here.

3.5 In the planned final analysis for rPFS (6 May 2012), 118 people (14.2%) randomised to enzalutamide and 321 people (40.1%) randomised to placebo experienced radiographic progression as determined by a central review team (HR 0.186; 95% CI 0.149 to 0.231; log rank p<0.0001). Progression continued to be measured after May 2012 but this was done by a study investigator rather than the central review team. The company did an additional analysis on 16 September 2013 and by this time the disease had progressed in 287 people (44.4%) in the enzalutamide arm and 502 people (59.4%) in the placebo arm (HR 0.307; 95% CI 0.267 to 0.353; log rank p<0.0001).

3.6 In PREVAIL patients continued treatment with the study drug until:

- their disease progressed, as confirmed by radiologists, or they experienced a skeletal-related event and

- they started on cytotoxic chemotherapy or an investigational drug for treating prostate cancer.

The company commented that it considered time to treatment discontinuation (TTD) in PREVAIL to be the best proxy for disease progression in clinical practice in the UK; clinical experts who they consulted advised that the decision to stop treatment is not made on a single measure of progression alone (such as rPFS). The company did a post hoc analysis of TTD in PREVAIL. In PREVAIL, 57.8% of people randomised to enzalutamide and 92.7% of people randomised to placebo had stopped treatment by September 2013. The median TTD in the enzalutamide arm was 17.71 months (95% CI 16.59 to 19.38) and in the placebo arm it was 4.55 months (95% CI 4.11 to 5.13).

3.7 The company measured quality of life using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) and European quality-of-life 5-domain scale (EQ-5D) questionnaires at baseline and again at weeks 5, 13 and then every 12 weeks until disease progression as defined by radiographic evidence or a skeletal-related event. These outcomes were exploratory because they had not been specified in the study protocol. People in both the enzalutamide and placebo arms showed a decrease in FACT-P scores from baseline (meaning a worsening of quality of life). However, the company stated that a 'clinically meaningful deterioration', which it defined as a decrease in FACT-P score of more than 6 points, was seen only in the placebo group. To estimate a treatment effect for enzalutamide relative to placebo, the company produced a mixed repeated measures model to estimate the change from baseline in utility value (derived from EQ-5D) in people who remained on treatment. Over the course of the study,

the utility value for people taking enzalutamide was 0.02 higher than for people taking placebo.

3.8 The overall incidence of adverse events with enzalutamide and placebo was similar (96.9% compared with 93.2%) across grades. The time on study treatment was longer in the enzalutamide arm than the placebo arm because patients randomised to enzalutamide took longer to have disease progression. There were 279 people (32.0%) in the enzalutamide arm and 226 people (26.8%) in the placebo arm who had a serious adverse event. The overall incidence of adverse events grade 3 or higher was 42.9% in the enzalutamide arm and 37.1% in the placebo arms. The incidence of grade 3 or higher adverse events in the first year of treatment was 32.0% with enzalutamide and 35.1% with placebo. Statistically significantly higher rates of grade 3 or higher hypertension measurements were seen with enzalutamide (6.8% compared with 2.3% for placebo, relative risk (RR) 3.01; 95% CI 1.81 to 5.00). The rate for cataracts was 1.3% in the enzalutamide arm compared with 0.1% in the placebo arm (RR 10.66; 95% CI 1.38 to 82.38). Other grade 3 or higher adverse events that were seen in 0.5% or more people in the enzalutamide arm than in the placebo arm respectively were: nausea 1.0% compared with 0.5%; general physical health deterioration 2.1% compared with 1.2%; pneumonia 1.3% compared with 0.8%; fall 1.4% compared with 0.7%; spinal cord compression 3.8% compared with 2.8%; and syncope 1.6% compared with 0.9%. Forty-nine people (5.6%) taking enzalutamide and 51 (6.0%) taking placebo stopped treatment because of an adverse event. Thirty-seven people (4.2%) in the enzalutamide arm died because of an adverse event compared with 32 (3.8%) in the placebo arm (RR 1.12; 95% CI 0.70 to 1.78).

3.9 There are no head-to-head trials comparing enzalutamide with abiraterone. The company therefore compared enzalutamide and abiraterone indirectly using data from PREVAIL and COU-AA-302 because both had placebo arms. COU-AA-302 was a double-blind, randomised-controlled trial of abiraterone 1000 mg daily plus prednisone 10 mg daily (n=546) compared with placebo plus prednisone 10 mg daily (n=542) in men with metastatic hormone-relapsed prostate cancer, who were asymptomatic or mildly symptomatic and in whom chemotherapy was not yet clinically indicated. COU-AA-302, like PREVAIL, also had a co-primary endpoint combining OS and rPFS (time from randomisation to the first evidence of radiographic disease progression, progression of soft tissue lesions measured by CT or MRI as defined in modified Response Evaluation Criteria in Solid Tumors criteria or death from any cause, whichever was first).

3.10 As in PREVAIL, COU-AA-302 had interim and final analyses, but unlike PREVAIL, it was unblinded early without meeting the pre-specified criterion for a statistically significant difference in OS at an interim analysis. The company used data from the September 2013 cut-off from PREVAIL (enzalutamide follow-up 22.2 months; placebo 22.4 months) and from the third analysis of COU-AA-302 (planned when 55% of events had been reached; follow-up median 27.1 months) in an indirect treatment comparison using a fixed-effect model. The HRs for OS and rPFS for abiraterone compared with placebo at the third interim analysis in COU-AA-302 were 0.79 (95% CI 0.66 to 0.95) and 0.53 (95% CI 0.45 to 0.61) respectively. In its indirect treatment comparison the company assumed that the treatment effect in the control arm of COU-AA-302 was the same as that in the control arm of PREVAIL. However, the company noted that the proportion of people taking corticosteroids in the control arm of COU-AA-302 (100% taking prednisone) differed from

that in PREVAIL (30% taking corticosteroids throughout the trial; 4% of people taking corticosteroids at baseline). The company considered that this may bias an indirect comparison of the 2 trials because of the potential effect of prednisone on the outcomes, but also the extent of prednisone's effect was unknown. The company has stated that the results of its indirect treatment comparison are academic in confidence and cannot be reported here.

3.11 The ERG considered that the PREVAIL population represented the population that would have enzalutamide before chemotherapy in clinical practice in the UK. Clinical advisers to the ERG stated that there were no subgroups of patients in PREVAIL that would have been eligible to start docetaxel at the point that they entered the trial. The ERG stated that both arms of the trial were balanced in terms of demographics, baseline disease characteristics and medical history.

