AWMSG Secretariat Assessment Report – Advice no. 0612
Abiraterone (Zytiga®▼) 250 mg tablets

This assessment report is based on evidence submitted by Janssen-Cilag Ltd on 5 October 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Abiraterone (Zytiga®▼) with prednisone or prednisolone* for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen[1].
Dosing	The recommended dose is 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food, as this increases systemic exposure to abiraterone. Abiraterone is to be taken with low dose (10 mg) prednisone or prednisolone. Refer to the Summary of Product Characteristics (SPC) for further information regarding routine monitoring[1].
Marketing authorisation date	5 September 2011[1].

2.0 DECISION CONTEXT

2.1 Background

Prostate cancer is the most common cancer affecting men in Wales, with a prevalence of 1%[2] and 2,406 cases reported in Wales during 2009, accounting for approximately 26% of newly diagnosed cancers in men[3]. 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 (24.6 and 24.5 per 100,000 population in Wales and the UK respectively)[4]. Metastatic prostate cancer occurs in 55–60% of cases, and these patients will commonly receive hormonal therapies that prevent the action of androgens by either surgical or medical castration[5,6]. Despite initial effectiveness in 80% of men with metastatic prostate cancer, after approximately 18 months patients will usually become resistant to hormone therapy, progressing to metastatic castration resistant prostate cancer (mCRPC), at which point the prognosis is poor and survival is not expected to exceed 9–12 months[5]. There is no curative treatment for mCRPC, and the aim of therapy is to improve symptoms, delay cancer progression and prolong life. Current treatment guidelines recommend the use of docetaxel as a first line therapy for patients with CRPC, while second line options include mitoxantrone, corticosteroids, cabazitaxel and docetaxel re-treatment[6–8].

Abiraterone is an inhibitor of the enzyme cytochrome P450c17 (CYP17), which is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. This is in contrast to other androgen deprivation therapies, which prevent androgen production in the testes but not in the tumour or adrenal tissues[1].

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

Abiraterone is licensed for use in combination with prednisone or prednisolone for the treatment of mCRPC in men whose disease has progressed on or after a docetaxel-based chemotherapy regimen[1]. Although the company submission provides clinical effectiveness evidence for the use of abiraterone in the entirety of its licensed indication, the company has highlighted patients who have received only one prior chemotherapy regimen, which is suggested to be more relevant to the patient population in Wales[9]. Additionally, the company notes that clinical opinion suggests that abiraterone will be used prior to cabazitaxel (Jevtana®▼) and other currently available second line chemotherapies in the majority of cases in the UK[9].

The applicant company believe that the use of abiraterone in the given patient population meets the end of life criteria set by National Institute for Health and Clinical Excellence (NICE)[9]; further consideration of this is required.

2.2 Comparators

The company submission includes prednisolone as a comparator, which is stated by the company to represent best supportive care[9]. Prednisone is a pro-drug of prednisolone, which has historically been preferred to prednisone in the UK on the grounds that it does not require conversion to the active substance. However, NICE has concluded that in practice the difference between prednisone and prednisolone is not clinically significant[5].

Following the company submission, clinical experts highlighted that mitoxantrone or cabazitaxel may also be suitable comparators.

2.3 Guidance and related advice

- European Association of Urology (EAU). Guidelines on prostate cancer (2011)[8].
- European Society for Medical Oncology (ESMO). Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2010)[10].
- NICE. Clinical Guidelines 58. Prostate cancer: diagnosis and treatment (2008)[6].
- NICE. Technology Appraisal 101. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (2006)[5].
- NICE. Single technology appraisal in progress. Abiraterone for the treatment of metastatic castration resistant prostate cancer following previous cytotoxic therapy. Expected publication date: May 2012[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Clinical evidence in the company submission is based on the results of one phase III trial, comparing abiraterone with placebo (each in combination with prednisone) for treatment of mCRPC following docetaxel-based chemotherapy. The submission included results from a primary analysis (median follow-up 12.8 months)[9], which has been published in a peer-reviewed journal[12], and a subsequent updated analysis (median follow-up 20.2 months)[9].

It should be noted that the clinical study protocol for the COU-AA-301 study specifies that patients could receive prednisone or prednisolone; in regions where prednisone is not marketed or available, prednisolone was administered[9].

3.1 Study COU-AA-301

This multinational, randomised, double-blind, phase III study compared abiraterone (1 g once daily) with placebo in patients with mCRPC who were receiving prednisone (5 mg twice daily) and had previously failed docetaxel-based chemotherapy[12]. Patients (n = 1195) were randomised 2:1 to receive prednisone in combination with either abiraterone (n = 797) or placebo (n = 398). Inclusion criteria included confirmed prostate cancer; medical or surgical castration; documented disease progression; an Eastern Cooperative Oncology Group (ECOG) performance status score of two or less (see Glossary for details); and prior treatment with one to two chemotherapy regimens, of which one must have included docetaxel treatment. Patients were excluded from the study if they had abnormal liver aminotransferase levels, chronic liver disease, viral hepatitis, prior therapy with ketoconazole, uncontrolled hypertension, or clinically significant heart disease[12].

