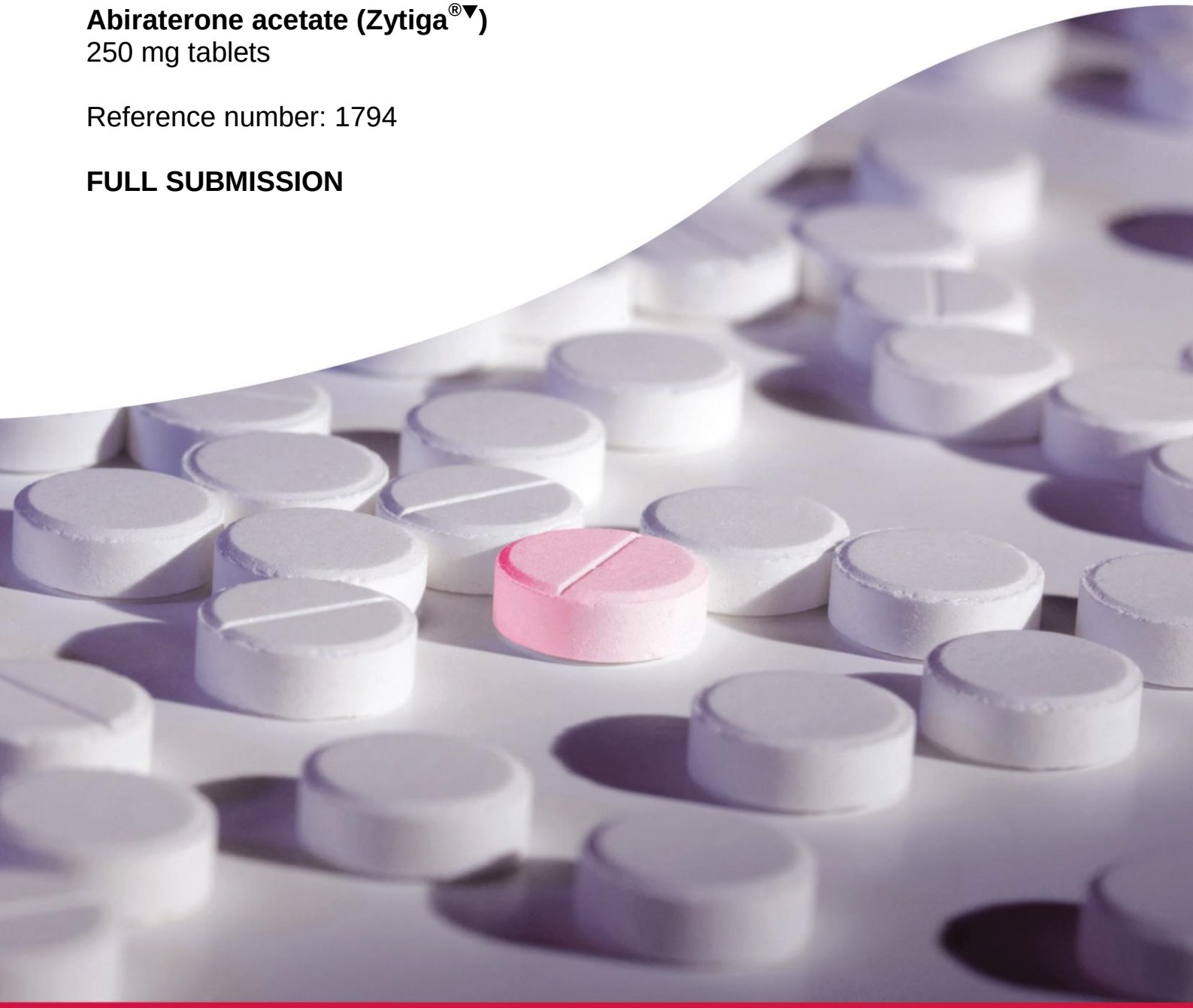
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Abiraterone acetate (Zytiga®▼)
250 mg tablets

Reference number: 1794

FULL SUBMISSION



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Abiraterone acetate (Zytiga®▼) 250 mg tablets

This assessment report is based on evidence submitted by Janssen-Cilag Ltd on 13 December 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Abiraterone acetate (Zytiga®▼) is indicated with prednisone or prednisolone* for the treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated[2].
Dosing	The recommended dose is 1,000 mg (four 250 mg tablets) taken as a single daily dose. Tablets should be taken at least two hours after eating and no food should be eaten for at least one hour thereafter. The recommended dose of prednisolone is 10 mg daily. Refer to the Summary of Product Characteristics (SPC) for further information on routine monitoring[2].
Marketing authorisation date	Date of licence extension 18 December 2012 (licensed for original indication on 5 September 2011)[3].