3.12 The ERG noted that the company stated TTD is the most appropriate endpoint to assess disease progression because it is standard practice to stop treatment once progression is diagnosed. The ERG noted that at the September 2013 cut-off, median TTD was comparable with median time to rPFS. The ERG commented that in the PREVAIL study there were about 2 months between patients stopping treatment with enzalutamide or placebo and starting second-line treatment. The ERG noted that the company used different data cut-off results for different variables in its model. The ERG commented that the company had used data up to June 2014 for TTD in its modelling, but that the earlier unblinding of the data in December 2013 might have influenced the decision on whether to continue or stop study treatment.

3.13 The ERG commented that the company considered its indirect treatment comparison was biased because the control groups in

PREVAIL and COU-AA-302 differed in corticosteroid use. The ERG agreed that the control groups were different, but did not think that comparing the active arms of the 2 trials would give more accurate results. The ERG stated that there was a lack of transparency in reporting the methods the company used to do its indirect treatment comparison, but it checked the results using standard methods (Bucher) and produced similar results to the company.

Cost effectiveness

3.14 The company produced a new Markov model to assess the cost effectiveness of enzalutamide compared with abiraterone or best supportive care in adults with metastatic hormone-relapsed prostate cancer who were asymptomatic or mildly symptomatic after androgen deprivation therapy failed and in whom chemotherapy was not yet indicated. The company assumed that the placebo arm of PREVAIL represented best supportive care because patients randomised to placebo could have, when needed: luteinising hormone-releasing hormone analogues, corticosteroids, blood transfusions, bisphosphonates, radiotherapy, analgesics and palliative surgery to treat skeletal-related events. The modelled population had the same characteristics as the PREVAIL population at baseline. The model ran over a lifetime horizon (10 years), and had a cycle length of 1 week with half-cycle correction. A 3.5% discount rate was applied for health effects and costs.

3.15 The model had 3 main health states: stable disease, progressed disease and death. People entered the model with stable disease after androgen deprivation therapy. Within the progressed health state, there were 3 further health states to reflect that after progressing on enzalutamide, abiraterone or best supportive care,

the disease may progress on subsequent treatments. These health states were:

- Post-progression 1: this state applied to all arms of the model. Patients moved into this health state upon progression with the first treatment (enzalutamide, abiraterone or best supportive care) In this health state all patients received docetaxel. Patients moved out of this health state upon progression (whilst on docetaxel treatment). In the best supportive care arm of the model patients moved to post-progression 2. In enzaluamide and abiraterone arms of the model, patients moved to palliative care.
- Post-progression 2: this state only applied to the best supportive care arm of the model. Patients moved into this health state upon progression during docetaxel treatment.In the base case, the company assumed that in this health state all patients had enzalutamide as an active treatment. Patients moved out of this health state upon progression, to the palliative care health state. .
- Palliative care: this state included patients whose disease had further progressed. In this state nobody had active treatment.

3.16 The company took estimates of survival and TTD from PREVAIL for enzalutamide and best supportive care, and from COU-AA-302 for abiraterone. The company used TTD as a proxy for progression for first-line treatments because it said that this reflected clinical practice. In its base case, to compare the effectiveness of enzalutamide and abiraterone, the company used results from its naive comparison rather than from its indirect treatment comparison. The company used data for TTD and OS for enzalutamide and best supportive care from the 30 June 2014 cut-off. By this time, the PREVAIL trial had been unblinded for

6 months and less than half of people in both arms had died (the company stated that the exact proportions of people who had died at this time is academic in confidence and cannot be reported here). For abiraterone, the company used OS and rPFS estimates from the third interim analysis from COU-AA-302 (55% deaths). Because there were no published TTD data from COU-AA-302 the company assumed that rPFS was equivalent to TTD for abiraterone because rPFS and TTD were similar for enzalutamide in PREVAIL. The OS estimates for enzalutamide and best supportive care were adjusted for treatment switching using the IPCW method resulting in an adjusted HR and weighted Kaplan–Meier curves. The company stated that it was not possible to adjust abiraterone OS data for treatment switching.

3.17 To extrapolate the rates of stopping the primary treatment or dying after the end of the trials, the company tested whether the HRs were proportional, and determined they were not. This meant that the company needed to find out which curves had the best fit to data for each treatment arm. The company tested 5 parametric models (exponential, Weibull, log logistic, log normal and generalised gamma) on each of the enzalutamide and placebo arms from PREVAIL and on the abiraterone arm from COU-AA-302 to extrapolate the survival curves for OS and TTD. The company considered that the exponential, log-normal and log-logistic curves gave implausible estimates for 5- and 10-year survival. The Weibull and gamma extrapolation of enzalutamide and best supportive care resulted in curves that crossed. Because the Weibull curve crossed later than the gamma curve, the company selected the Weibull curve in its base case to extrapolate the enzalutamide and best supportive care OS trial data. The company also extrapolated the OS curve for abiraterone using a Weibull distribution. TTD curves

for enzalutamide, best supportive care and abiraterone were extrapolated using a gamma distribution.

3.18 The company chose exponential curves to reflect TTD for second- and third-line treatments. The company estimated the TTD for people having docetaxel from Tannock et al. (2004; TAX 327, a trial of docetaxel with prednisone compared with mitoxantrone with prednisone for advanced hormone-refractory prostate cancer). The company estimated the TTD for people having third-line enzalutamide or third-line abiraterone using the median number of administrations of enzalutamide and abiraterone in AFFIRM and COU-AA-301 respectively. AFFIRM and COU-AA-301 were placebo-controlled trials of enzalutamide and abiraterone respectively, taken after docetaxel for metastatic hormone-relapsed prostate cancer.

3.19 To estimate the changes from baseline EQ-5D score during the trial among people remaining on their first-line treatment in PREVAIL, the company developed a mixed repeated measures model. The company used the results from this model to determine a baseline utility value (0.844) using UK tariffs for people in the stable disease health state having best supportive care. The company applied an additional utility increment for people having enzalutamide (0.022), from its modelled estimate of a 'treatment effect' of enzalutamide on quality of life from PREVAIL. The treatment effect was the difference between the degree to which quality of life decreased over time with enzalutamide and with placebo. The company assumed that abiraterone would have the same on-treatment utility benefit as enzalutamide.

3.20 As the investigators in PREVAIL collected EQ-5D only from people on treatment (enzalutamide or placebo before chemotherapy) who by definition did not have progressed disease, the company

estimated utility values in the progressed health states from the published literature. The company used a weighted average from 2 publications that had assessed the quality of life of people who were on chemotherapy, who had previously had chemotherapy, and who had metastatic hormone-relapsed prostate cancer. The company used this to estimate a utility value of 0.658 for post-progression state 1 (when the disease had progressed on enzalutamide, abiraterone or best supportive care and people were having docetaxel) and 0.612 for post-progression state 2 (when the disease had progressed on best supportive care and docetaxel and people were having enzalutamide). In line with NICE's technology appraisal on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen, the company applied an on-treatment utility gain of 0.04 for enzalutamide after docetaxel in people who had best supportive care before docetaxel. This on-utility gain for enzalutamide was assumed to be the same as that for abiraterone in an evidence submission the manufacturer of abiraterone had made to the Dutch Healthcare Insurance Board. The company estimated a utility value of 0.500 for people who had palliative care after their disease progressed on active treatment (Sandblom et al. 2004).

