NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy is not yet clinically indicated

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| The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using enzalutamide in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the [Committee papers](https://www.nice.org.uk/guidance/indevelopment/gid-tag457/documents)).The Appraisal Committee is interested in receiving comments on the following:* Has all of the relevant evidence been taken into account?
* Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
* Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
* Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
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| **Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**After consultation:* The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
* At that meeting, the Committee will also consider comments made by people who are not consultees.
* After considering these comments, the Committee will prepare the final appraisal determination (FAD).
* Subject to any appeal by consultees, the FAD may be used as the basis for NICE’s guidance on using enzalutamide in the NHS in England.

For further details, see the [Guides to the technology appraisal process](http://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance).**The key dates for this appraisal are:**Closing date for comments: 2 July 2015Second Appraisal Committee meeting: 9 July 2015Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9. |

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* + - 1. Appraisal Committee’s preliminary recommendations
	1. Enzalutamide is not recommended for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, and when chemotherapy is not yet clinically indicated.
	2. People whose treatment with enzalutamide was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
		+ 1. The technology
	3. Enzalutamide (Xtandi, Astellas Pharma) 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’.
	4. The most common adverse reactions of treatment 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.
	5. The cost 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. Had enzalutamide been recommended, this scheme would have provided a simple discount to the list price of enzalutamide 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 would not constitute an excessive administrative burden on the NHS.
		+ 1. The company’s submission

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

* 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 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 participants 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). The majority of people in both arms had an ECOG status of 0 (enzalutamide 67.0%; placebo 69.2%).
	2. The co-primary endpoints in PREVAIL were overall survival (OS) and radiographic progression-free survival. 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 discontinuing treatment, whichever was first. It was planned that to demonstrate a statistically significant treatment effect, the p value for OS should be less than 0.049 and the p value for rPFS should be less than 0.001 at the final analysis. The study was powered on a target hazard ratio of 0.83 for OS (equal to 80% power, based on765 deaths), and 0.57 for progression-free survival (>99% power). The company planned 1 (final) analysis for progression-free survival when 410 patients had evidence of radiographic progression; this was done on 6 May 2012, at which point 439 people had progressed. The company planned 2 analyses of OS; 1 interim 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 could not exceed 0.012 in order for it to be considered statistically significant at an interim analysis for OS. The company performed another (post-‘final’, post hoc) analysis of rPFS at the same time as the interim OS analysis. Following 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 participants and presented an analysis of OS done on 30 June 2014.
	3. Patients remained on the study drug until they experienced disease progression that was radiographically confirmed or a skeletal-related event (SRE), and 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, clinicians would offer chemotherapy, but 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 precise numbers 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.
	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. Overall survival with enzalutamide was longer than with placebo (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). Overall survival 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 therefore 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, which would not be given at this position in the treatment pathway in clinical practice in the UK (see section 3.3) These were the inverse probability of censoring weights (IPCW) and a ‘2-stage method’. Applying these adjustments resulted in a larger OS benefit of enzalutamide relative to placebo than the unadjusted estimates. The Company has stated that the actual data is academic in confidence and cannot be reproduced here.
	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 287 people (44.4%) in the enzalutamide arm and 502 people (59.4%) in the placebo arm had progressed (HR 0.307; 95% CI 0.267 to 0.353; log rank p<0.0001).
	6. In PREVAIL patients continued treatment with the study drug until they reached 2 points:
* their disease progressed, as confirmed by radiologists, or they experienced an SRE, and
* they had started on cytotoxic chemotherapy or an investigational drug for treating prostate cancer.

The company commented that it considered treatment discontinuation 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 discontinue treatment is not made on a single measure of progression alone (such as rPFS). The company did a post-hoc analysis of time to treatment discontinuation (TTD) in PREVAIL. In PREVAIL, 57.8% of people randomised to enzalutamide and 92.7% of people randomised to placebo had discontinued 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).