2.0 DECISION CONTEXT

2.1 Background

Prostate cancer represents the most common form of male cancer in the UK and Wales, accounting for 24.8% and 26.4% of all cancers in men, respectively[4]. While prostate cancer age-standardised mortality rates are similar across the UK, the incident rate varies from 90 new cases per 100,000 men in Scotland, to 116 new cases per 100,000 men in Wales (UK average: 105 new cases per 100,000 men)[4]. However, it has been suggested that such variations may relate to the differences in uptake of Prostate Specific Antigen (PSA) testing, and therefore differences in levels of diagnosis rather than true incidence of prostate cancer[5]. Metastatic disease occurs in approximately 55–65% of men with prostate cancer, the majority (90%) of whom, despite initial effectiveness, eventually become resistant to first line standard hormone therapy (androgen deprivation therapy)[6]. This stage of the disease is described as metastatic castration-resistant prostate cancer (mCRPC) and is associated with a poor prognosis. Providing estimates of overall survival in this patient population is complicated by changes in the definition of the disease. Previous estimates indicated an overall survival of 9-12 months[7]. However earlier diagnosis, advancements in treatments and changes in terminology suggest that overall survival is likely to be higher than previous estimates.

* Abiraterone acetate would be prescribed with prednisolone as prednisone is not used in NHS Wales.

Prostate cancer is an androgen-receptor dependent disease. Preventing the action of androgens has been the standard treatment for men with prostate cancer providing symptom relief and tumour regression in most (80%) patients; however, androgen-receptor signalling can reactivate in advanced cases indicating a transition to a castration-resistant state[7]. Current NICE clinical guidelines recommend docetaxel (in combination with prednisone or prednisolone) as first line chemotherapy for mCRPC associated with a Karnofsky performance-status score of 60% or more[7,8]. In 2012, the All Wales Medicines Strategy Group (AWMSG), and subsequently the National Institute of Health and Care Excellence (NICE), recommended abiraterone acetate for the treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen[9,10].

Abiraterone acetate is an inhibitor of the enzyme cytochrome P450c17 (CYP17), which is required for androgen biosynthesis in several tissues; overexpression of CYP17 represents one pathway by which mCRPC maintains androgen-receptor signalling in testicular, adrenal and prostatic tumour tissues[11]. Abiraterone acetate is an orally active synthetic pregnenolone derivative that selectively and irreversibly inhibits CYP17. Inhibition of CYP17 results in down-regulation of endogenous steroids including testosterone and dihydrotestosterone, the two major androgens in men[12].

A licence extension for abiraterone acetate was approved by the European Medicines Agency in December 2012 for the treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated[13].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC), represented by the following treatments[1]:

- No treatment
- bicalutamide
- bicalutamide withdrawal
- low dose glucocorticoids (such as prednisolone)
- patient may be enrolled in a clinical trial

Patients who are not yet indicated for chemotherapy would be followed up in clinic with regular monitoring of symptoms and rate of disease progression[14].