3.21 The company incorporated the rates of skeletal-related events seen in PREVAIL for people randomised to enzalutamide or placebo (using data from the September 2013 data cut-off). The model included the rates of adverse events of grade 3 or higher from PREVAIL and COU-AA-302. Adverse events while on docetaxel came from Tannock et al. (2004). The company assumed that the rates of adverse events for third-line enzalutamide and abiraterone were the same as for first-line treatment. To estimate the disutility associated with adverse events, the company sourced values from the published literature for adverse events of grade 3 or above.

Because no data on the rates of adverse events were available for the period people were taking abiraterone in COU-AA-302, the company assumed that these were the same as for enzalutamide. The disutility associated with a skeletal-related event was applied for 1 month and was derived from EQ-5D data from PREVAIL.

3.22 Both enzalutamide and abiraterone have confidential patient access schemes (price discounts) established when NICE appraised each of the drugs for use after docetaxel. At the request of NICE, the company provided its base-case results incorporating the list prices for enzalutamide and abiraterone. NICE requested that the ERG provide the results of the company's modelling and its own exploratory analyses, including both the list price and the discounts. The company assumed that the same proportion of people would have corticosteroids plus enzalutamide or best supportive care as in PREVAIL and that all people having abiraterone would also have corticosteroids. The company used the price of docetaxel listed in the electronic market information tool from the Department of Health (£47.30 per 160-mg infusion vial). The dosing regimen for docetaxel was once every 3 weeks and the modelled administration cost was £301.56 (NHS reference cost).

3.23 The ERG commented that adjusting OS for treatment switching using the IPCW method resulted in reduced estimates for OS compared with the unadjusted results in the placebo arm, but increased estimates for OS compared with the unadjusted results in the enzalutamide arm. This effect was found when using either the September 2013 data cut-off or the June 2014 data cut-off, but the difference was greater when using the June 2014 data (as used by the company in its base case). The ERG considered that for OS, it preferred the June 2014 data cut-off with IPCW adjustment rather than the September 2013 cut-off because the later data provided

more endpoints. The ERG stated that modelled curves had long tails that were not consistent with the trial Kaplan–Meier data and resulted in a large modelled survival gain after most people in the trial had died or were censored, which was not justified.

3.24 The ERG commented that the company had modelled TTD estimates for enzalutamide and best supportive care using PREVAIL data from the June 2014 cut-off, 6 months after unblinding the study. The ERG considered that unblinding the study might have influenced a clinician's or a patient's decision to stop or continue with treatment. The ERG considered that the choice of curve (gamma) to extrapolate TTD was appropriate, but that using the data from the September 2013 cut-off was more appropriate for modelling.

3.25 For abiraterone, the ERG noted that in the model the TTD curve (extrapolated with a gamma distribution) crossed the OS curve (extrapolated with a Weibull distribution); this was also seen with enzalutamide, but at a later time point. The ERG noted that this implied that patients die before disease progression. To account for this, the company assumed that after the curves crossed, the time of death reflected the time at which patients stop abiraterone. However, this meant the company could not model subsequent treatments after abiraterone from the point at which the curves crossed. The ERG noted that using a Weibull distribution rather than a gamma distribution to extrapolate the abiraterone TTD curve meant that the curve did not cross over the OS curve. The ERG noted that, although the enzalutamide TTD and OS curves also crossed, this occurred later and had less of an effect on the incremental cost-effectiveness ratio (ICER) estimates than did abiraterone's earlier-crossing curves.

3.26 The ERG commented that in the model, a patient's probability of dying at a particular time point was the same regardless of their health state. The ERG considered this to be implausible because it meant that people with stable, asymptomatic or mildly symptomatic disease on their first treatment had the same risk of dying as people with progressive disease on palliative care after up to 3 lines of active treatment had failed.

3.27 The ERG discussed how the company had modelled the quality-of-life data from PREVAIL using the mixed model with repeated measures approach. The ERG stated that the increment for enzalutamide compared with best supportive care (0.022) was based on quality of life decreasing from a baseline of 0.844 with best supportive care (by 0.064), but decreasing less so with enzalutamide (by 0.042). The ERG thought that it would have been more appropriate for the company to apply the decrease in quality of life from an average baseline utility for placebo and enzalutamide rather than adding the utility increment to a baseline value.

3.28 The ERG noted that while the company had modelled quality of life separately for enzalutamide and best supportive care, it had analysed the impact of having skeletal-related events by pooling both treatment arms. Therefore, the impact of skeletal-related events on quality of life might have already been captured in the analysis of quality of life by treatment arm and already reflect any reduction in the rates of skeletal-related events with enzalutamide compared with best supportive care.

3.29 The ERG noted that the company based drug costs on the number of people having the drug at the end, rather than the start, of each cycle. The company assumed that clinicians prescribe enzalutamide and abiraterone weekly, rather than monthly, as

implied by the package size. The ERG assumed that clinicians would prescribe a 1-month course of tablets at a time.

3.30 The ERG noted that the company chose higher monitoring costs for abiraterone (monitoring visits every 4 weeks) than for enzalutamide (monitoring visits every 8 weeks). The ERG noted that the summary of product characteristics for abiraterone stipulates the frequency of monitoring for patients taking abiraterone, but the summary of product characteristics for enzalutamide does not state this. The ERG stated that its clinical experts had advised that the frequency of monitoring of people taking enzalutamide and abiraterone would be expected to be the same. The ERG also noted that monitoring for people having enzalutamide in the company's model was less frequent than for those having best supportive care (every 8 weeks and every 6 weeks respectively). The ERG stated that it expected the monitoring frequency for a person having enzalutamide or best supportive care to be the same.

3.31 The ERG used its preferred assumptions applied to the company's model to produce an ERG exploratory base case:

- Assuming that people who had enzalutamide before docetaxel could have abiraterone after docetaxel and people who had abiraterone before docetaxel could have enzalutamide after docetaxel, and applying the quality-of-life gain for active treatments taken after docetaxel.
- Using the September 2013 TTD curves rather than the June 2014 TTD curves extrapolated with a gamma curve.
- Calculating the drug costs using the number of patients at the start, rather than the end, of a cycle.

- Assuming clinicians would prescribe a 1-month supply of enzalutamide or abiraterone at a time rather than a 1-week supply.
- Subtracting the decrease in utility value derived from PREVAIL for the enzalutamide and placebo arms from the baseline utility value at the start of PREVAIL.
- Assuming the utility value for people having active treatment (enzalutamide or abiraterone) after docetaxel was the value derived from AFFIRM.
- Removing the utility decrement associated with skeletal-related events.
- Assuming the monitoring costs for enzalutamide and abiraterone are the same.
- Including a cost for ongoing treatment with luteinising hormone-releasing hormone analogues.
- Applying current reference costs for outpatient appointments and scans and the current costs paid by the NHS for docetaxel and its administration.