* 1. 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 SRE. 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 observed only in the placebo group. To estimate a treatment effect for enzalutamide relative to placebo, the company produced a mixed model with a 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.
	2. The overall incidence of adverse events with enzalutamide and placebo were 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 over 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 observed 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 observed 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 (5.6%) people taking enzalutamide and 51 (6.0%) taking placebo discontinued 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. 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 RECIST criteria or death from any cause, whichever was first).
	4. As in PREVAIL, COU-AA-302 had interim and final analyses, but unlike PREVAIL, it was stopped early without the criterion for a statistically significant difference in OS being met. 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 to 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.
	5. 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.
	6. The ERG noted the company’s assertion that 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 radiographic progression (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 may have influenced the decision on whether to continue or stop study treatment.
	7. The ERG commented that the company considered its indirect treatment comparison biased because the control groups in PREVAIL and COU-AA-302 differed in terms of 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

* 1. The company produced a de novo 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 SREs. 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 was applied for utility values and costs.
	2. The model had 3 main health states: stable disease, progressed disease and death. People entered the model with stable disease having had prior 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, people may progress on subsequent treatments. These health states were:
* Post-progression 1: this state included patients who initially had either enzalutamide, abiraterone or best supportive care and having progressed from stable disease, moved on to a second line of treatment but had not yet further progressed. In this state all patients had docetaxel.
* Post-progression 2: this state included patients who initially had best supportive care before docetaxel, and having progressed on docetaxel had moved to a third line of active treatment, but had not yet further progressed. In the base case, the company assumed that all patients had enzalutamide as an active treatment after docetaxel, having had best supportive care before docetaxel. In a scenario analysis it assumed all people had abiraterone rather than enzalutamide.
* Palliative care: this state included patients who had progressed (on docetaxel if their initial treatment was enzalutamide or abiraterone, or on enzalutamide taken after docetaxel if their initial treatment was best supportive care). In this state nobody had active treatment.
	1. The company took estimates of survival and time to treatment discontinuation 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, the company used results from its naive comparison rather than from its indirect treatment comparison to compare the effectiveness of enzalutamide and abiraterone. 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 study had been unblinded for 6 months) and fewer than half of people in both arms had died (the company has 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 estimates from the third interim analysis from COU-AA-302 (55% deaths). As there were no published TTD data from COU-AA-302 the company assumed that rPFS was equivalent to TTD for abiraterone on the basis that rPFS and TTD were similar for enzalutamide in PREVAIL. The OS estimates for enzalutamide and best supportive were adjusted for treatment switching using the IPCW adjustment 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.
	2. To extrapolate the likely rates of discontinuing 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. 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 observations of 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.
	4. 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 model repeated measures approach. The company used the results from this model to determine a baseline utility value 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, 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 an equivalent on-treatment benefit as enzalutamide. The company has stated that the utility values derived from PREVAIL are academic in confidence and cannot be reported here.
	5. As the investigators in PREVAIL collected EQ-5D only from people on-treatment (enzalutamide or placebo before chemotherapy), the company estimated utility values in the progressed health states from the published literature. The company used a weighted average of 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 post progression state 1 (when people had progressed on enzalutamide, abiraterone or best supportive care and were having docetaxel) and 0.612 for post progression state 2 (when people had progressed on best supportive care and docetaxel and 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](http://www.nice.org.uk/guidance/ta316), the company applied an on-treatment utility gain of 0.04 for enzalutamide after docetaxel in people who had best supportive care before docetaxel. The company estimated a utility value of 0.500 for people who had palliative care after progressing on active treatment (Sandblom et al. 2004).
	6. The company incorporated the rates of SREs observed 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 event 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 SRE was applied for 1 month and was derived from EQ-5D data from PREVAIL.
	7. Both enzalutamide and abiraterone have a confidential patient access scheme (price discount) 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 base-case, sensitivity analyses and its own exploratory analyses including both the list price and with the discounts. NICE made the assumption that the cost of abiraterone to the NHS through the cancer drugs fund would be the same as the cost of abiraterone taken after cytotoxic chemotherapy which is provided to the NHS with the patient access scheme discount. The company assumed that the same proportion of people would have concomitant corticosteroids alongside 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 database on pharmaceutical electronic market information 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 £301.56 (NHS reference cost).
	8. In the company’s deterministic base case, best supportive care was associated with 1.657 quality-adjusted life years (QALYs); abiraterone with 2.120 QALYs and enzalutamide with 2.274 QALYs. When the patient access schemes for enzalutamide and abiraterone were included, abiraterone was extendedly dominated by best supportive care and by enzalutamide (meaning that best supportive care or enzalutamide would give more benefit than abiraterone and would also cost less). The incremental cost-effectiveness ratio (ICER) for enzalutamide compared with best supportive care was between £30,000 and £40,000 per QALY gained. NICE cannot report the exact ICERs in this document for the analyses that include both patient access schemes because this could allow the intervention company to back-calculate the exact level of the confidential discount in the abiraterone patient access scheme.
	9. The Company did a sensitivity analysis around its base case (in which it had used list prices for enzalutamide and abiraterone). The Company’s scenario analyses included:
* Using data from different data cut-offs from PREVAIL.
* Changing the assumptions surrounding adjustment for subsequent treatments not used in the NHS in PREVAIL.
* Using different parametric curves to extrapolate OS and progression-free survival.
* Changing the cost assumptions for docetaxel, unscheduled costs and the costs of spinal cord compression.
* Including a Pharmaceutical Payment Regulation Scheme (PPRS) rebate of 10.36%.
* Changing the assumptions surrounding the duration of SREs.
* Assuming people could have abiraterone after docetaxel if they had best supportive care before docetaxel.
* Not including adverse events in the modelling and using data from AFFIRM to derive the utility value for enzalutamide taken after docetaxel.