2.3 Guidance and related advice

- NICE. Clinical Guideline 175. Prostate cancer: diagnosis and treatment (2014)[8]. (Replaces NICE Clinical Guideline 58[15])
- NICE. Abiraterone acetate in mCRPC not previously treated with chemotherapy (final guidance anticipated October 2014).
- London Cancer New Drugs Group Rapid Review. Abiraterone pre-docetaxel for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (2013)[16].
- NICE. Technology Appraisal 259. Abiraterone acetate in castration-resistant metatstatic prostate cancer previously treated with a docetaxel-containing regimen (2012)[10].
- NICE. Technology Appraisal 101. Docetaxel for the treatment of hormone refractory prostate cancer (2006)[7].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Clinical effectiveness evidence

Clinical evidence included in the company submission is based on the results from one phase III, multinational, randomised, double-blind, placebo-controlled study (COU-AA-302), comparing abiraterone acetate plus prednisolone* (AAP) versus placebo plus prednisolone* alone (PP) in patients with asymptomatic or mildly symptomatic mCRPC who had failed androgen deprivation therapy but had yet to receive cytotoxic chemotherapy[1]. The submission included results from the third of three planned interim analyses (median follow-up 27.1 months); results from the second interim analysis (median follow-up 22.2 months) have been published in a peer-reviewed journal[17]. Although the study is ongoing, as of January 2013 patients on PP were allowed to cross over to AAP after the second interim analysis and therefore the results from the final analysis are not anticipated to add any additional information to the results presented in this report.

Patients (n = 1088) were randomised 1:1 (stratified by baseline Eastern Cooperative Oncology Group [ECOG] performance status) to receive either AAP (n = 546) or PP (n = 542), each in combination with prednisolone 5 mg twice daily. Seventy six percent of subjects in each arm had a baseline ECOG performance status score of 0. Treatment was continued until disease progression. The median cohort age was 70 years and 94.9% of the subjects where Caucasian (2.6% black, 1.2% Asian)[13]. Of note, four Welsh patients were recruited onto the trial[1].

The co-primary endpoints were radiographic progression-free survival (rPFS; determined by a radiologist blinded to treatment allocation) and overall survival (OS), with the trial powered to detect a two month increase in rPFS (power = 91%) and a 5.5 month increase in OS (power = 85%) in the AAP group versus the PP group. Prespecified secondary endpoints included time to initiation of cytotoxic therapy, time to opiate use for cancer-related pain, time to deterioration in ECOG performance status by at least 1 grade and time to PSA progression. Health-related quality of life was assessed via the Functional Assessment of Cancer Therapy–Prostate (FACT-P) instrument[1].

The study design included three planned interim analyses; at the second interim analysis the trial was unblinded by the Independent Data Monitoring Committee due to a statistically significant increase in rPFS observed between the treatment arms (hazard ratio for AAP versus PP: 0.53; 95% CI 0.45–0.62; p < 0.0001). An increase in median OS was also observed between groups (hazard ratio for AAP versus PP: 0.75; 95% CI 0.61–0.93; p < 0.0097), but did not cross the prespecified boundary for significance (p = 0.0005)[13].

At the third interim analysis the median follow-up was 27.1 months and 434 death events had been observed (200 [37%] in the AAP group and 234 [43%] in the placebo group). This represented 56% (1% more than anticipated) of the planned 773 death events required for the final analysis. The statistically significant increase in rPFS in the AAP group compared with PP persisted (16.5 months versus 8.2 months; hazard ratio: 0.52; 95% CI 0.45–0.61; p < 0.0001), as did the increased OS (35.3 months versus 30.1 months; hazard ratio: 0.79; 95% CI 0.66–0.96; p = 0.0151; significance boundary p = 0.0034)[1].

All secondary endpoints were also statistically significantly in favour of AAP compared with PP. A statistically significant difference in health-related quality of life in favour of AAP over PP were observed from the FACT-P Total Score (time to deterioration of

* Throughout Europe and in countries where prednisone is not marketed or available, prednisolone was administered[1].

functional status [Commercial in confidence data removed] versus [Commercial in confidence data removed]; hazard ratio: [Commercial in confidence data removed]) and subscales, with the exception of the social/family wellbeing subscale[1].

Co-primary and secondary endpoint values at the third interim analysis are summarised in Table 1 and 2, respectively.