3.32 Currently, Enzalutamide is available to the NHS for patients after treatment with docetaxel through a patient access scheme (PAS). During the course of the appraisal, the company submitted a revised simple PAS with an increased discount. The company also submitted a revised base case that compared 2 treatment pathways:

- Enzalutamide then docetaxel then palliative care. The cost of enzalutamide was based on the new PAS.
- Best supportive care then docetaxel then enzalutamide then palliative care. The cost of enzalutamide was based on the cost currently available in the NHS, that is, the existing PAS used in NICE technology appraisal guidance on enzalutamide for

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

3.33 The company's revised base case included the following assumptions incorporating:

- The September 2013 TTD data instead of the June 2014 TTD data
- The ERG's preferred assumption on the frequency of prescribing and calculating the drug costs based on the number of people at the start of each modelled cycle, instead of at the end (see section 3.31).
- The ERG's preferred assumptions for utility values of treatment before docetaxel (taken from PREVAIL, by subtracting the decrease in utility value for the enzalutamide and placebo arms from the baseline utility value) (see section 3.27).
- The company's revised utility value for people who had enzalutamide after docetaxel. The company stated that the baseline utility value for people in AFFIRM was 0.688 and quality of life decreased by 0.05 in the best supportive care arm of AFFIRM over the course of 25 weeks. The company therefore assumed the utility value for best supportive care after docetaxel was 0.638 and enzalutamide had an additional quality of life of 0.04 (see section 3.20). This meant that the utility value for enzalutamide after docetaxel was 0.678.
- All the other modelling assumptions in the revised base case were the same as the company's original base case.

3.34 The company's revised base case resulted in an ICER for enzalutamide compared with best supportive care of £27,036 per quality-adjusted life year (QALY) gained. The company did not present the comparison between enzalutamide and abiraterone

with its new PAS because the Committee had concluded in a previous meeting that best supportive care was the key comparator to enzalutamide (section 4.2).

3.35 The one-way sensitivity analyses that had the greatest effect on the company base case assumed that either no one or everyone in the best supportive care arm goes on to have docetaxel. This increased the ICER to £37,453 or decreased the ICER to £24,361 per QALY gained respectively. The company also presented a scenario in which the utility value for people having enzalutamide after docetaxel was 0.688. This scenario increased the ICER to £28,208 per QALY gained.

3.36 The ERG agreed that it was appropriate to use the existing PAS for calculating the cost of enzalutamide taken after docetaxel in the best supportive care arm of the model (see section 3.32). The ERG noted that company's revised base case included some, but not all, of the ERG's preferred assumptions. It noted that the revised base case did not include:

- A luteinising hormone-releasing hormone analogue cost.
- NHS reference costs for outpatient appointments.
- Revised docetaxel costs.
- Equal monitoring for enzalutamide and best supportive care (the company assumed monitoring on best supportive care would be more frequent than on enzalutamide after 3 months).
- A utility value of 0.688 for people receiving enzalutamide after docetaxel.

Including these assumptions increased the company's base case to £32,949 per QALY gained. Including the ERG assumptions on luteinising hormone-releasing hormone analogue, docetaxel and outpatient costs and monitoring, but keeping the company's

assumption on post-docetaxel utility values, resulted in an ICER of £31,579 per QALY gained.

3.37 The ERG noted that the company had presented new data from AFFIRM to adjust the utility value for post-docetaxel best supportive care by the decrease in utility seen in the trial. The ERG noted that the uplift in utility the company had applied for enzalutamide was not based on data from the AFFIRM trial, but rather came from a separate source (a submission for abiraterone to the Dutch Healthcare Insurance Board, see section 3.20). The ERG noted that the uplift in utility for enzalutamide calculated from the AFFIRM trial was greater than that used in the company's base case (the exact value of the uplift cannot be reported here because it is commercial in confidence).

3.38 The ERG carried out an additional scenario analysis in which it used the two-stage method for adjusting OS for subsequent treatments that prolong life, but which is not used in the NHS. Applying the two-stage method, including the ERG's assumptions on luteinising hormone-releasing hormone analogue, docetaxel and outpatient costs and monitoring, but keeping the company's assumption on post-docetaxel utility value resulted in an ICER of £34,759 per QALY gained.

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

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of enzalutamide, having considered evidence on the nature of metastatic hormone-relapsed prostate cancer before chemotherapy is indicated and the value placed on the benefits of enzalutamide by people with the condition, those

who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee discussed the current treatments available in clinical practice in England for people with metastatic hormone-relapsed prostate cancer, who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy and in whom chemotherapy is not yet clinically indicated. It was aware that enzalutamide and abiraterone are licensed and are currently available through the Cancer Drugs Fund for this indication. It heard that people may be under the care of a urologist at the time when enzalutamide or abiraterone is indicated, but only oncologists are permitted to apply for drugs through the Cancer Drugs Fund. It heard from the clinical experts that people who do not have enzalutamide or abiraterone receive best supportive care, and this includes corticosteroids. The Committee noted that some people can have enzalutamide but not abiraterone, including:

- people with visceral disease (they cannot have abiraterone through the Cancer Drugs Fund)
- people with severe liver dysfunction
- people who cannot take corticosteroids (abiraterone must be taken with prednisone or prednisolone).

The Committee concluded that in clinical practice, all people at this position in the treatment pathway have access to best supportive care, and some have access to abiraterone through the Cancer Drugs Fund.

4.2 The Committee discussed whether best supportive care and abiraterone were relevant comparators for enzalutamide. It noted that although people currently have abiraterone through the Cancer Drugs Fund, the current funding arrangements within the Cancer

Drugs Fund will come to an end in April 2016. The Committee was aware that abiraterone is currently being appraised by NICE and that preliminary recommendations had not recommended abiraterone. The Committee agreed that because abiraterone was not embedded in the NHS, it should not be considered as a comparator. The Committee concluded that best supportive care was the relevant comparator for its decision making

4.3 The Committee heard from clinical experts that people taking enzalutamide or best supportive care have regular monitoring visits. The Committee noted that the summary of product characteristics for enzalutamide does not stipulate a monitoring frequency. The Committee noted that the company considered that after the first 3 months of treatment, monitoring would be less frequent in people taking enzalutamide (every 8 weeks) than in those having best supportive care (every 6 weeks). It heard that the company's rationale was that people taking best supportive care would have progressive disease after failure of hormonal therapy, and clinicians would monitor the extent of progression more frequently compared with people having enzalutamide, in whom the disease would be stabilised. The Committee considered that doctors would monitor disease and prescribe enzalutamide in the same visit. Also, because enzalutamide is an active treatment, clinicians would monitor both disease progression and adverse reactions in people taking enzalutamide. The Committee concluded that the frequency of long-term monitoring with best supportive care and enzalutamide would be expected to be similar.