The ICER for enzalutamide (including the patient access schemes) compared with best supportive care was between £20,000 and £30,000 per QALY gained for the scenarios surrounding docetaxel, unscheduled costs and the PPRS rebate. In all other scenarios the ICERs for enzalutamide (including the patient access schemes) compared with best supportive care were between £30,000 and £40,000 per QALY gained.

* 1. The ERG stated that advice from its clinical specialists was that people who have enzalutamide before docetaxel would be likely to be treated with abiraterone after docetaxel and likewise, people who had abiraterone before docetaxel would be likely to be treated with enzalutamide after docetaxel.
	2. 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 than the September 2013 cut-off because the later data provided more endpoints.
	3. 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 may have influenced a clinician’s or patients’ 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.
	4. 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 observed for enzalutamide but at a later time point. The ERG noted that this implied that patients died 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, as a consequence, 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 ICER estimates than did abiraterone’s earlier-crossing curves.
	5. The ERG commented that in the model, a patient’s probability of dying per cycle was the same in each 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.
	6. 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 was based on quality of life decreasing from baseline with best supportive care but decreasing less so with enzalutamide . 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.
	7. 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 an SRE by pooling both treatment arms. Therefore, the impact of SREs on quality of life may have already been captured in the analysis of quality of life by treatment arm and already reflect any reduction in the rates of SREs with enzalutamide compared with best supportive care.
	8. 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 the 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.
	9. 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 the summary of product characteristics for abiraterone stipulates the frequency of monitoring of 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.
	10. The ERG used its preferred assumptions in the company’s model to produce an ERG exploratory base case including:
* 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’s supply of enzalutamide or abiraterone at a time rather than a 1-weeks’ 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 SREs.
* 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.

In the ERG exploratory base case incorporating these assumptions and the patient access schemes for both drugs, abiraterone remained extendedly dominated by best supportive care. The ICER for enzalutamide compared to best supportive care was between £40,000 and £50,000 per QALY gained.

* 1. Full details of all the evidence are in the [Committee papers](https://www.nice.org.uk/guidance/indevelopment/gid-tag457/documents).
		+ 1. 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 when chemotherapy is not yet clinically 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.