Table 1. Co-primary end points from COU-AA-302 study third interim analysis[1]

	AAP (N = 546)	PP (N = 542)
rPFS		
Number of patients with rPFS event, n (%)	¶	¶
Median time to event [months] (95% CI)	16.5 ¶	8.2 ¶
HR* (95% CI)	0.52 ¶	
p value†	< 0.0001	
OS		
Number of deaths, n (%)	200 (36.6)	234 (43.2)
Median OS§ [months] (95% CI)	35.3 (31.2–35.3)	30.1 (27.3–34.1)
HR (95% CI)	0.79 (0.66–0.96)	
p value†	0.0151	
p value required for significance	0.0034	

AAP: abiraterone acetate plus prednisolone; CI: confidence interval; HR: hazard ratio; OS: overall survival; PP: placebo plus prednisolone; rPFS: radiographic progression free survival.
* HR is from a stratified proportional hazards model. HR < 1 favours AAP.
† p-value is from a log-rank test stratified by ECOG performance status score (0 or 1).
§ Survival time of living patients was censored at the last date a patient was known to be alive or lost to follow-up as of the cut-off date for the interim analysis.
¶ Commercial in confidence data removed

Table 2. Secondary end points from COU-AA-302 study third interim analysis[1]

	AAP	PP	HR (95% CI)*	p value†
	Median, months (95% CI)			
Endpoint				
Time to opiate use for cancer pain	NE ¶	23.7 ¶	0.71 (0.59–0.85)	0.0002
Time to initiation of cytotoxic chemotherapy	26.5 ¶	16.8 ¶	0.61 (0.51–0.72)	< 0.0001
Time to deterioration in ECOG PS (≥ 1 increase)	12.3 ¶	10.9 ¶	0.83 (0.72–0.94)	0.0052
Time to PSA progression§	11.1 ¶	5.6 ¶	0.50 (0.43–0.58)	< 0.0001

AAP: abiraterone acetate plus prednisolone; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Score; HR: hazard ratio; OS: overall survival; NE: not estimable; PP: placebo plus prednisolone; PSA: Prostate Specific Antigen.
* Hazard ratio is from stratified proportional hazards model. HR < 1 favours AAP.
† p value is from a log rank test stratified by ECOG performance status score (0 or 1).
§ PSA response defined as a ≥ 50% decline from baseline according to adapted Prostate Cancer Working Group 2 (PCWG2) criteria.
¶ Commercial in confidence data removed

3.2 Comparative safety

Evidence for the comparative safety of abiraterone acetate is derived from the phase III COU-AA-302 trial. A similar proportion of patients experienced related treatment-

emergent adverse events (TEAEs) between the AAP and PP arms ([Commercial in confidence data removed] and [Commercial in confidence data removed], respectively), with a similar proportion resulting in discontinuation between groups ([Commercial in confidence data removed] and [Commercial in confidence data removed] for AAP and PP, respectively). Drug-related serious adverse events (SAEs) were also observed at a similar frequency between AAP ([Commercial in confidence data removed]) and PP ([Commercial in confidence data removed]) groups[1]. TEAEs resulting in death were reported in [Commercial in confidence data removed] of patients treated with AAP versus [Commercial in confidence data removed] of patients treated with PP[1].

Adverse events were also analysed following standardisation for the difference in median treatment duration between the AAP (13.8 months) and PP (8.3 months) groups; standardised rates showed few differences between groups. Adverse events with a difference of ≥ 5 events per 100 patient years were considered adverse drug reactions (ADRs). Four new ADRs were observed in COU-AA-302: dyspepsia, increased aspartate aminotransferase (AST), rash and haematuria.

At the time of issuing the licence extension, the Committee for Medicinal Products for Human Use (CHMP) provided an overview of the safety profile of abiraterone acetate in all previous studies[13]. Adverse events of special interest were generally in keeping with the known safety profile of abiraterone acetate. As expected from the pharmacodynamic consequence of increased mineralocorticoid levels resulting from CYP17 inhibition, fluid retention/oedema, hypokalaemia and hypertension were observed more frequently for subjects treated with abiraterone acetate. The management of such toxicities is included in the Risk Management Plan[13].