4.4 The Committee heard from patient experts about their experience of prostate cancer and treatments for prostate cancer. The patient experts stated that delaying the need for cytotoxic chemotherapy for as long as possible is important to people because of the side

effects associated with chemotherapy. They stated that people prefer to have the benefits of enzalutamide when they are feeling fitter rather than after docetaxel when their quality of life might be worse. People also value having several treatment options. A patient expert stated that he is currently taking enzalutamide, having previously had docetaxel. He said that he had experienced very few side effects with enzalutamide and is able to live an active life, whereas docetaxel had profoundly and negatively affected his quality of life. The Committee concluded that enzalutamide is a well-tolerated treatment, and that people with metastatic hormone-relapsed prostate cancer would welcome having more treatment options to delay cytotoxic chemotherapy.

4.5 The Committee discussed the sequence of treatments people with metastatic hormone-relapsed prostate cancer would have in clinical practice in England. It noted that the Cancer Drugs Fund stipulates that abiraterone should not be used after enzalutamide, unless enzalutamide had to be stopped within 3 months of starting it because of toxicity, and only when the disease had not progressed further during that time. The Committee heard from the clinical experts that, in clinical practice in the UK abiraterone is not used after enzalutamide. It heard from the clinical experts that the evidence for the efficacy of abiraterone taken after enzalutamide was limited, but that small retrospective studies suggested that the benefit of each drug dropped when taken after the other. The Committee was aware that there is an ongoing trial comparing treatment sequences for metastatic hormone-relapsed prostate cancer. The Committee concluded that in England it is not standard care for people to have both enzalutamide and abiraterone, and people who have enzalutamide before chemotherapy do not have abiraterone after chemotherapy.

Clinical effectiveness

4.6 The Committee discussed the estimates for overall survival (OS) for enzalutamide compared with placebo from the PREVAIL trial. The Committee noted that the trial had been unblinded early for benefit, and that the company had presented data from the interim analysis of OS (on which the decision to stop the trial was made), and from what would have been the final analysis (according to the study protocol) after the study had been unblinded for 6 months. The Committee noted that, at both time points, OS was longer with enzalutamide than with placebo and that the differences between enzalutamide and placebo were statistically significant ($p<0.05$). The Committee was aware that, once the disease progressed, people on the study drug in PREVAIL could move on to subsequent treatments, and that the company considered that some of these treatments (such as cabazitaxel and sipuleucel-T, cytotoxic chemotherapy other than docetaxel, and investigational treatments) prolonged life but were unlikely to be used in England at this position in the treatment pathway. The company also noted that in clinical practice people would not have enzalutamide or abiraterone if they aready had taken enzalutamide. The Committee noted that most people in PREVAIL went on to have docetaxel after disease progression, which reflects the treatment pathway in England. However, it agreed that, although currently offered via the Cancer Drugs Fund, cabazitaxel is not recommended for prostate cancer in NICE's technology appraisal on cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen and that the marketing authorisation for sipuleucel-T has been withdrawn. The Committee also agreed that cabazitaxel and sipuleucel-T prolong life and, if these were disproportionately taken by patients in the placebo group after progression or unblinding in PREVAIL, the survival estimates for

enzalutamide compared with placebo would be biased against enzalutamide. The Committee accepted that people whose cancer progresses on enzalutamide would not receive subsequent abiraterone or enzalutamide and having both enzalutamide and abiraterone in the trial did not reflect clinical practice in England. The Committee concluded that enzalutamide improves OS compared with placebo and that it is appropriate to adjust the results for subsequent life-extending treatments not available in the NHS that people received in PREVAIL.

4.7 The Committee discussed the methods the company used to adjust its OS estimates, noting that the company had presented results using the inverse probability of censoring weights (IPCW) method and the 'two-stage method'. The Committee was aware of other possible complex methods for adjustment, including marginal structural models and rank-preserving structural nested failure time models. It heard that the company had pre-specified adjusting for treatment switching using the IPCW and two-stage methods in its statistical analysis plan; the Committee considered it good practice to pre-specify the methods of adjustment. It further noted the inherent assumption in both methods was that there were no unmeasured confounders affecting the association between moving on to another treatment and dying. The Committee appreciated that the company provided the list of covariates identified as potential confounders in response to the appraisal consultation document, and considered the list to be generally appropriate. The Committee was aware that both methods improved the effectiveness of enzalutamide compared with placebo, but that the IPCW method improved it considerably more. The Committee heard the company's rationale for preferring the IPCW over the two-stage method. One reason given was that it needed fewer assumptions. The Committee heard from the company that the two-stage method

involves using a 'second baseline' that, in this case, assesses patients' characteristics when their disease progressed and they switched to their second treatment. However, the company stated that there was a period of about 6 weeks between a patient's disease progressing and them starting a new treatment, and during this time their characteristics may have changed. The Committee identified potential issues with adjusting OS using either the two-stage or IPCW method. First, these methods need proportional hazards between the treatment arms, but the PREVAIL data did not appear to meet this criterion. Second, the company had adjusted only for non-NHS, life-extending treatments that were taken second-line in PREVAIL, and not for treatments taken third -line, because of insufficient data. The Committee noted that, although the issue of non-NHS, life-extending third-line treatment would apply to any method of adjustment, it meant that people who received active, non-NHS, third-line treatments in PREVAIL may have survived longer than would be expected in clinical practice in England. The Committee concluded that it was unclear which method of adjustment provided estimates that represented the true difference in survival between enzalutamide and placebo, but the true value was likely to lie nearer to the estimates from the IPCW method than the two-stage method and unadjusted estimates.

4.8 The Committee discussed the estimates for progression-free survival (PFS) for enzalutamide from PREVAIL. It noted that the company had used a radiographic measure of progression as its primary outcome, but the company considered that time to treatment discontinuation (TTD) was the most appropriate endpoint to reflect PFS in clinical practice. The Committee heard from the clinical experts that the measures of progression used in clinical practice include Response Evaluation Criteria in Solid Tumors radiographic criteria and measuring prostate specific antigen (PSA)

levels. The Committee noted that TTD had been used as a proxy for PFS in other appraisals of hormone-relapsed prostate cancer and may reflect staying on treatment until confirmed progression. However, it also noted that people may stop treatment before disease progression if they have severe side effects. The clinical experts noted that, because enzalutamide is relatively well-tolerated, few people stop taking it because of side effects. The Committee recognised that TTD better captured the costs of treatment than radiographic disease progression. The Committee concluded that enzalutamide had been shown to delay disease progression using either measure. It considered that, although a TTD estimate includes people who stop treatment before disease progression, because enzalutamide is well-tolerated, the number of people stopping before progression would be low. Overall, the Committee concluded that TTD was a relevant proxy to estimate disease progression and provided the advantage of better capturing costs.

