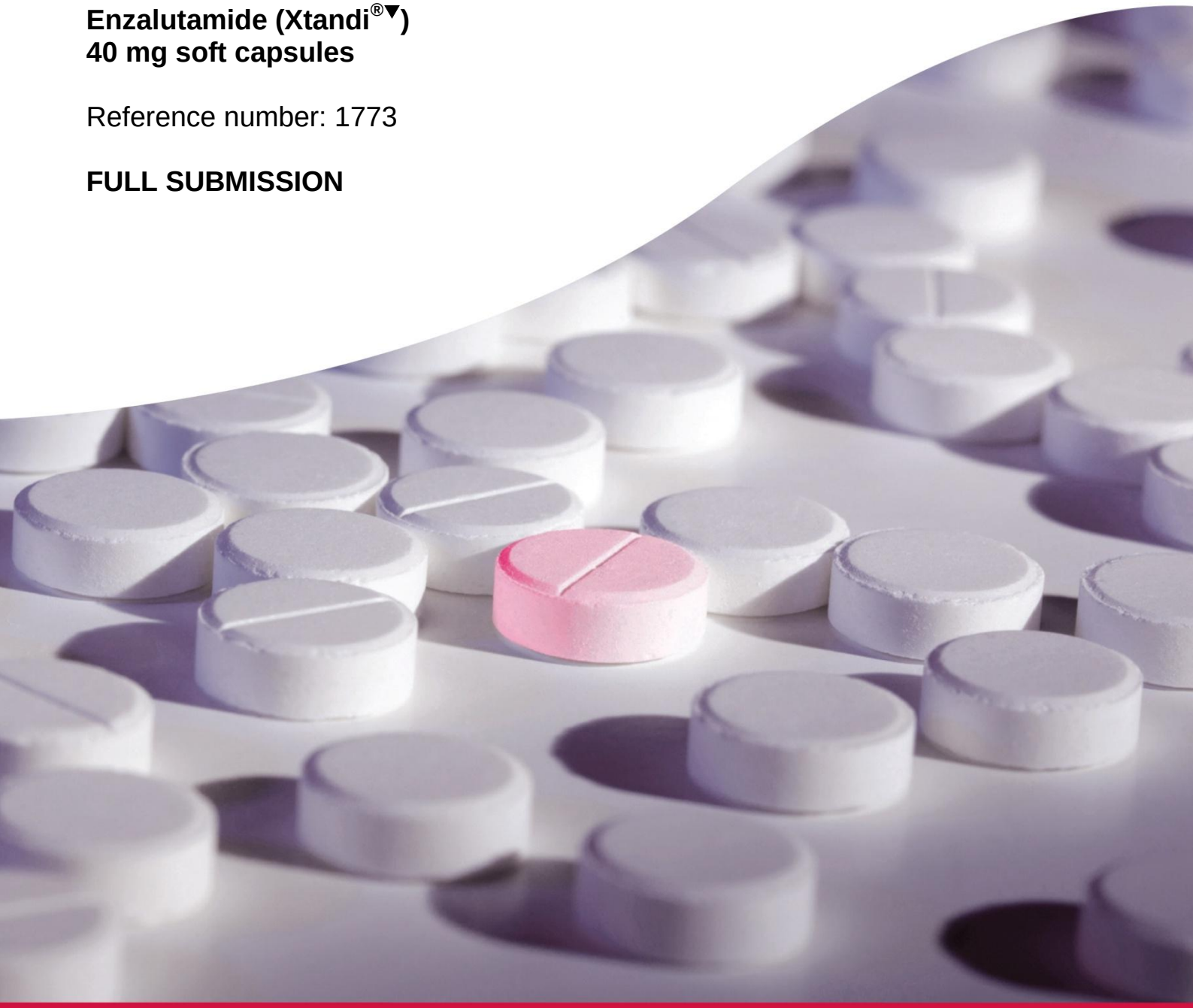
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Enzalutamide (Xtandi®▼)
40 mg soft capsules

Reference number: 1773

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Enzalutamide (Xtandi®▼) 40 mg soft capsules. Reference number: 1773. April 2015.

AWMSG Secretariat Assessment Report
Enzalutamide (Xtandi®▼) 40 mg soft capsules

This assessment report is based on evidence submitted by Astellas Pharma Ltd on 14 January 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Enzalutamide (Xtandi®▼) 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. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	The recommended dose is 160 mg enzalutamide (four 40 mg capsules) as a single oral daily dose. Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated. Refer to the SPC for further dosing information[2].
Marketing authorisation date	28 November 2014[3] (also licensed for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy; 21 June 2013[4]).