3.3 AWTTC critique

- NICE clinical guidelines state that there is no standard treatment for mCRPC. Treatment options include hormonal therapy (e.g. dexamethasone), chemotherapy, and targeted therapies for specific complications[8].
- BSC is considered to be a relevant comparator for asymptomatic and mildly symptomatic mCRPC patients (see section 2.2). In current clinical practice in the NHS in Wales, symptomatic patients are offered chemotherapy (predominantly docetaxel)[1].
- The phase III trial, COU-AA-302, compared abiraterone plus prednisolone versus placebo plus prednisolone; since the use of corticosteroids is often classified as an element of best supportive care, this is considered to be an appropriate comparator. The relative efficacy and safety of abiraterone acetate compared to other current therapies is not available.
- Treatment with abiraterone acetate requires additional monthly monitoring of blood pressure, serum potassium, and fluid retention; serum transaminases should be measured before treatment, every two weeks for the first three months, and then monthly thereafter. Moreover, due to the risk of cardiac toxicity, patients with a significant risk of congestive heart failure require monitoring every two weeks for the first three months of treatment, and monthly thereafter[2]. The company note that clinical opinion suggests that monitoring in post-chemotherapy patients would occur approximately every 6–8 weeks[18].
- In the phase III trial, COU-AA-302, there was a one month interval between the protocol amendment following study unblinding at the second interim analysis and the data cut off for the third interim analysis, during which time only three patients had crossed over from PP to AAP. All analyses on clinical effectiveness data included in the company submission were conducted on the intention-to-treat (ITT) population, not adjusting for crossover, as the impact of crossover at this analysis point was judged to be negligible[1].
- A definition of 'minimally symptomatic' was discussed by the London Cancer New Drugs Group when considering the addition of abiraterone for this indication to the Cancer Drugs Fund. It was determined that this should be

based on pain scores and that minimally symptomatic patients would not require opiates for disease-related pain[19].

- The findings from one retrospective study of patients refractory to first line abiraterone suggest that the clinical antitumour activity of docetaxel may be reduced when given post-abiraterone[20].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission described a cost utility analysis of AAP compared to PP to treat men with asymptomatic or mildly symptomatic mCRPC. A discrete event simulation model was used[1]. With PP, men are monitored until disease progression and docetaxel is commenced. After docetaxel, men who remain mildly symptomatic may receive treatment, including AAP; if disease has progressed, palliative care commences. In the AAP arm, docetaxel commences after first-line AAP; those unsuitable transition to palliative care. After docetaxel, men can receive further active treatment or palliative care.

Patient-level data from the pivotal trial, COU-AA-302, informed equations predicting time to discontinuation of treatments, grade 3/4 adverse events and death. Utility values were taken from a UK study of men with mCRPC, using the EQ-5D tool, except for end state disease where a value was obtained from a Swedish study.

The model included the costs of:

- Medication, including granulocyte colony-stimulating factor (G-CSF) and administration.
- AEs with docetaxel sourced from literature.
- Resources to treat AEs informed by an Advisory Board
- Planned monthly medical resource use, obtained from a survey of 53 oncologists;
- Unplanned monthly medical resources from the trial;
- One-off hospice/care at home at death.

Unit costs were mainly taken from NHS Reference Cost 2011/12[21]. A lifetime horizon, NHS Wales perspective and 3.5% discount rates for costs and benefits were adopted.

4.1.2 Results

The base case (with Patient Access Scheme [PAS]) incremental cost effectiveness ratio (ICER) is £46,601 per Quality-adjusted life year (QALY) gained based on incremental costs of [Commercial in confidence data removed] and incremental QALYs of 0.57 (Table 3). The AAP arm incurred higher cost of [Commercial in confidence data removed] in the pre-docetaxel stage [Commercial in confidence data removed] compared to [Commercial in confidence data removed] PP); and saved about [Commercial in confidence data removed] in the on- and post- docetaxel stages of the pathway. A QALY gain of 0.71 is estimated for the pre-docetaxel stage ([Commercial in confidence data removed]). The higher costs and QALYs correspond to the extended duration of time on AAP compared to PP.

Table 3. Results of the base case analysis

	AAP	PP	Difference
Total costs	¶	¶	£26,336
Total life-years	¶	¶	0.62
Total QALYs	¶	¶	0.57
ICER (£/QALY gained)	£46,601		
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year ¶ Commercial in confidence data removed			

Extensive sensitivity and scenario analyses were provided. Table 4 shows those reporting an ICER which is ≥ 10% lower (below £41,941) or ≥ 10% higher (over £51,261) than base case or where case is judged highly plausible.