Cost effectiveness

4.9 The Committee considered the structure of the company's economic model. It agreed that people taking enzalutamide before chemotherapy would not get abiraterone after chemotherapy. It agreed with the company that patients on best supportive care before chemotherapy would have an active treatment (such as enzalutamide or abiraterone) after chemotherapy. It noted that the company had applied the survival estimates from PREVAIL to the whole model, meaning that the duration of treatment with docetaxel or third-line active treatment (for people who first had best supportive care before docetaxel) did not affect how long patients were modelled to live. The Committee could not judge whether the modelled TTD with docetaxel or enzalutamide (when taken after

docetaxel) reflected that seen in clinical practice because the company had not presented clinical data to show that its modelled estimates were plausible. The Committee noted that the company's survival modelling approach meant that the risk of death was related to time rather than health state. So, at any point in time the risk of death was the same for people whose disease had not progressed on multiple treatments, as those who had progressed, which the Committee and clinical experts considered implausible. The Committee concluded that the model structure was appropriate in terms of the sequence of treatments people would have in clinical practice in England. However, there was still uncertainty about whether the time spent on treatments after enzalutamide in the model reflected clinical practice.

4.10 The Committee noted that the company assumed in the model that more than 80% of people in both treatment arms would go on to have docetaxel, but heard from the clinical experts that in clinical practice in England this figure would be around 40%. The Committee understood that that both the company and Evidence Review Group (ERG) had done sensitivity analyses around the proportion of people taking docetaxel. However, the Committee noted that because of the way OS was applied in the model (that is, modelled OS was independent of modelled duration of treatment) these sensitivity analyses only captured the costs of varying the proportion of people who had docetaxel and not the impact of OS. The Committee concluded that the model overestimated the proportions of people who would go on to have docetaxel compared with clinical practice, but how this impacted the modelled survival and cost effectiveness estimates was unclear.

4.11 The Committee noted that, to estimate the mean life extension associated with enzalutamide, the company needed to extrapolate

OS from the trial data in its model. The Committee noted that, at both the September 2013 and June 2014 data cut-offs, most of the trial population were still alive. The Committee agreed that it was better to extrapolate OS from the June 2014 cut-off because the trial patients were followed up for longer and also because this reflected the planned final analysis for OS. However, the Committee acknowledged that there was still uncertainty because less than half of the trial population had died at this cut-off. The Committee was aware that the company had selected the parametric curve for extrapolating OS by testing the fit of various parametric curves to the trial data, both statistically and by using predicted 5- and 10-year survival rates as a measure of face validity. It was concerned that the company had not further checked the validity of the extrapolated data. The Committee noted that this was particularly important because of the immaturity of the trial data and because of the small population at risk at the end of the trial follow-up (those who had not died or had been otherwise censored). This meant that a large proportion of the estimated survival benefit was based on the extrapolated period rather than the trial data. The Committee noted that the Weibull distribution, used in the company's base case, gave a more conservative estimate than the log-logistic and log-normal curves the company had dismissed because they gave implausible 5- and 10-year survival estimates (section 3.17). The Committee noted that, in response to the appraisal consultation document, the company confirmed that it had used the AFFIRM study to model transition probabilities in the model, but had stated that it could not use data from AFFIRM to validate the modelled post-docetaxel survival estimates for enzalutamide because the follow-up period in AFFIRM was not long enough. The Committee concluded that enzalutamide increased survival compared with best supportive

care, and that the company had chosen a conservative model, but the Committee was uncertain about the extent of the survival benefit with enzalutamide over the period after trial follow-up had ended.

4.12 The Committee noted that, in addition to extrapolating OS, the company had extrapolated TTD from PREVAIL. The Committee agreed that it was more appropriate to extrapolate the data on TTD from the September 2013 cut-off data from PREVAIL, rather than the June 2014 cut-off, because the June 2014 estimates may be biased (favouring enzalutamide) because of unblinding. The Committee noted the company's comment that bias because of unblinding would be minimal because only 7.2% of people were still on placebo after September 2013. The Committee preferred using the September 2013 cut-off data for TTD because the reduced potential for bias outweighed the benefit of the additional data provided by the June 2014 cut-off data. The Committee concluded that the most appropriate data cut-offs from PREVAIL to model were June 2014 for OS and September 2013 for TTD.

4.13 The Committee discussed the utility values that had been calculated from EQ-5D data collected in PREVAIL for best supportive care and enzalutamide. It noted that, in PREVAIL, quality of life had decreased over time while people had best supportive care or enzalutamide, but it did so to a lesser extent with enzalutamide. Because quality of life as measured by EQ-5D and Functional Assessment of Cancer Therapy – Prostate (FACT-P) decreased over time, the Committee did not consider the company's approach of adding a utility increment for enzalutamide to the estimated utility value before treatment had started to be appropriate. The Committee preferred the approach suggested by the ERG, in which the utility decrement over time seen with best

supportive care and enzalutamide was subtracted from the starting utility value. The Committee noted that the company used an estimate from the literature for the utility experienced when taking enzalutamide after docetaxel, rather than using its own estimate reflecting data from AFFIRM that it had presented in NICE's technology appraisal on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. The Committee accepted the company's revision to its base case, which used a utility value from AFFIRM that was adjusted for the drop in quality of life with best supportive care seen in the trial. The Committee also accepted the company's approach of using a utility gain for enzalutamide from a source other than AFFIRM, because this was accepted as a plausible utility uplift with enzalutamide in a NICE's technology appraisal on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. The Committee also noted that the utility assumed by the company for people having palliative care (0.500) did not match the value reported in the reference (Sandblom et al. 2004) cited by the company. The company responded to the appraisal consultation document that in its model, it had used a weighted average of utility values from Sandblom et al. to estimate utility values for people with a life expectancy similar to people modelled to be having palliative care. The Committee noted that the company did not give the formula it used to get the weighted value. The Committee concluded that its preferred utility values were those proposed by the ERG for the stable disease health state, and those based on AFFIRM presented by the company for people having enzalutamide after docetaxel.

4.14 The Committee considered how the company had applied the enzalutamide PAS in the model. It was aware that there is an

existing simple discount PAS for enzalutamide, which was agreed as part of the appraisal of enzalutamide after docetaxel (TA316). It noted that if the current appraisal recommended enzalutamide, then a new simple PAS with an increased discount would apply to enzalutamide used either before or after docetaxel. The Committee noted that the company used the new increased PAS to model the costs of enzalutamide before docetaxel, and the existing PAS to model the costs of enzalutamide after docetaxel (for people who have best supportive care before docetaxel). The Committee also noted that the ERG agreed with the company's approach, but additionally provided a scenario in which the new increased PAS was applied to all costs of enzalutamide in the model to show what the costs for each treatment option would be if enzalutamide were recommended. The Committee recognised that, if the current appraisal did not recommend enzalutamide before docetaxel, then the existing PAS would apply for patients having enzalutamide after docetaxel. Therefore, the Committee concluded that the company's approach to applying the PAS in the model was appropriate.