* 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, in whom chemotherapy is not yet clinically indicated. It was aware that enzalutamide, abiraterone and sipuleucel-T are all licensed for use in this condition. The Committee was aware that NICE did not recommend use of sipuleucel-T in its technology appraisal guidance on [sipuleucel‑T for asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer](http://www.nice.org.uk/guidance/ta332) and that a NICE technology appraisal of abiraterone is ongoing. The Committee was further aware that enzalutamide and abiraterone are currently available through the Cancer Drugs Fund for this indication. However, Committee heard from the patient and clinical experts that access to abiraterone varies throughout England. It heard that larger clinical centres have better access to therapies offered by the Cancer Drugs Fund than smaller centres, and that oncologists have better access than urologists. It heard from the clinical experts that people who do not have enzalutamide or abiraterone have best supportive care, and this includes taking corticosteroids. The Committee noted that people with visceral disease cannot have abiraterone, but can have enzalutamide through the Cancer Drugs Fund and people with liver dysfunction cannot have abiraterone, but can take enzalutamide. Additionally because abiraterone is taken with corticosteroids, (prednisone or prednisolone) enzalutamide is more suitable for people who cannot take corticosteroids. The Committee heard from clinical experts that people taking enzalutamide or abiraterone have regular monitoring visits to assess liver function; frequency of monitoring needed for abiraterone is greater than for enzalutamide. The Committee concluded that because NICE has not issued technology appraisal guidance on abiraterone and has not recommended sipuleucel-T taken before cytotoxic chemotherapy, because access to abiraterone through the Cancer Drugs Fund varies, and because there are some people who cannot have abiraterone but can take enzalutamide or best supportive care, the main comparator for enzalutamide is best supportive care.
	2. 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 of great importance to patients because of the side effects associated with chemotherapy. Patients also value having a number of 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 patient experts stated that people would welcome the opportunity to experience the benefits of enzalutamide before cytotoxic chemotherapy. The Committee concluded that enzalutamide is a well-tolerated treatment, and that patients would welcome having more treatment options in order to delay cytotoxic chemotherapy.
	3. The Committee discussed the sequence of treatments people with metastatic hormone-relapsed prostate cancer would have in clinical practice in England. It was aware that NICE technology appraisal guidance [on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen](https://www.nice.org.uk/guidance/ta316) and [abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen](https://www.nice.org.uk/guidance/ta259) recommend enzalutamide and abiraterone as treatment options after docetaxel. The Committee was also aware that the technology appraisal guidance on enzalutamide did not make recommendations on the sequential use of abiraterone and enzalutamide reflecting the Committee’s awareness that patients in AFFIRM, the key trial, had not had previous treatment with abiraterone. Furthermore, the Committee noted that the summary of product characteristics for enzalutamide states that the efficacy of enzalutamide in patients who have previously had abiraterone acetate has not been studied. It further noted that the Cancer Drugs Fund stipulates that enzalutamide should not be used after abiraterone and vice versa unless the first drug had to be stopped within 3 months of use because of toxicity and only when the disease had not further progressed. The Committee heard from the clinical experts that in clinical practice in the UK, enzalutamide is not used after abiraterone and abiraterone is not used after enzalutamide. It heard from the clinical experts that the evidence for the efficacy of enzalutamide taken after abiraterone and 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 or abiraterone before chemotherapy do not have enzalutamide or abiraterone after chemotherapy.