The results are sensitive (> ±10% change in ICER) to baseline utility value, and choice of parametric function to model duration of first-line treatment. In addition, the ICER's increase under two plausible scenarios: adherence increased to 100% and the case where AAP is not used post-docetaxel.

The results are not sensitive to a reduced (10 year) time horizon, most changes in discount rates, non-truncating the survival curve, cost of planned or unplanned medical resources or utility values at other stages in the pathway. The scenario analyses which did not change results by > ±10% are: adopting resource use advised by urologists, or the average for oncologists and urologists, utilities from a cancer specific quality of life (QoL) study mapped to EQ-5D, a different end-of-life utility and substituting dexamethasone for prednisolone in PP.

Probability sensitivity analysis estimated there is a 0% probability of AAP being cost effective at cost effectiveness threshold of £20,000 and £30,000 per QALY.

Table 4. Results of sensitivity and scenario analyses

Parameters and Scenarios	ICER	Plausibility
Base case	£46,601	Upside potential materially greater than any reduction.
Discount rates costs 0% to 5%	£44,895 to £51,732	Not directly relevant.
Weibull curve for first line treatment duration	£51,646	Plausible alternative parametric function to have reduced adherence.
Adherence 95% (98% in base case)	£45,038	Plausible in clinical setting.
Utility at baseline ±20% from [Commercial in confidence data removed]	£37,989 to £60,262	Lower baseline utility plausible when compared to average utilities of the UK general adult population.
Patients in BSC do not receive active treatment post-docetaxel	£48,697	Plausible.
Base case no PAS	£103,418	Not plausible.

4.1.3 AWTTC critique

The ICER of £46,601 is derived from a robust economic model, using patient-level data from the pivotal trial to inform equations predicting treatment duration and overall survival. The results are highly sensitive to choice of baseline utility value ([Commercial in confidence data removed] for comparator for AAP arm), with a lower baseline utility giving a higher ICER. They are quite sensitive to duration of first line treatment but not to one-way sensitivity analysis of costs. Each of the identified weaknesses could increase the ICER from the base case, suggesting there is upward potential.

Strengths

- The model is a discrete event simulation, including appropriate subsequent treatment regimens post-progression, for the AAP arm.
- Efficacy data, including time dependencies are derived from patient level data from the pivotal trial. Discussion of potential parametric functions, together with measures of goodness of fit, is helpful.
- Model predictions of progression and overall survival calibrate well to clinical trial data.
- Resource use includes patient-level data from the trial.
- Sources of unit cost information are appropriate.
- Utility data are informed by a well-conducted study of UK patients with mCRPC.
- Extensive sensitivity and scenario analyses explore uncertainties in the model.

Weaknesses

Model structure

- Time to treatment discontinuation recorded in the pivotal trial was adopted as a proxy for progression free survival. However, about a quarter of patients discontinued treatment for reasons other than disease progression: the impact of these patients on the mean time is not known.
- Patients were assumed to spend seven to eight months post-progression before treatment with docetaxel. This phase is associated with a large decrement in utility (from [Commercial in confidence data removed]). This delay may not capture NHS practice.
- Some patients in the PP arm received AAP and other active treatments post-docetaxel. The company states the post-docetaxel treatment in the PP arm '*is probably not reflective of the average mCRPC patient in the UK*'. No information on hospital prescribing of AAP is available to inform the proportion receiving such active treatment. Hence, as a sensitivity analysis, all costs were removed which increased the ICER to £48,697 per QALY gained.

Utilities

- The baseline utility value of [Commercial in confidence data removed], with an added increment of [Commercial in confidence data removed] for patients treated with AAP is high compared to the average utility obtained from a sample of the UK population of a similar age[22]. The mean utility for the UK general population aged 60 to 69 years was 0.80 (n = 475), falling to 0.74 in those aged 70 to 79 years (n = 406).
- The end stage utility of 0.50 was taken from a QoL study of Swedish men (n = 1,243) with prostate cancer, in which QoL was measured from 16 months before death, to death[23]. The utility at 16 months was less than 0.60, significantly below the [Commercial in confidence data removed] value modelled for QoL post-docetaxel. Pain was the key driver in the Swedish study, and better pain management may have improved QoL. However, sensitivity analysis indicates these utility values are not a major driver of the economic model.