4.15 The Committee considered that the following modelling assumptions were the most plausible:

- The company's assumption that people who had enzalutamide or abiraterone before docetaxel would not have active treatment again after docetaxel.
- The ERG's assumptions on utility values for the stable disease health state.
- The company's assumption in its revised base case for the utility of people taking enzalutamide after docetaxel.
- The ERG's assumption that data from the September 2013 data cut-off rather than the June 2014 cut-off should be used to model TTD.

- The ERG's assumptions on how to determine the number of people having drugs in each model cycle and that drugs are prescribed every 4 weeks, rather than weekly.
- The ERG's assumption that the frequency of monitoring visits would be similar after the first 3 months of treatment with enzalutamide and best supportive care.

The Committee was aware that the ERG's analysis using these assumptions, and the IPCW method to adjust for subsequent treatments, gave an ICER of £31,600 per QALY gained. It had previously concluded that the true survival benefit of enzalutamide is likely to fall nearer to the IPCW and two-stage method estimates than to the unadjusted estimate. It noted that the ERG's analysis using the assumptions listed above, and the two-stage method to adjust for subsequent treatments, gave an ICER of £34,800 per QALY gained, but that the covariates required for the two-stage method were not measured at the so-called second baseline (section 4.7). The Committee took into account its concerns about the uncertainty of extrapolating mortality beyond the PREVAIL data and the uncertainty of the impact on survival estimates of third-line, life-extending, treatments used in PREVAIL that are not available in the NHS. It concluded that the most plausible ICER for enzalutamide compared with best supportive care was nearer to £31,600 than to £34,800 per QALY gained.

4.16 The Appraisal Committee considered whether it should take into account the Pharmaceutical Pricing Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising enzalutamide. The Committee noted NICE's position statement in this regard, and accepted 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost

effectiveness of branded medicines'. The Committee queried why the company, in its original submission (before the revised PAS submission) for the appraisal, had presented a scenario analysis that included a 10.36% price rebate to reflect the PPRS. The company clarified that this percentage had been calculated by the Department of Health and applied to all Astellas' products. The company stated in its response to the appraisal consultation document that it repays the PPRS into a 'Health General Cash' account. It acknowledged that the rebate would be unlikely to be returned to commissioning groups relative to the amount of enzalutamide prescribed in the population covered by its marketing authorisation. The Committee agreed that there was no detailed and transparent justification of how the PPRS would directly affect the acquisition cost of enzalutamide to the NHS (in a way that would represent a nationally available price reduction). It also heard from the company that the 10.36% rebate level was 'likely to remain for 3 years'. The Committee did not accept that this could function as the guarantee needed for this to be acceptable as a 'nationally available price reduction', as envisaged in the Guide to the methods of technology appraisal 2013. In summary, the Committee heard nothing to suggest that there is any basis for taking a different view on the relevance of the PPRS to this appraisal of enzalutamide. It therefore concluded that the PPRS payment mechanism was irrelevant for considering the cost effectiveness of enzalutamide.

4.17 The Committee noted that the company did not propose that enzalutamide taken before docetaxel meets the end-of-life criteria. The Committee nevertheless considered whether enzalutamide met these criteria. It noted that, in both the placebo and enzalutamide arms of PREVAIL the median OS was more than 30 months and as such, the mean life expectancy at this point in

the treatment pathway was more than 24 months. The first end-of-life criterion is that the treatment is indicated for patients with a short life expectancy, normally less than 24 months. Because enzalutamide did not meet this criterion, the Committee did not consider the other criteria. It concluded that enzalutamide did not meet end-of-life criteria for treating metastatic hormone-relapsed prostate cancer in people for whom chemotherapy is not yet indicated.

4.18 The Committee discussed whether enzalutamide was innovative and whether it had substantial, demonstrable and distinctive benefits adequately captured in the modelling of the QALYs. The Committee noted that enzalutamide offers people with hormone-relapsed disease a first-line active treatment before cytotoxic chemotherapy. The Committee noted that enzalutamide was the only treatment option for people with visceral disease, for whom abiraterone is not available through the Cancer Drugs Fund, or with severe liver dysfunction for whom abiraterone is contraindicated, or who cannot take corticosteroids. It further noted the comments, received in response to the appraisal consultation document, that enzalutamide is an important treatment option for people who have tried abiraterone but have stopped taking it because of severe side effects. It considered that, although enzalutamide is not a new treatment, it is the only treatment that can give these benefits at this position in the treatment pathway, and so is innovative. The Committee noted that the patient experts stated that delaying chemotherapy was of great importance to patients. The Committee was aware that delaying chemotherapy may mean that some people would no longer be eligible for chemotherapy. However, it noted that, despite this possibility, people wanted pre-chemotherapy treatments to be available to them. The Committee considered whether the model captured the benefits of delaying

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

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

- The company had chosen a conservative parametric distribution to model overall survival, and this reduced the level of uncertainty around the ICER (section 4.11).
- The utility values in the model may not fully capture the benefit to patients of delaying cytotoxic chemotherapy.
- Enzalutamide provides an active treatment option for some people whose only alternative is best supportive care, and in that respect enzalutamide is a step change in treatment at this point in the treatment pathway.

Taking all of these factors into account, the Committee agreed that the ICER for enzalutamide compared with best supportive care would likely fall below £30,000 per QALY gained, and it considered enzalutamide to be a cost-effective use of NHS resources. The Committee concluded that enzalutamide should be recommended within its marketing authorisation, for treating metastatic hormone-

relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, but before chemotherapy is indicated.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is clinically indicated	Section
Key conclusion		
Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer: • in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated • and only when the company provides it with the discount agreed in the patient access scheme		1.1
The Committee concluded that, with its preferred assumptions, the resulting incremental cost-effectiveness ratio (ICER) for enzalutamide compared with best supportive care was likely to be between £31,600 and £34,800 per quality-adjusted life year (QALY) gained. This range was dependent on the method used to adjust survival estimates for active treatments not used in the NHS. Furthermore, it was likely to be nearer to the lower end of this range.		4.15
The Committee concluded that enzalutamide is innovative, and that taking into account factors which had not been fully accounted for in the modelling, agreed that the ICER for enzalutamide compared with best supportive care was below £30,000 per QALY gained, and		4.18, 4.19