2.0 DECISION CONTEXT

2.1 Background

Prostate cancer represents the most common form of male cancer in Wales with 2,634 reported cases in 2013, accounting for approximately 27% of newly diagnosed cancers in men[5]. Although Wales has the highest incidence of prostate cancer in the UK, mortality rates are very similar to those for the whole of the UK (23.3 and 23.8 per 100,000 population in Wales and the UK, respectively)[6]. Metastatic disease occurs in approximately 55–65% of men with prostate cancer, the majority (90%) of who, despite initial effectiveness, eventually become resistant to first-line standard hormone therapy (androgen deprivation therapy) which leads to disease progression[7]. This stage of the disease is described as metastatic castration-resistant prostate cancer (mCRPC) and is associated with poor prognosis. The aim of treatment is to improve symptoms, prolong life and slow disease progression[8].

The treatment of patients with mCRPC often includes anti-androgens (such as bicalutamide, nilutamide or flutamide); however these agents have the potential to stimulate androgen receptor signalling and can accelerate tumour cell growth[9]. Enzalutamide is an oral androgen receptor signalling inhibitor designed to inhibit multiple steps in the androgen receptor signalling pathway resulting in decreased growth of prostate cancer cells; cancer cell death and tumour regression[9].

There are currently two alternative treatments licensed for use in the same chemotherapy-naive indication as enzalutamide, these are abiraterone acetate (Zytiga®▼) and sipuleucel-T (Provenge®). Abiraterone (Zytiga®▼) and sipuleucel-T (Provenge®) are not currently recommended for use in NHS Wales following a negative recommendation from the All Wales Medicines Strategy Group (AWMSG) in September 2014[10] and the National Institute for Health and Care Excellence (NICE) in February 2015[11], respectively. Therefore, the current treatment option for these

patients is best supportive care (BSC); including gonadotrophin-releasing hormone analogues (if not surgically castrated), and corticosteroids, blood transfusion, bisphosphonates, radiotherapy, analgesics and palliative surgery to treat skeletal-related events, when needed[1,12].

2.2 Comparators

The comparator included in the company submission was BSC[1]; abiraterone (Zytiga®▼) was also included in the pharmacoeconomic evaluation.

2.3 Guidance and related advice

- NICE. Single Technology Appraisal (TA) in progress. Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy. Expected publication date: To be confirmed[13].
- NICE. TA 332. Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer (2015)[11].
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines®). Prostate cancer (2014)[14].
- NICE. TA 316. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (2014)[15].
- European Association of Urology. Guidelines on prostate cancer (2014)[16].
- NICE. Clinical Guideline (CG) 175. Prostate cancer: diagnosis and treatment (2014)[12].
- European Society for Medical Oncology (ESMO). Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2013)[17].
- NICE. TA 255. Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (2012)[18].
- NICE. TA 259. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (2012)[19].
- NICE. TA 101. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (2006)[8].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of abiraterone acetate (Zytiga®▼)[10].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included the PREVAIL study which was designed to assess the efficacy and safety of enzalutamide in chemotherapy-naive men with progressive mCRPC who have failed androgen deprivation therapy (ADT; i.e. treatment with a luteinising hormone-releasing hormone [LHRH] analogue or bilateral orchiectomy). The company submission also included data from a placebo-controlled study, which evaluated the safety and efficacy of abiraterone in chemotherapy-naive men with mCRPC (COU-AA-302). This study will not be discussed further because abiraterone is not currently recommended for use in NHS Wales for chemotherapy-naive patients. Due to the lack of comparative data, the company also carried out a systematic literature review; however no additional studies were identified which were relevant to this submssion[1].

3.1 PREVAIL study (MDV3100-03)

This was a randomised, phase III, multi-national, double-blind, placebo-controlled study of enzalutamide in chemotherapy-naive men with progressive mCRPC, who have failed ADT[1,9,20]. Patients were eligible for study inclusion if they had an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1 and were asymptomatic (score of 0–1) or mildly symptomatic (score of 2–3), as measured on the Brief Pain Inventory (BPI) short form. Patients with a history of seizure or a condition that could confer a predisposition to seizure were excluded. Participants (n = 1,717) were

randomised 1:1 to receive either enzalutamide 160 mg (n = 872) or placebo (n = 845) once daily and were allowed, but not required to take prednisone (maximum daily dose 10 mg or equivalent). Treatment was continued (alongside ADT where appropriate) until the occurrence of unacceptable side effects or confirmed disease progression (evidence of radiographic progression, skeletal-related event, or clinical progression). In addition, treatment was discontinued prior to the initiation of cytotoxic chemotherapy or an investigational agent. The median duration of treatment was substantially longer in the enzalutamide group than in the placebo group (16.6 months versus 4.6 months) [1,9,20].

The co-primary endpoints were radiographic progression-free survival (rPFS; defined as the time from randomisation to the first objective evidence of radiographic disease progression or death due to any cause) and overall survival (OS; defined as the time from randomisation to death from any cause)[1,9,20].