Resources and costs

- The trial excluded patients on opiates; if patients indicated for the medication in Wales are on opiates they may be sicker than those in the studies and hence survival may not generalise.
- No resource use was assumed to deliver oral chemotherapy. The 2012–13 NHS Reference Cost for this activity is £156 (SB11Z)[21].
- Patients who are mildly symptomatic and treated with docetaxel were assumed to have the same unplanned resource as patients in whom the disease has progressed; this was four times more than those receiving first-line therapy. However, sensitivity analysis indicates these costs are not a major driver of the economic model.

- There is uncertainty associated with resource use estimations obtained from Advisory Group members, as they may not reflect NHS practice or adjust for case mix.
- The model includes the prophylactic use of G-CSF in patients receiving docetaxel. International guidelines state use of G-CSF in prophylaxis of chemotherapy-induced neutropenia is not warranted unless the risk of febrile neutropenia exceeds 20%, or there are special circumstances[24].
- The Excel model is transparent, clearly set-out and easy to use. However, it is non-executable and hence verifications and sensitivity analyses could not be undertaken.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of AAP in this indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company adopted a NICE assumption that 0.019% of the population has mCRPC and applied this to the 2014 population estimates for Wales to derive an estimate of 598 with mCRPC in 2014. Clinicians advised 60% of such patients are chemotherapy-naïve; company data indicated 70.5% are asymptomatic or mildly symptomatic and consequently eligible for treatment with AAP in the chemotherapy-naïve setting. This equates to [Commercial in confidence data removed] eligible patients in 2014, rising to [Commercial in confidence data removed] patients in 2018. A 40% market share in 2014, rising to 85% in 2018 is applied. Other patients are managed with a corticosteroid. The unit costs applied in the economic model are used. Total AAP cost is forecast at [Commercial in confidence data removed] in 2014, rising to [Commercial in confidence data removed] in 2018.

5.1.2 Results

Table 5. Company-reported costs associated with use of abiraterone acetate with prednisolone for the treatment of mCRPC (with PAS)

	Year 1 (2014)	Year 2 (2015)	Year 3 (2016)	Year 4 (2017)	Year 5 (2018)
Number of eligible patients	¶	¶	¶	¶	¶
Uptake (%)	¶	¶	¶	¶	¶
Treated patients	¶	¶	¶	¶	¶
Total costs					
Medication costs ¶	¶	¶	¶	¶	¶
Monitoring £2,337/year/patient	¶	¶	¶	¶	¶
Total AA cost	¶	¶	¶	¶	¶
Prednisolone for remaining patients (£1,150/year/patient)	¶	¶	¶	¶	¶
Annual budget impact	¶	¶	¶	¶	¶

¶ Commercial in confidence data removed

Table 6 provides a company estimate of the cost of current treatment and gives the incremental budget impact. This is [Commercial in confidence data removed] in 2014 rising to [Commercial in confidence data removed] in 2018.

Cost savings are forecast as fewer patients receive AAP post-docetaxel. Four oncologists judged 70% of patients are currently eligible for AAP ([Commercial in confidence data removed]). This is forecast to fall to [Commercial in confidence data removed] in 2018. Associated savings rise from [Commercial in confidence data removed] in 2014 to [Commercial in confidence data removed] in 2018. The net budget impact, after deducting savings in the post-docetaxel setting, is [Commercial in confidence data removed] in 2014, rising to [Commercial in confidence data removed] in 2018.

Table 6. Company-reported cost of current treatment, incremental budget impact cost savings post-docetaxel and net budget impact.