enzalutamide could be considered a cost-effective use of NHS resources.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	Enzalutamide is a well-tolerated treatment, and people welcome having more treatment options to delay cytotoxic chemotherapy. Enzalutamide and abiraterone (taken before chemotherapy is clinically indicated) are currently available through the Cancer Drugs Fund. Although abiraterone before docetaxel is available to some people, it is not embedded within current NHS funding arrangements because its future is not guaranteed. It was therefore not considered as a comparator. There are some people who can have enzalutamide but not abiraterone in clinical practice (people who can't take corticosteroids, people with visceral disease and people with severe liver disease).	4.4 4.1 4.2 4.21
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?	Enzalutamide is the preferred treatment option for people with visceral disease and liver dysfunction, in whom abiraterone is contraindicated at this position in the treatment pathway, or for people who can't take corticosteroids. Although enzalutamide is not a new treatment, it is the only treatment that can give these benefits at this position in the treatment pathway and so is innovative.	4.18
What is the position of the treatment in the pathway of care for the condition?	Enzalutamide is indicated for people with metastatic hormone-relapsed prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy, before chemotherapy is indicated.	4.1
Adverse reactions	Enzalutamide is a well-tolerated treatment.	4.4
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The efficacy estimates for enzalutamide came from PREVAIL. Enzalutamide increased overall survival (OS) compared with placebo. The Committee considered that adjusting the OS estimated from the trial for subsequent life-extending treatments taken by people in the trial, but which are not available in the UK, was appropriate.	4.6

Relevance to general clinical practice in the NHS	The Committee was aware that in PREVAIL, once the disease progressed, people on enzalutamide could move on to subsequent treatments. It was also aware that the company considered that some of these treatments (such as abiraterone, enzalutamide, cabazitaxel, sipuleucel-T, cytotoxic chemotherapy other than docetaxel and investigational treatments) would not be used in England at this position in the treatment pathway. The Committee agreed that it was appropriate to adjust the survival estimates for people having these treatments.	4.6
Uncertainties generated by the evidence	The extent of adjustment needed to the OS estimates (to account for subsequent treatments that people had in PREVAIL that are not available in clinical practice in England) was uncertain. It was unclear which of the methods the company had used for adjustment (the Inverse Probability of Censoring Weights or the two-stage method) was better, however IPCW was associated with fewer assumptions.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None identified.	

Estimate of the size of the clinical effectiveness including strength of supporting evidence	Enzalutamide increased OS compared with placebo, but the extent of the difference was uncertain because some people went on to have further active treatments in both study arms. The company tried to adjust for this but there was uncertainty about which method of adjustment was appropriate	4.6, 4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The company developed a new model and needed to extrapolate OS and time to treatment discontinuation from the trial data in its model.	4.9. 4.11, 4.12

Uncertainties around and plausibility of assumptions and inputs in the economic model	The model structure was appropriate in terms of the sequence of treatments people would have in clinical practice in England, but there was uncertainty about whether time spent on treatments after enzalutamide reflected clinical practice. The Committee was concerned that that the company had not further checked the validity of the extrapolated data. This was particularly important because of the immaturity of the trial data and because of the small population at risk at the end of the trial follow-up (those who had not died or had been otherwise censored). This meant that a large proportion of the estimated survival benefit was based on the extrapolated period rather than the trial data.	4.9 4.11

Incorporation of health-related quality-of-life benefits and utility values 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 considered whether the model captured the benefits of delaying chemotherapy, which is important to patients. The Committee agreed that the model predicted that people having enzalutamide had more time with better utility than people on best supportive care, but it was unclear whether the benefit of delaying chemotherapy had been fully captured by the utility values included in the modelling. The Committee concluded that enzalutamide is innovative.	4.18, 4.19
Are there specific groups of people for whom the technology is particularly cost effective?	None.	
What are the key drivers of cost effectiveness?	The data cut-offs from PREVAIL that are used in the modelling and the utility value estimates.	4.11, 4.12, 4.13

Most likely cost-effectiveness estimate (given as an ICER)	The most plausible ICER for enzalutamide compared with best supportive care was nearer to £31,600 than to £34,800 per QALY gained. The Committee also concluded that enzalutamide is innovative and taking into account factors which had not been fully accounted for in the modelling agreed that the ICER for enzalutamide compared with best supportive care was below £30,000 per QALY gained	4.15, 4.19
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS. The company revised its patient access scheme over the course of this appraisal to increase the discount to the cost of enzalutamide for the NHS.	2.3 4.14

End-of-life considerations	The company did not make a case for enzalutamide meeting end of life criteria. The Committee considered that the first criterion for end-of-life (the treatment is indicated for patients with a short life expectancy, normally less than 24 months) had not been met. Therefore, the Committee did not consider the other criteria and concluded that enzalutamide did not meet end-of-life criteria for treating metastatic hormone-relapsed prostate cancer in people for whom chemotherapy is not yet indicated.	4.17
Equalities considerations and social value judgements	No equality issues were raised.	

5 Implementation

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

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

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

Published

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

Under development

- Radium-233 dichloride for treating metastatic hormone-relapsed prostate cancer with bone metastases. NICE technology appraisal guidance, publication expected January 2016.

- Abiraterone acetate for the treatment of metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. NICE technology appraisal guidance. The anticipated date of publication is to be confirmed.

7 Review of guidance

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

Amanda Adler
Chair, Appraisal Committee
November 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

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

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

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

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

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

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

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

Professor John Cairns

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

Mr Matthew Campbell-Hill

Lay member

Professor Imran Chaudhry

Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

Professor Daniel Hochhauser

Consultant in Medical Oncology, UCL Cancer Institute

Dr Neil Iosson

Locum GP

Mrs Anne Joshua

NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Sanjay Kinra

Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

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 John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay Member

Mr Alun Roebuck

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

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Dr Nicky Welton

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

NICE project team

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

Mary Hughes

Technical Lead

Fay McCracken, Eleanor Donegan and Rosie Lovett

Technical Advisers

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 Aberdeen Health Technology Assessment Group:

- Robertson C, Cummins E, Fielding S et al., Aberdeen Health Technology Assessment Group, April 2015B.

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

I. Company:

- Astellas

II. Professional/expert and patient/carer groups:

- British Association of Urological Nurses
- British Association of Urological Surgeons
- British Uro-Oncology Group
- Cancer Research UK
- Prostate Cancer UK
- Tackle Prostate Cancer
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Institute of Cancer Research
- MRC Clinical Trials Unit
- National Collaborating Centre for Cancer

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Institute of Cancer Research
- MRC Clinical Trials Unit
- National Collaborating Centre for Cancer

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

- Professor Noel Clarke, Professor of Urological Oncology, The Christie and Salford Royal Hospitals, Manchester, nominated by the British Association of Urological Surgeons – clinical expert
- Dr Suneil Jain, Consultant Clinical Oncologist and Clinical Senior Lecturer, Queen's University Belfast, nominated by the Royal College of Physicians
- Hugh Gunn, nominated by Tackle Prostate Cancer
- Stuart Watson, nominated by Prostate Cancer UK – patient expert

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

- Astellas