## Clinical effectiveness

* 1. 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 stopped early for benefit, and that the company had presented data both from the interim analysis on which the decision to stop the trial was made, and from what would have been the final analysis in 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 were statistically significant. The Committee was satisfied that the magnitude of the unadjusted hazard ratio estimated from what would have been the final analysis was not affected by the bias that can occur when trials end early for benefit. The Committee was aware that once people progressed on the study drug in PREVAIL, they could move on to subsequent treatments, and 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 noted that the majority of people in PREVAIL went on to have docetaxel after disease progression on the study drug, which reflected the treatment pathway in England. However, it agreed that cabazitaxel and sipuleucel-T are not recommended for prostate cancer in NICE’s technology appraisals [on cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen](https://www.nice.org.uk/guidance/ta255) and [sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer](https://www.nice.org.uk/guidance/ta332). It also agreed that abiraterone, enzalutamide, cabazitaxel and sipuleucel-T prolong life, and if these were disproportionately taken in the placebo group after progression or unblinding by participants in PREVAIL, then the survival estimates for enzalutamide compared with placebo would be biased against enzalutamide. The Committee also agreed that people whose cancer progressed on enzalutamide would not have subsequent abiraterone or enzalutamide, but noted that people whose cancer progressed on placebo (or best supportive care) would have the option to have enzalutamide or abiraterone after docetaxel in clinical practice in England. The Committee noted that both methods used to adjust the OS estimates for the effect of subsequent treatments that are not used in England decreased the hazard ratio (that is, it resulted in a larger difference) for enzalutamide compared with placebo, but that the IPCW method reduced it more. The Committee was aware that the IPCW method assumed that there were no unmeasured confounders affecting the association between moving onto another treatment and mortality. However, the company was not able to tell the Committee during the Committee meeting which confounders the company had included in its models. The Committee agreed that it was appropriate to adjust OS for subsequent active treatments not used in the NHS, and that might prolong life. However, it was not clear which of the 2 methods used by the company (or indeed other possible methods, including marginal structural models and rank preserving structural nested failure time models) would give the most appropriate adjustment and capture the true treatment effect of enzalutamide over best supportive care. The Committee concluded that enzalutamide increased OS compared with placebo, but the extent of the difference was uncertain, and the Committee was unclear whether the company’s choice of adjustment method provided estimates that represented the true difference in survival between enzalutamide and placebo.
	2. The Committee discussed the estimates for progression-free survival 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 progression-free survival in clinical practice. The Committee heard from the clinical experts that the measures of progression used in clinical practice include RECIST (Response Evaluation Criteria In Solid Tumors) radiographic criteria and measuring prostate specific antigen (PSA) levels. The clinical experts stated that PSA measurements were not always reliable and progression of bone metastases, which is common in metastatic prostate cancer, can be difficult to detect radiographically, even with CT scanning. The Committee noted that TTD had been used as a proxy for progression-free survival in other appraisals of hormone-relapsed prostate cancer and may reflect staying on treatment until progression is confirmed. However, it also noted that this measure does not take into account 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 further concluded that although TTD does not take into account discontinuation of treatment as a result of side effects, because enzalutamide is well-tolerated, TTD was a relevant proxy to estimate disease progression and provided the advantage of better capturing costs.
	3. The Committee discussed the clinical effectiveness of enzalutamide relative to abiraterone submitted by the company, noting that there were no head-to-head trials comparing enzalutamide with abiraterone. The Committee noted that the company had done an indirect treatment comparison of enzalutamide with abiraterone using data from the PREVAIL and COU-AA-302. The Committee agreed with the company’s concern that the placebo groups in these trials were not comparable because the marketing authorisation for abiraterone stipulates that abiraterone be given with prednisone or prednisolone, so all people in the placebo arm of COU-AA-302 but only 30% of participants in PREVAIL had corticosteroids. It also agreed the trial populations differed because PREVAIL included people with visceral disease who have a poorer prognosis, whereas COU-AA-302 did not. The Committee heard from the clinical experts that although there is no evidence for an effect of corticosteroids on OS, they are ‘active treatments’. It heard from the clinical experts that time to progression in the placebo arm of COU-AA-302 was greater than in the placebo arm of PREVAIL. The Committee noted that the company had carried out a naïve comparison of the treatment effect of enzalutamide relative to placebo in PREVAIL with the treatment effect of abiraterone relative to placebo in COU-AA-302. The estimated treatment effect for the study drug from each trial (enzalutamide or abiraterone) would not be affected by corticosteroid use because within each trial the same proportion of people were taking corticosteroids in the study drug arm and the placebo arm. The Committee considered that there were limitations to the company’s indirect comparison and it was unclear whether using a naive comparison of the results in the enzalutamide and abiraterone arms from these trials would give more accurate estimates than those from the indirect comparison. However, it accepted the use of the naïve comparison to inform the economic modelling. The Committee further noted that the company had not presented an estimate for OS for abiraterone that had been adjusted for the active treatments people had after abiraterone that are not available on the NHS and that may prolong life, as it had done for enzalutamide (see section 4.4). It considered that it was not unreasonable to expect the effect of enzalutamide and abiraterone on survival to be similar. However, by adjusting for the effects of subsequent therapy not available on the NHS on the effect of enzalutamide, but not on abiraterone, survival estimates from the company inappropriately favoured enzalutamide.