At the pre-specified rPFS analysis (data cut-off 410 events) the median rPFS was not reached in the enzalutamide group as compared with 3.9 months in the placebo group[1,9,20]. Enzalutamide demonstrated a statistically significant improvement compared to placebo with a reduction in risk of radiographic progression or death of 81% (hazard ratio [HR]: 0.19; 95% confidence interval [CI]: 0.15–0.23; $p < 0.001$)[20]. A follow up analysis of rPFS was conducted and the median rPFS was 19.7 months for enzalutamide versus 5.4 months for placebo. Enzalutamide reduced the risk of radiographic progression compared to placebo by 69% (HR: 0.31; 95% CI: 0.27–0.35; $p < 0.0001$)[1,9,20].

At the pre-specified interim analysis for OS (data cut-off 540 events) the median OS was 32.4 months and 30.2 months for patients taking enzalutamide and placebo, respectively[1,9,20]. Enzalutamide demonstrated a statistically significant improvement compared to placebo with a reduction in risk of death of 29% (HR: 0.71; 95% CI: 0.60–0.84; $p < 0.001$)[20]. Following a post-hoc analysis at a mature data cut-off (775 events) the median OS was 33.5 months and 31.0 months in the enzalutamide and placebo groups, respectively. Enzalutamide significantly reduced the risk of death by 24% (HR: 0.76; 95% CI: 0.66–0.88; $p < 0.001$)[1,9,20].

The benefit of enzalutamide was also shown to be statistically significant with respect to all secondary endpoints (see Table 1), including the time until initiation of cytotoxic chemotherapy, the time until first skeletal-related event, a complete or partial soft tissue response, the time until PSA progression and the rate of decline of ≥ 50% in PSA[1,9,20]. Health-related quality of life (HRQoL), was a pre-specified exploratory endpoint and showed enzalutamide to be associated with a statistically significantly better HRQoL[1,9,20].

Table 1. Key efficacy outcomes for the PREVAIL study[1,9,20,21]

		Enzalutamide	Placebo	HR (95% CI) or difference in response rates (95% CI)	p-value
Co-primary efficacy endpoints					
OS	Median OS (months)	32.4	30.2	0.71 (0.60–0.84)	< 0.0001
	Deaths, n/N (%)*	241/872 (27.6%)	299/845 (35.4%)		
rPFS	Median rPFS (months)	NYR	3.9	0.19 (0.15–0.23)†	< 0.0001
	Events, n/N (%)*†	118/832 (14.2%)	321/801 (40.1%)		
Secondary efficacy endpoints					
SRE	Median time to first SRE (months)	31.1	31.3	0.72 (0.61–0.84)	< 0.0001
	Events, n/N (%)*	278/872 (31.9%)	309/845 (36.6%)		
Initiation of cytotoxic chemotherapy	Median time (months)	28.0	10.8	0.35 (0.30–0.40)	< 0.0001
	Events, n/N (%)*	308/872 (35.3%)	515/845 (60.9%)		
PSA progression	Median time to PSA progression (months)	11.2	2.8	0.17 (0.15–0.20)	< 0.0001
	Events, n/N (%)*	532/872 (61.0%)	548/845 (64.9%)		
PSA response ≥ 50%	Responders (≥ 50% reduction), n/N (%)**	666/854 (78.0%)	27/777 (3.5%)	74.5% (71.5–77.6%)	< 0.0001
Best overall soft tissue response	Best objective response (CR or PR)¶	233/396 (58.8%)	19/381 (5.0%)	53.9% (48.5–59.2%)	< 0.0001
Exploratory efficacy endpoint					
HRQoL	Median time to degradation of FACT-P (months)	11.3	5.6	0.625 (0.54–0.72)	< 0.0001
	Events, n/N (%)	456/872 (52.3%)	409/845 (48.4%)		

CI: confidence interval; CR: complete response; FACT-P: Functional Assessment of Cancer Therapy Prostate; HR: hazard ratio; NYR: not yet reached; OS: overall survival; PR: partial response; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival; SRE: skeletal-related event

The interim analysis data cut-off date was 16 September 2013 for all efficacy analyses except rPFS that used the final analysis cut-off date of 6 May 2012.

* Number of events observed on or prior to analysis data cut-off/ITT population. HR and its 95% CI from a Cox proportional hazards model with treatment group as covariate. P-value from an unstratified log-rank test.

† Based on earliest contributing event (radiographic progression or death due to any cause within 168 days after treatment discontinuation).

¶ Based on investigator assessment of target, non-target, and new lesions.

** Confirmation required a subsequent consecutive assessment conducted at least three weeks later

3.2 Safety

In the PREVAIL study almost all patients (97% [844/871] in the enzalutamide group versus 93% [787/844] in the placebo group) experienced at least one adverse event (AE)[1,9,20]. The types of AEs (all grades) reported by patients in the two treatment groups were similar. The median reporting period for AEs was 17.1 months and 5.4 months in the enzalutamide and placebo groups, respectively. Enzalutamide-treated patients had a higher incidence of AEs that were ≥ grade 3 (enzalutamide: 43% [374/871]; placebo: 37% [313/844]). This was also true for serious AEs (SAEs; enzalutamide: 32% [279/871]; placebo: 27% [226/844]); however, the difference between groups is primarily due to the longer duration of exposure in the enzalutamide group. The median time to first AE that was ≥ grade 3 or first SAE were longer in the enzalutamide group than in the placebo group (AE ≥ grade 3: 22.3 months versus 13.3 months; SAE: not yet reached versus 23.3 months)[1,9,20].