	Year 1 (2014)	Year 2 (2015)	Year 3 (2016)	Year 4 (2017)	Year 5 (2018)
Number of eligible patients	¶	¶	¶	¶	¶
Total costs					
Medication costs £20.31/month/patient	¶	¶	¶	¶	¶
Monitoring £906.24/year/patient	¶	¶	¶	¶	¶
Total cost	¶	¶	¶	¶	¶
Incremental budget impact	¶	¶	¶	¶	¶
Cost savings reduction in AAP post-chemotherapy	¶	¶	¶	¶	¶
Net budget impact	¶	¶	¶	¶	¶

¶ Commercial in confidence data removed

Without a PAS the net budget impact is forecast at [Commercial in confidence data removed] in 2014, rising to [Commercial in confidence data removed] in 2018.

5.1.3 AWTTC critique

Limited verification of the estimated patient numbers for mCRPC has been possible.

As all costs are derived from the economic model, the limitations of the economic model apply to the budget impact estimates. Also, the net financial costs of introducing AAP in practice may not be equivalent to the opportunity costs calculated for the economic analysis.

5.2 Comparative unit costs

Table 7 provides unit costs for abiraterone acetate with prednisone or prednisolone and prednisone or prednisolone only. Docetaxel and other treatments used when disease has progressed are not directly comparable.

Table 7. Abiraterone acetate with prednisone or prednisolone for mCRPC

Regimens	Example doses	Cost per year
Abiraterone acetate with prednisone or prednisolone	1 g (4 x250 mg tablets) orally daily plus 10 mg prednisolone orally daily	¶ + £16.06
Prednisone or prednisolone only	10 mg prednisolone orally daily	£16.06
¶ Commercial in confidence data removed		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company anticipate that abiraterone acetate (Zytiga®▼) may be supplied by a home healthcare provider.

6.2 Ongoing studies

Although the study is ongoing, patients on PP were allowed to cross over to AAP after the second interim analysis and therefore the company state that the results from the final analysis are not anticipated to add any additional information to the results presented in this report. The cut-off date for the final analysis is 31 March 2014, with a final clinical study report planned for August 2014 and a registry study planned to report in 2015[1].

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: 19 December 2013
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines

Consideration is required as to whether abiraterone acetate in the given patient population meets the end of life criteria set by the AWMSG Policy on appraising life-extending, end-of-life medicines.

The criteria for appraising life-extending, end-of-life medicines apply when the most plausible ICER estimate exceeds £30,000 per QALY gained, and all the following conditions are satisfied:

- The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).
- There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional three months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival.

- AWMSG/New Medicines Group (NMG) will consider the cumulative population of each licensed indication of the medicine to be small.

In the submission the company presents the following case for why abiraterone acetate meets the above criteria[1]:

- Patients randomised to receive placebo in the COU-AA-302 study demonstrate a median life expectancy of approximately 30.1 months; however, in their submission, the company note that patients in the trial are likely to have gone on to receive other clinical trial technologies post-docetaxel and therefore the survival observed for these patients is probably not reflective of the average mCRPC patient in the UK. The company refer to European Association of Urology (EAU) estimates of the mean survival of patients with asymptomatic disease to be dependent on the extent of metastases, ranging from 9–27 months[25].
- A 5.2 month increase in median overall survival was observed in patients receiving abiraterone compared to placebo in study COU-AA-302.
- The company estimate that in 2014, 253 patients in Wales will have asymptomatic or mildly symptomatic mCRPC post-androgen deprivation therapy. Assuming that patients receive treatment post-androgen deprivation therapy instead of post-docetaxel, therapy then the company assume that the overall number of patients will remain small (estimated 273 patients in 2017).

GLOSSARY

Eastern Cooperative Oncology Group (ECOG) performance status score
A scale from 0 to 5, where: 0 indicates that the patient is fully active and able to undertake all pre-disease activities without restriction; 1 indicates the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 indicates that the patient is ambulatory and up and about more than 50% of waking hours and is capable of all self-care but unable to carry out any work activities[26].

Functional assessment of cancer therapy – prostate (FACT-P)
This questionnaire assesses symptoms and problems specific to men undergoing prostate cancer therapy in order to evaluate quality of life[27].

Karnofsky performance-status score
Describes a patient's functional status as a comprehensive 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death)[28].

Overall survival (OS)
The time from randomisation to death from any cause[17].

Prostate-specific antigen (PSA)
PSA is a serum marker that can be used to aid diagnosis, risk stratification and monitoring of patients with prostate cancer[8,25].

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