##  Cost effectiveness

* 1. The Committee considered the structure of the company’s economic model. It agreed that people having enzalutamide or abiraterone before chemotherapy would not have abiraterone or enzalutamide 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 and COU-AA-302 to the whole model, meaning that the length of time people had docetaxel or third-line active treatment (for people who initially had best supportive care before docetaxel) did not affect how long patients were modelled to live. It further noted that in the model it was assumed that more than 80% of people would go on to have docetaxel, but in clinical practice in England that figure would be around 40%. The Committee could not judge whether the modelled TTD with docetaxel or enzalutamide (when taken after docetaxel) reflected that observed in clinical practice because the company had not presented clinical data to demonstrate that its modelled estimates were plausible. The Committee also considered that the company’s survival modelling approach meant that people who had more advanced prostate cancer were assumed to have the same risk of death as people who had not progressed on multiple treatments, 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, but that the face validity of the model had not been demonstrated, and there was still uncertainty surrounding whether the time spent on subsequent treatments reflected clinical practice.
	2. The Committee discussed how OS and TTD had been modelled by the company. The Committee noted that 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 the majority of the trial population remained alive and agreed that it was better to extrapolate the June 2014 data because they had a longer follow-up duration, but because of the relative ‘immaturity’ of the June 2014 data, considerable uncertainty remained. The Committee discussed the company’s approach of selecting the parametric curve for extrapolation 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. The Committee considered that the company had selected the parametric curve based on the predicted survival rates rather than the curve with the best statistical fit to the trial data and was concerned that that the company had not done further checks of the face validity of the extrapolated data. For example, the Committee queried why the company had not compared the modelled results with data from trials assessing treatments later in the treatment pathway than PREVAIL or COU-AA-302. The Committee was aware that the company would have had access to the individual patient-level data from the AFFIRM trial of enzalutamide after docetaxel, which could inform the course of patients on first-line best supportive care in this appraisal. The Committee also queried why the company had chosen the same parametric curves to reflect both enzalutamide and best supportive care, when the company’s own statistical analyses suggested that different curves better reflected the course of the disease. The Committee noted that in addition to extrapolating OS, the company had also extrapolated TTD from PREVAIL and progression-free survival data from COU-AA-302 (which did not publish results on TTD). The Committee agreed that it was more appropriate to extrapolate the September 2013 data on TTD from PREVAIL rather than the June 2014 data cut-off because the June 2014 estimates would have the potential to be biased (favouring enzalutamide) by the unblinding of the study. The Committee further noted that for both enzalutamide and abiraterone, the extrapolated OS and TTD curves crossed, which was implausible because it suggested that patients died before their disease progressed. The Committee noted this was a big issue for the abiraterone estimates because the curves crossed sooner for abiraterone than for enzalutamide, and as such biased the model against abiraterone. The Committee concluded that the most appropriate data cut-offs from PREVAIL to use in the model were June 2014 for OS and September 2013 for TTD. It further concluded that although trial data needed to be extrapolated to estimate the average difference in survival because not all patients in the trials had died, the Committee had concerns that the company had not adequately evaluated the uncertainties, and that the face validity of the extrapolation curves selected by the company had not been fully demonstrated.
	3. 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 decreases over time, the Committee did not consider the company’s approach appropriate to add a utility increment for enzalutamide to the estimated utility value before treatment had started. It considered the approach suggested by the ERG, in which the utility decrement over time observed with best supportive care and enzalutamide was subtracted from the starting utility value, to be more appropriate. 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](http://www.nice.org.uk/guidance/ta316). The Committee considered that the AFFIRM data was relevant to determine this utility value. The Committee also noted that the utility assumed by the company for people having palliative care did not match the value reported in the reference (Sandblom et al. 2004) cited by the company. The Company stated at the meeting that it had rounded down the utility value from 0.526 to 0.500. The Committee did not consider rounding of some utility values, but not others, to be appropriate. 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 data for people having enzalutamide after docetaxel.
	4. The Committee queried why the company had presented a scenario analysis that included a 10.36% price rebate claiming to reflect the Pharmaceutical Pricing Regulation Scheme (PPRS). The company could not explain how this value had been calculated. The Committee agreed that without detailed and transparent justification of how the PPRS would affect enzalutamide, it could not include a rebate in the modelling. The Committee then considered more broadly whether it should take into account the consequences of PPRS 2014, and in particular the PPRS payment mechanism, when appraising enzalutamide. The Committee noted NICE’s position statement in this regard, and accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. 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 not relevant when considering the cost effectiveness of enzalutamide.
	5. The Committee noted that the incremental cost-effectiveness ratio (ICER) for enzalutamide compared with best supportive care was between £30,000 and £40,000 per quality-adjusted life year (QALY) gained in the company’s base case and between £40,000 and £50,000 per QALY gained in the ERG’s exploratory base case, when the patient access schemes were applied. It further noted that abiraterone was extendedly dominated by a combination of best supportive care and enzalutamide in both the company’s base case and the ERG’s exploratory base case, meaning that having the option of either best supportive care or enzalutamide was less costly and more effective than abiraterone. The Committee considered the key modelling assumptions that differed in the company’s base case and the ERG’s exploratory base case and concluded 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 an active treatment after docetaxel.
* The ERG’s assumptions on utility values for the stable disease health state and for people having enzalutamide post-docetaxel.
* The ERG’s assumption that data from September 2013 rather than June 2014 should be used to model TTD.
* The ERG’s assumptions on how to determine the number of people having drugs per model cycle and that drugs are prescribed every 4 weeks, rather than weekly.
* The company’s assumptions on the frequency of monitoring visits a person has while on enzalutamide and abiraterone (section 4.1).