AEs occurring in > 20% of patients receiving enzalutamide were fatigue, back pain, constipation and arthralgia[20]. The most common grade ≥ 3 AE in the enzalutamide group was hypertension (7%); the most common cardiac event was atrial fibrillation (enzalutamide: 2%; placebo: 1%). One patient in each group had a seizure[20]. The overall incidence of AEs that were the primary reason for treatment discontinuation and AEs leading to death were similar between treatment groups[1]. There was no evidence of hepatotoxicity, as measured by AEs or laboratory assessments, in the enzalutamide group[1,20].

The number of deaths due to disease progression in the enzalutamide group were lower than in the placebo group (21% versus 27%)[22].

When adjusted for the longer exposure to treatment, the AEs that occurred more frequently with enzalutamide than with placebo included hot flush, hypertension, fall and dysgeusia[1,20,21]. AEs ≥ grade 3 that were more commonly reported with enzalutamide than with placebo, after adjusting for longer exposure, were cataracts and hypertension[1,20,21].

3.3 AWTTC critique

- The Committee for Medicinal Products for Human Use (CHMP) concluded that treatment with enzalutamide significantly reduced the risk of death in patients with mCRPC who are not yet candidates for docetaxel-chemotherapy. This positive and robust finding is accompanied by a meaningful delay in disease progression. In addition, other clinical endpoints such as time to the initiation of chemotherapy, time to skeletal-related events and PSA response all support the main outcomes[9].
- Following the interim analysis on OS, the study was stopped because of the statistically and clinically significant benefit of enzalutamide over placebo, thus allowing patients in the placebo group to receive enzalutamide[1,9,20]. Therefore, the data obtained from the post-hoc analysis at a mature data cut-off should be interpreted with caution[9].
- For treatment with enzalutamide the concurrent use of glucocorticoids (i.e. prednisolone) is permitted but not required[2,9,20]. The use of abiraterone acetate (Zytiga®▼) in this indication requires administration with a glucocorticoid[23].
- Tolerability is of main importance in advanced cancer disease[9]. Abiraterone acetate (Zytiga®▼) is associated with liver toxicity[19]; however, in the PREVAIL study, enzalutamide-treated patients showed no evidence of hepatotoxicity, as measured by AEs or laboratory assessments[20].
- At the time of authoring this report, abiraterone acetate (Zytiga®▼) is undergoing Health Technology Assessment (HTA) by NICE for this indication[13].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of enzalutamide for the treatment of adult men with mCRPC, who are asymptomatic or mildly symptomatic after failure of ADT, in whom chemotherapy is not yet clinically indicated[1]. The company considers the primary comparator to be watchful waiting/BSC, which may include LHRH analogues (if not surgically castrated), corticosteroids, blood transfusions, bisphosphonates, radiotherapy, analgesics and palliative surgery, as per the placebo arm of the PREVAIL study. A comparison against abiraterone, which is also licensed for this indication[23], has been conducted as a secondary comparison; however, as abiraterone is not recommended by AWMSG for use in NHS Wales[10], the primary comparison against BSC is most relevant to the decision problem and is the focus of the discussion of the company's economic evidence.

The analysis is based on a lifetime (10-year) Markov model. Patients enter the model in a progression-free state having received prior ADT, and can receive enzalutamide or BSC as a first-line therapy. Upon disease progression, patients may receive docetaxel as a second-line therapy. Upon further progression they may receive enzalutamide or abiraterone (depending on their first-line therapy) as third-line therapy, followed by palliative care or, for those who receive BSC as first-line therapy, fourth-line abiraterone followed by palliative care[1].

Transitions between health states in the model are defined by OS and time to treatment discontinuation (TTD) curves for enzalutamide and BSC. The proportion of patients progressing from the PFS state to a progressed state is modelled as the difference between the OS and TTD (PFS) curves, which have each been extrapolated over the model lifetime. OS and TTD data for enzalutamide and BSC were derived from the enzalutamide and placebo-arms of the PREVAIL study, with adjustment for patient crossover to other active treatments that are not routinely available in NHS Wales. The proportion of patients moving to second-line docetaxel treatment is based on the data from the PREVAIL study. Treatment discontinuations for docetaxel and subsequent lines of therapy are derived from median treatment durations in key trials of those agents, or assumptions that these data apply.