The primary endpoint was overall survival (OS), defined as the time from randomization to death from any cause. Secondary endpoints included the prostate-specific antigen (PSA) response rate, time to PSA progression, progression-free survival (PFS), time to first skeletal-related event (SRE), and pain palliation rate[12,13]. See Glossary for definitions of endpoints. The median duration of treatment was eight months in the abiraterone group compared with four months in the control group[12].

Primary endpoint investigation demonstrated that median OS time was extended in abiraterone-treated patients at the time of primary analysis (median survival time: 450 days versus 332 days) and updated analysis (median survival time: 482 days versus 341 days)[12,13]. As can be seen in Table 1, all secondary endpoints analysed were also significantly superior in the abiraterone group, including indicators of progression, SREs and quality of life scores, such as pain palliation.

Table 1. Overview of endpoint results from study COU-AA-301. Commercial in confidence data removed

Endpoints		Primary analysis[9,12,13]		Updated analysis[9,13]	
		Abiraterone	Control	Abiraterone	Control
Primary endpoint					
OS	Median OS (days)	450	332	482	341
	Deaths n (%)	333 (42%)	219 (55%)	501 (62.9%)	274 (68.8%)
	HR (95% CI)	0.65 (0.54,0.77)		0.74 (0.64, 0.86)	
	p-value	< 0.001		< 0.0001	
Secondary and ancillary endpoints					
PSA response rate	Patients with confirmed PSA response	29%	6%	*	*
	p-value	< 0.001		*	
Time to PSA progression	PSA progression events	254 (31.9%)	120 (30.2%)	Not reported	
	Median days to event	309	200		
	p-value	< 0.001			
Radiographic PFS	Median days to event	171	110	*	*
	p-value	< 0.0001		*	
SRE	Median days to first event	301	150	*	*
	p-value	0.0006		*	
Proportion of patients experiencing pain palliation	BPI-SF: worst pain intensity	44%	27%	*	*
	p-value	0.002		*	
	BPI-SF: pain interference	59%	38%	*	*
	p-value	0.0004		*	
	FACT-P total scale	48%	32%	*	*
	p-value	< 0.0001		*	
	BFI worst fatigue intensity	58%	40%	*	*
	p-value	0.0001		*	
	BFI fatigue interference	55%	38%	*	*
	p-value	0.0096		*	

BFI: brief fatigue inventory; BPI-SF: brief pain inventory – short form; CI: confidence interval; FACT-P: functional assessment of cancer therapy; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PSA: prostate serum antigen; SRE: skeletal-related event.
*** Commercial in confidence information removed.**

3.1.1 Analysis of patients in study COU-AA-301 who had received only one prior chemotherapy regimen

Similar to the overall population, patients in study COU-AA-301 who had received only one prior chemotherapy regimen (n = 832) showed improvements in OS in the abiraterone arm, with a median survival during the updated analysis of 17 months compared with 11.7 months for the control group (HR, 0.71; 95% CI, 0.60, 0.86)[9]. Additionally, using treatment discontinuation as a proxy, the risk of disease progression was reduced by abiraterone treatment.

3.1.2 Summary of evidence on comparative safety from study COU-AA-301

Treatment discontinuation due to disease progression occurred in 219 (27.7%) and 112 (28.4%) of patients in the abiraterone and control groups respectively; 98 (12.4%) and 70 (17.8%) discontinued due to adverse events (AEs). Treatment-emergent AEs were observed in 98.9% and 99.0% of patients in the abiraterone and control groups respectively, of which 54.5% and 58.4% were grade 3–4[13]. The most frequently reported AEs were fatigue (44% and 43% of the abiraterone and control groups

respectively), back pain (30% and 33%), nausea (30% and 32%) and constipation (26% and 31%), consistent with the natural history of mCRPC[12,13]. AEs reported more frequently in abiraterone-treated patients included hypokalaemia (17% versus 8%; a difference of 18 events/100 patient years when standardised for duration of treatment), fluid retention/oedema (31% versus 22%; a difference of 6 events/100 patient years) and urinary tract infection (12% versus 7%; a difference of 6 events/100 patient years)[13]. AEs leading to treatment discontinuation occurred in 19% and 23% of the abiraterone and control groups respectively, of which the most common were increased aminotransferase levels and cardiac failure. Incidence of cardiac events was slightly higher in the abiraterone group (13% versus 11%); however, in both groups the rates of cardiac-related death (1%) and death due to myocardial infarction (1 patient in each group) were similarly low. There was also a slight increase in the number of hepatotoxicity AEs reported in abiraterone-treated patients (10% versus 8%). During treatment with abiraterone, two cases of drug-induced liver injury were identified, and the Committee for Medicinal Products for Human Use (CHMP) concluded that the role of abiraterone in hepatotoxicity is not fully understood. Additionally, it was noted that the potential of abiraterone for drug interactions is not fully elucidated. The Risk Management Plan (RMP) reflects the need for further insight into drug interactions and the role of abiraterone in hepatotoxicity[13].