The Committee noted that these preferred assumptions combined with the Committee’s concerns about the uncertainty over extrapolating mortality beyond the observations available in PREVAIL and the methods by which the company adjusted the results from PREVAIL, resulted in an ICER for enzalutamide compared with best supportive care above £40,000 per QALY gained, which was above the range that could be considered a cost-effective use of NHS resources.

* 1. The Committee noted that the company did not propose that enzalutamide taken before docetaxel meets 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 (and also the placebo arm of COU-AA-302) 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 criterion for end-of-life 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 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.
	2. 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 was the only treatment option for people with visceral disease and liver dysfunction, for whom abiraterone is contraindicated, or for people who cannot take corticosteroids. 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, in this regard, was innovative. The Committee noted that the patient experts stated that delaying chemotherapy was of great importance to patients. The Committee also acknowledged that delaying chemotherapy may mean some people would no longer be eligible to have chemotherapy, but noted that, despite this possibility, patients 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, but it was unclear whether the benefit of delaying chemotherapy perceived by the patients had been fully captured by the utility values included in the modelling. The Committee concluded that enzalutamide was innovative, but, even taking this into account, could not be considered a cost-effective use of NHS resources. Therefore, the Committee could not recommend enzalutamide for people with metastatic hormone-relapsed prostate cancer for whom chemotherapy is not yet clinically indicated.