Rates of AEs with a severity ≥ grade 3 and an incidence ≥ 2% in the trials for any treatment group were included. SREs (spinal cord compression, pathological bone fractures, radiation to the bone, and surgery to the bone) are specifically included based on PREVAIL data in the PFS state, and based on abiraterone post-chemotherapy trial data in the post-progression states, assuming equal rates for abiraterone and enzalutamide.

Enzalutamide acquisition costs are based on a Department of Health agreed Patient Access Scheme (PAS), which provides a confidential discount on the list price. Resource use associated with monitoring is based on a previous technology appraisal of enzalutamide[15] and the Summaries of Product Characteristics recommendations[2,23], and costed with published unit costs. Concomitant medication use is based on that observed in the PREVAIL study. Progressive disease state costs are based on medication, administration and monitoring costs of the sequential lines of therapy, and include palliative and terminal care costs, based on previous estimates in the literature[24] and a technology appraisal of abiraterone in the post-chemotherapy setting[19]. AE and SRE costs are based on NHS reference costs.

Utility values for the PFS state are based on EQ-5D data collected during the PREVAIL study. A utility increment over BSC while on first-line enzalutamide or abiraterone treatment is assumed. Disutilities associated with SREs are also derived from the

PREVAIL data, while (dis)utility values for progressed states, and for the AEs and their assumed durations, are based on several sources from the literature and the technology appraisal of abiraterone in the post-chemotherapy setting[19].

Cost and outcomes beyond one year are discounted at 3.5% per annum.

4.1.2 Results

The results of the base case analyses are presented in Table 2. Compared with the primary comparator BSC, enzalutamide had an incremental cost per QALY gained of [commercial in confidence data removed], based on additional costs of around [commercial in confidence data removed] and a gain of [commercial in confidence data removed] QALYs. The main drivers of the results are the greater acquisition cost of enzalutamide and the longer PFS with enzalutamide, which as modelled maintains patients at a higher quality of life for longer than the comparator.

Table 2. Base case CUA results over 10-year (lifetime) horizon[1]

	Enzalutamide	BSC	Key plausibility considerations
Medicine acquisition cost	¶¶	¶¶	• TTD from PREVAIL used to reflect PFS state, but only 70.4% of discontinuations on enzalutamide and 73.7% of discontinuations on BSC were due to disease progression[9]. • Possibility of reduced effect of second- or subsequent lines of therapy following enzalutamide treatment[9] or abiraterone not considered. • Data adjusted for treatment crossover. Extrapolation for short term OS data in long term. • Baseline utility value for PFS appears high relative to usually-quoted mean estimates for population norms[25].
Other costs	£23,499	£33,946	
Total costs	¶¶	¶¶	
LYG	¶¶	¶¶	
QALYS	¶¶	¶¶	
ICER (enzalutamide vs. BSC)	¶¶		
Probability ICER < 20,000/QALY	**0%**		
Probability ICER < £30,000/QALY	**57%**		

BSC: best supportive care; ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained); LYG: life years gained; PFS: progression-free survival; QALY: quality-adjusted life years; TTD: time to discontinuation

¶¶ Commercial in confidence figures removed

In probabilistic sensitivity analyses, the probability of enzalutamide having an incremental cost per QALY gained below £20,000 was 0%, and below £30,000 was 57% compared with BSC.

A wide range of one-way sensitivity and scenario analyses were conducted to explore parameter uncertainty and assumptions on treatment switching and survival modelling. Analyses for which the incremental cost-effectiveness ratio (ICER) estimates were most sensitive are presented in Table 3.

Table 3. Key sensitivity/scenario analyses

Scenario description	Scenario details	Incremental cost per QALY	Key plausibility considerations
Alternative discount on list price of enzalutamide	¶¶	¶¶	Demonstrates the sensitivity of the ICER estimate to assumed price of enzalutamide. However, the PAS price of enzalutamide is fixed
% patients on first-line BSC receiving second-line treatment with docetaxel	54% to 81%	¶¶	Base case assume 55% on enzalutamide and 68% on BSC go on to receive second-line treatment, based on adjusted analyses of PREVAIL. Model outputs sensitive to proportion of patients assumed to move on to second-line treatment. Unclear which assumed value most plausible, but the lower the proportion for enzalutamide relative to BSC, the greater the ICER estimate.
Same % all patients receiving second-line treatment with docetaxel	62% to 85%	¶¶	
Shorter treatment durations	Only enzalutamide shorter: Enzalutamide: 12.3 months BSC: 5.7 months	¶¶	Company suggests first-line treatment duration in practice could be shorter than in the study, based on market research for abiraterone tretament duration. ICER sensitive to assumed treatment durations – Shorter treatment duration for enzalutamide only (BSC duration same as base case) increases ICER. Reduction in duration of treatment with both marginally reduces ICER
	Both enzalutamide and BSC shorter: Enzalutamide: 12.3 months BSC: 3.7 months	¶¶	
Alternative OS data and extrapolation	Gamma distribution instead of Weibull	¶¶	Demonstrate uncertainty associated with extrapolation methods and adjustment for crossover. Base case is more favourable vs. BSC. However, not clear these alternative approaches are more plausible.
	Weibull unadjusted for treatment crossover	¶¶	
	Alternative adjustment method (2 stage)	¶¶	
Alternative TTD (PFS) data and extrapolation	rPFS, September 2013, Weibull function (instead of TTD, June 2014, Gamma function)	¶¶	Demonstrate uncertainty associated with approach to modelling PFS and extrapolation methods. Base case assumptions generate more favourable ICER vs. BSC but unclear that Weibull function clinically plausible as results in higher proportion of patients remaining on first-line treatment a five years

ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained); PFS: progression-free survival; rPFS: radiographic progression-free survival; QALY: quality-adjusted life years; TTD: time to discontinuation

* dominant: more effective and less costly than comparator
¶¶ Commercial in confidence figures removed

4.1.3 AWTTC critique

At the time of writing, the comparison of enzalutamide versus BSC appears to be the most relevant to address the decision problem.

The model structure appears to be appropriate. Clinical efficacy data for enzalutamide are derived from a placebo-controlled trial, which was terminated following interim analyses demonstrating superior efficacy. Uncertainties in the modelled efficacy of enzalutamide and BSC relate to the use of TTD as a proxy for duration of PFS, and OS data are adjusted for treatment crossover and extrapolated over the long-term; sensitivity and scenario analyses demonstrate the ICER estimates are sensitive to the approaches employed to model these. Other uncertainties, which individually have the potential to increase the ICER estimate above £30,000/QALY, include the assumed duration of enzalutamide treatment and the baseline utility value assumed for progression-free patients. Collectively, it is plausible that the ICER could be larger than that estimated in the base case analysis.

Key strengths of the economic evidence include:

- The company has made efforts to address the limitations of the available efficacy data for enzalutamide arising from the termination of the trial at interim analysis and treatment crossover.
- A wide range of sensitivity and scenario analyses have been conducted to explore the impact of key assumptions required in the modelling.

Key limitations and uncertainties in the economic evidence include:

- Uncertainties exist in the modelled relative treatment efficacy of enzalutamide and BSC. Individually and collectively, the ICER estimates are sensitive to these uncertainties:
    - Treatment crossover has the potential to confound the OS data. Different methods of handling treatment crossover have been explored and the ICER estimates are sensitive to these.
    - The company has used TTD as a proxy for PFS on the basis that rPFS alone (a co-primary endpoint of the PREVAIL study) would not adequately determine disease progression and prompt treatment switching in practice; however, a large proportion of patients in the PREVAIL study discontinued treatment for reasons other than progression (only 70.4% on enzalutamide and 73.7% on BSC discontinued due to progression[9]), which introduces uncertainty into the assumed time in a PFS state in the model and time to initiation of second-line docetaxel. Time in PFS is the key driver of the greater effectiveness of enzalutamide as modelled. The company suggests treatment duration may be shorter in practice than observed in the PREVAIL study, and an alternative scenario limiting enzalutamide treatment duration to 12.3 months (but retaining base case BSC duration) increases the ICER vs. BSC to [commercial in confidence data removed]/QALY.
    - Relatively short-term survival data are extrapolated in the long-term.
    - Second- and subsequent lines of therapy also contribute to the overall ICER estimates. The EPAR notes that treatment efficacy was less favourable in enzalutamide-treated patients who received subsequent treatment with docetaxel, and a possible cross-resistance between treatments cannot be ruled out[9]. Second-line docetaxel efficacy is modelled using published trial data, which does not account for a possible reduced docetaxel treatment duration following enzalutamide treatment in practice. Whilst this may overestimate docetaxel-related costs, it may also overestimate the total QALY gains with enzalutamide relative to BSC. The net impact of this on the ICER is unclear.

- Utility data for PFS states are derived from EQ-5D data collected in the PREVAIL study. Trial-based EQ-5D data are normally preferred over other external sources; however, the baseline utility value of [commercial in confidence data removed], which is applied throughout the PFS state, is somewhat greater than the usually-quoted mean estimates of population norms for this age group (mean values in range 0.78 to 0.75 for males aged 65 to > 75 years[25]). A key driver of the ICER is the longer PFS with enzalutamide, which as modelled maintains patients at a higher quality of life for longer than the comparator. The company has explored a narrow range of alternative utility values, but the range does not cover the usually quoted mean values. AWTTC analyses indicate that the ICER would increase to [commercial in confidence data removed]/QALY using the usually-quoted mean population norm utility values for mean aged 65 years and over.
- The secondary comparison against abiraterone is of limited relevance to the current decision problem. Compared with abiraterone, enzalutamide had an incremental cost per QALY gained of [commercial in confidence data removed], based on additional costs of around £1,000 and a gain of [commercial in confidence data removed] QALYs. The analysis relies on unadjusted, indirect comparison of trial data, as baseline characteristics of patients enrolled in each trial were deemed to be too different to provide meaningful adjusted indirect comparisons. Unadjusted comparisons are subject to potential bias and uncertainties, which would be further compounded by the use of different outcome measures extracted for enzalutamide (TTD) and abiraterone (rPFS) to reflect time to disease progression. Results of that analysis are also based on an assumed price of abiraterone that is subject to uncertainty. Therefore there are a range of additional uncertainties relating to that analysis.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost-effectiveness analyses of enzalutamide in the pre-chemotherapy setting of reliance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on market research data, the company estimates there would be 619 mCRPC patients in Wales in 2015. Based on a previous technology appraisal of abiraterone in the pre-chemotherapy setting[13], the company reports 60% of patients are chemotherapy-naive[26], and of these, 76% are estimated to be asymptomatic or mildly symptomatic based on a US patients survey[27]. Therefore, the company estimates there would be 282 patients potentially eligible for enzalutamide treatment in Wales in 2015. Uptake in 2015 is estimated to be 40%, rising to 80% by 2019.

Two scenarios are considered: enzalutamide is assumed to replace either BSC, or abiraterone in all eligible patients. Enzalutamide acquisition costs are based on a PAS-agreed confidential discount on the list price. The acquisition cost of abiraterone as a comparator is assumed to be the same as for enzalutamide. It is assumed that patients receive only one year of treatment. Other resource use and costs associated with treatment monitoring and concomitant medication are derived from the company's economic model.

5.1.2 Results

The company estimates the net budget impact in Wales 2015-19 as in Table 4. For 2015, only 50% of the company's assumed uptake is included in the estimates to reflect the assumed timing of positive AWMSG guidance.

Table 4. Company estimates of net cost implications associated with use of enzalutamide in the pre-chemotherapy setting, versus BSC

	2015	2016	2017	2018	2019
Number of eligible patients	141	288	293	299	304
Uptake (%)	40%	50%	60%	70%	80%
Treated patients	56	144	176	209	243
Comparison vs. BSC					
Medicine acquisition costs vs. BSC	¶¶	¶¶	¶¶	¶¶	¶¶
Monitoring costs vs. BSC	–£35,278	–£90,716	–£110,875	–£131,664	–£153,083
Concomitant medication costs vs. BSC	–£1,835	–£4,717	–£5,766	–£6,847	–£7,961
Total net cost vs. BSC	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶ Commercial in confidence figures removed

Compared with abiraterone, the company estimates total cost savings of £26,732 in 2015, rising to –£155,998 per year in 2019.

Sensitivity analyses included variation in the number of patients estimated to be treated with enzalutamide in the range +/- 10%, with results as would be expected.

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of patients eligible for treatment with enzalutamide.
- The company includes abiraterone as a comparator in the budget impact analysis and [commercial in confidence data removed]; however, abiraterone is not currently recommended for use in this indication in NHS Wales[10]. A NICE technology appraisal of abiraterone in this indication is in process pending a review of the current PAS for abiraterone. Estimated cost savings are subject to uncertainty.
- The company has assumed treatment with enzalutamide and abiraterone for one year only, based on market research demonstrating treatment with abiraterone in practice may be shorter than observed in the trial; however, median exposure to enzalutamide in the PREVAIL study was 16.6 months. The company has not explored the budget impact based on alternative treatment durations.
- It should be noted that the cost savings due to differences in monitoring, as incorporated in the economic model, reflect opportunity costs rather than financial costs. There is no evidence to suggest that these would be realised as budgetary cost savings in practice.
- Collectively, the company's budget impact estimates are subject to uncertainty and would appear to underestimate the net costs compared with BSC and overestimate the net savings compared with abiraterone.

5.2 Comparative unit costs

Based on its current list price[28], enzalutamide would have an annual cost per patient treated of £35,650 (excluding VAT). A PAS provides enzalutamide to the NHS at a confidential discount on its list price.

The only other agents licensed specifically for use in this patient population are abiraterone and sipuleucel-T, neither of which are currently recommended for use in NHS Wales. Based on current list prices, the annual cost per patient treated with