## Summary of Appraisal Committee’s key conclusions

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| --- | --- | --- |
| **TAXXX** | **Appraisal title: Enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy is not yet clinically indicated** | **Section** |
| **Key conclusion** |
| Enzalutamide is not recommended for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, and when chemotherapy is not yet clinically indicated.The Committee concluded that with its preferred assumptions the resulting incremental cost-effectiveness ratio (ICER) for enzalutamide compared with best supportive care was above £40,000 per quality-adjusted life years (QALY) gained.The Committee concluded that enzalutamide was innovative, but, even taking this into account, could not be considered a cost-effective use of NHS resources.  | 1.1 4.11 4.13 |
| **Current practice** |
| Clinical need of patients, including the availability of alternative treatments | Enzalutamide is a well-tolerated treatment, and that patients would welcome having more treatment options in order to delay cytotoxic chemotherapy.The Committee was aware that enzalutamide and abiraterone (taken before chemotherapy is clinically indicated) are currently available through the Cancer Drugs Fund. However, Committee heard from the patient and clinical experts that access to abiraterone varies throughout England. | 4.24.1 |
| **The technology** |
| Proposed benefits of the technologyHow innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | Enzalutamide is the only treatment option for people with visceral disease and liver dysfunction, who may not be eligible for abiraterone at this position in the treatment pathway or for people who cannot take corticosteroids. The Committee 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, in this regard, was innovative.  | 4.13 |
| 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, in whom chemotherapy is not yet clinically indicated | 4.1 |
| Adverse reactions | Enzalutamide is a well-tolerated treatment. | 4.2 |
| **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 an adjustment of the trial OS estimates for subsequent treatments taken by people in the trial, but which are not available in the UK, was appropriate.There were no head-to-head trials comparing enzalutamide with abiraterone. The company carried out an indirect treatment comparison and a naïve comparison. The Committee agreed with the company that there were limitations to the indirect comparison because of differences in the placebo controlled groups in the enzalutamide and abiraterone trials, but it was unclear whether using a naive comparison of the results in the enzalutamide and abiraterone arms from these trials would give more accurate estimates. | 4.44.6 |
| Relevance to general clinical practice in the NHS | The Committee was aware that once people progressed on the study drug in PREVAIL, they could move on to subsequent treatments, and 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. The Committee noted that the majority of people in PREVAIL went on to have docetaxel after disease progression on the study drug, which reflected the treatment pathway in England. | 4.4 |
| 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 and it was unclear whether the company’s adjusted estimates represented the true difference in survival between enzalutamide compared with placebo. | 4.4 |
| 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. | 4.4 |
| **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. | 4.7, 4.8 |
| 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 the face validity of the model had not been demonstratedThe Committee had concerns that the company had not adequately evaluated the uncertainties surrounding and the face validity of the extrapolation curves it selected to extrapolate OS and time to treatment discontinuation | 4.74.8 |
| Incorporation of health-related quality-of-life benefits and utility valuesHave 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 perceived by the patients had been fully captured by the utility values included in the modelling. The Committee considered enzalutamide to be innovative. | 4.13 |
| 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 |
| Most likely cost-effectiveness estimate (given as an ICER) | The Committee considered the ICER for enzalutamide compared with best supportive care was above £40,000 per QALY gained. | 4.11 |
| **Additional factors taken into account** |
| Patient access schemes (PPRS)  | The company has agreed a patient access scheme with the Department of Health. If enzalutamide had been recommended, this scheme would have provided a simple discount to the list price of enzalutamide 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 would not constitute an excessive administrative burden on the NHS. | 2.3 |
| End-of-life considerations | 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. | 4.12 |
| Equalities considerations and social value judgements | No equality issues were raised. |  |

* + - 1. Implementation
	1. NICE has developed tools [link to [www.nice.org.uk/guidance/TAXXX](http://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.
	+ - 1. 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](http://www.nice.org.uk).

**Published**

* [Prostate cancer: diagnosis and treatment](http://www.nice.org.uk/guidance/cg175). NICE clinical guideline 175 (2014).
* [Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer](http://www.nice.org.uk/guidance/ta332). NICE technology appraisal guidance 332 (2015).
* [Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen](http://www.nice.org.uk/guidance/ta316). NICE technology appraisal guidance 316 (2014).
* [Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen](http://www.nice.org.uk/guidance/ta259). NICE technology appraisal guidance 259 (2012).
* [Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen](http://www.nice.org.uk/guidance/ta255). NICE technology appraisal guidance 255 (2012).
* [Docetaxel for the treatment of hormone-refractory metastatic prostate cancer](http://www.nice.org.uk/guidance/ta101). 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 July 2015.
* 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.
	+ - 1. Proposed date for review of guidance
	1. NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
May 2015

* + - 1. 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

**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.

**Dr Mary Hughes**
Technical Lead(s)

**Fay McCracken**
Technical Adviser

**Jeremy Powell**
Project Manager

1. 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 are 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