abiraterone is the same as for enzalutamide. Sipuleucel-T is not currently available in the UK.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, enzalutamide (Xtandi®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that enzalutamide (Xtandi®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 3 February 2015
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Astellas Pharma Ltd. Form B: Detailed appraisal submission. Enzalutamide (Xtandi®▼). Jan 2015.
2 Astellas Pharma Ltd. Xtandi®▼. Summary of Product Characteristics. Jan 2015. Available at: http://www.medicines.org.uk/emc/medicine/27912. Accessed Feb 2015.
3 European Medicines Agency. Xtandi®▼. Procedural steps taken and scientific information after the authorisation. Jan 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/002639/WC500176824.pdf. Accessed Feb 2015.
4 European Medicines Agency. Authorisation details. Xtandi®▼. Jun 2014. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002639/human_med_001663.jsp&mid=WC0b01ac058001d124. Accessed Feb 2015.
5 Welsh Cancer Intelligence and Surveillance Unit. Cancer in Wales: A summary report of the population cancer incidence, mortality and survival. Feb 2015. Available at: http://www.wcisu.wales.nhs.uk/sitesplus/documents/1111/WCISU%20Official%20Stats%20Report%20Final%20English.pdf. Accessed Feb 2015.
6 Office for National Statistics. Statistical Bulletin: Cancer incidence and mortality in the United Kingdom, 2008-10. Dec 2012. Available at: http://www.ons.gov.uk/ons/dcp171778_289890.pdf. Accessed Feb 2015.
7 National Institute for Health and Care Excellence. Single Technology Appraisal. Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. Final scope. Nov 2014. Available at: http://www.nice.org.uk/guidance/indevelopment/gid-tag457/documents. Accessed Feb 2015.
8 National Institute for Health and Care Excellence. Technology Appraisal 101. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. Jun 2006. Available at: http://www.nice.org.uk/guidance/ta101. Accessed Feb 2015.
9 European Medicines Agency. Assessment Report for Xtandi®▼. Procedure No.: EMEA/H/C/002639/II/0008. Oct 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002639/WC500180617.pdf. Accessed Feb 2015.
10 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1794. Abiraterone acetate (Zytiga®) 250 mg tablets. Jun 2014. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1794. Accessed Feb 2015.
11 National Institute for Health and Care Excellence. Technology Appraisal 332. Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer. Feb 2015. Available at: http://www.nice.org.uk/guidance/ta332. Accessed Feb 2015.
12 National Institute for Health and Care Excellence. Clinical Guideline 175. Prostate cancer: diagnosis and treatment. Jan 2014. Available at: http://www.nice.org.uk/guidance/cg175. Accessed Feb 2015.
13 National Institute for Health and Care Excellence. Prostate cancer (metastatic, hormone relapsed, not treated with chemotherapy) - abiraterone acetate (with prednisolone) [ID503]. Sep 2014. Available at: http://www.nice.org.uk/guidance/indevelopment/gid-tag434. Accessed Feb 2015.

14 Mohler JL, Armstrong AJ, Bahnson RR et al. NCCN clinical practice guidelines in oncology (NCCN guidelines®). Prostate cancer. Oct 2014. Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed Feb 2015.
15 National Institute for Health and Care Excellence. Technology Appraisal 316. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Jul 2014. Available at: http://www.nice.org.uk/guidance/ta316. Accessed Feb 2015.
16 Mottet N, Bastian PJ, Bellmunt J et al. European Association of Urology. Guidelines on prostate cancer. Apr 2014. Available at: http://www.uroweb.org/gls/pdf/09%20Prostate%20Cancer_LRLV2.pdf. Accessed Feb 2015.
17 Horwich A, Parker C, de Reijke T et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2013; 24 (6): vi106-vi114.
18 National Institute for Health and Care Excellence. Technology Appraisal 255. Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. May 2012. Available at: http://www.nice.org.uk/guidance/ta255. Accessed Feb 2015.
19 National Institute for Health and Care Excellence. Technology Appraisal 259. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. Jun 2012. Available at: http://www.nice.org.uk/guidance/ta259. Accessed Feb 2015.
20 Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *The New England Journal of Medicine* 2014; 371 (5): 424-33.
21 Medivation Inc, Astellas Pharma Ltd. Clinical Study Report: PREVAIL. A multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy. Feb 2014.
22 European Medicines Agency. Assessment Report for Spedra®▼. Procedure No.: EMEA/H/C/002581/0000. Apr 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002581/WC500145207.pdf. Accessed Feb 2015.
23 Janssen-Cilag Ltd. Zytiga®▼. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/24976. Accessed Feb 2015.
24 Guest JF, Ruiz FJ, Greener MJ et al. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *European Journal of Cancer Care* 2006; 15 (1): 65-73.
25 Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Nov 1999. Available at: https://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf. Accessed Mar 2015.
26 Janssen-Cilag Ltd. National Institute for Health and Care Excellence (NICE). Manufacturer submission for abiraterone acetate: Abiraterone acetate (Zytiga®) for the treatment of metastatic castration-resistant prostate cancer in men not previously treated with chemotherapy. Single Technology Appraisal (STA). Feb 2014. Available at: http://www.nice.org.uk/guidance/gid-tag434/documents/prostate-cancer-metastatic-hormone-relapsed-not-treated-with-chemotherapy-abiraterone-acetate-with-prednisolone-id503-evaluation-report2. Accessed Mar 2015.

27 Autio KA, Bennett AV, Jia X et al. Prevalence of pain and analgesic use in men with metastatic prostate cancer using a patient-reported outcome measure. *Journal of Oncology Practice/American Society of Clinical Oncology* 2013; 9 (5): 223112-229.
28 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Feb 2015. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Mar 2015.