Serious AEs (SAEs) were observed in 37.5% and 41.4% of patients in the abiraterone and control groups respectively. Treatment emergent SAEs reported more commonly in abiraterone-treated patients included cardiac disorders (2.9% versus 1.3%), vascular disorders (1.6% versus 0.5%) and infections and infestations (7.7% versus 5.1%). The incidence of AEs leading to death that occurred at any time during the study or follow-up period were 11.6% and 14.7% in the abiraterone and control groups respectively[13].

Separate analyses of AEs have not been conducted for patients in study COU-AA-301 who had received only one prior chemotherapy regimen; it is suggested by the company that the AEs observed in this population would either not be expected to differ from that of the overall population or may be less likely as the patients would be less heavily treated[9].

3.2 Summary of evidence on abiraterone safety: CHMP overview

At the time of licensing, CHMP provided an overview of the safety profile of abiraterone in all previous studies[13]. CHMP considered the safety profile of abiraterone acceptable and generally manageable with basic medical interventions. Reported toxicities in abiraterone-treated patients were generally mild and resulted in infrequent dose reductions, dose interruptions, or discontinuations, which CHMP noted was distinct from that typically induced by conventional cytotoxic agents. CHMP concluded that AEs such as hypertension or hypokalaemia are generally asymptomatic and fluid retention/oedema or urinary tract infections may be more disturbing to the patient. Management of hypertension, hypokalaemia and fluid retention/oedema is included in the RMP[13].

3.3 WMP critique

- In the pivotal study COU-AA-301, abiraterone plus prednisone demonstrated a favourable adverse events profile while improving OS compared to placebo plus prednisone in CRPC patients[12]. However, the efficacy and safety of abiraterone has yet to be compared with that of other current therapies. The company suggests that prednisolone, with supportive care as necessary, is most representative of the best supportive care received by patients in the UK following docetaxel therapy[9]. Furthermore, the company suggests that there is limited clinical use in Wales of mitoxantrone[9], although it is recommended in mCRPC cases where docetaxel is contraindicated or poorly tolerated[6,8,10]. The

company submission does not include a comparison with cabazitaxel; clinical expert opinion provided as part of the company submission suggests that abiraterone will be used prior to cabazitaxel and other currently available second line therapies, such as mitoxantrone and docetaxel re-treatment, in the majority of cases[9]. Recent guidance states that in patients with relapse following first-line docetaxel chemotherapy, cabazitaxel and abiraterone are regarded as the first choice option for second line treatment[8]. Clinical expert opinion obtained by WMP also suggests that cabazitaxel could be an additional relevant comparator.

- Abiraterone treatment is not associated with the toxicities typically induced by conventional cytotoxic agents, such as myelosuppression, diarrhoea, mucositis, asthenia and alopecia, which often have a major impact on the patient's quality of life. CHMP concludes that this is particularly relevant in the context of non-curative therapy for an end-stage disease[13]. In contrast to intravenously administered chemotherapies, such as mitoxantrone or cabazitaxel, abiraterone can be taken orally at home, which is less invasive and avoids the use of medical resources and healthcare professional time associated with intravenous administration[9].
- CHMP noted the limited number of non-Caucasian patients (7%) in the pivotal study COU-AA-301[13], which may not accurately reflect prostate cancer incidence[14]. The patient population of the pivotal trial is reflected in the abiraterone SPC and use in non-white patients is reflected as important missing information in the RMP[13].
- In the pivotal study COU-AA-301, the eligibility criteria excluded enrolment of patients that had received previous ketoconazole therapy; this was subsequently one of the most common protocol deviations[13]. Although ketoconazole, an antifungal drug, is not approved for the treatment of prostate cancer[15], use in this indication is suggested by European guidelines[8,10]. Lower response rates have been observed in earlier studies of abiraterone in mCRPC patients that had prior treatment with ketoconazole[13]; for example, a PSA response rate of 26% was observed in patients having received prior ketoconazole treatment and 45% in those with no prior ketoconazole therapy[16]. CHMP noted that this effect has not been properly assessed in a controlled clinical trial, and this has been reflected in the SPC for abiraterone[13].
- ECOG performance status score for the pivotal study was not considered by CHMP to reflect the target population for the intended indication, as patients with high scores were not included. CHMP acknowledge that patients with a poor performance score are not generally suitable for chemotherapy, but this would not be the case for an oral drug such as abiraterone, which has a favourable safety profile[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 abiraterone in combination with prednisolone (AAP) compared to placebo plus prednisolone (PP), and compared to mitoxantrone in combination with prednisolone (MP), for the treatment of mCRPC in adult men whose disease has progressed on or after one docetaxel-based chemotherapy regimen[9]. The analysis is based on a survival-based simulation model consisting of three health states: progression-free survival (PFS) state, post progression (PPS) state and dead state. The patients enter the model in PFS upon completion of docetaxel-based chemotherapy regimen. From the progression-free

health state patients proceed to the PPS state and death. The number of patients remaining in each health state at each model cycle was calculated directly from the OS curves and proxy PFS curves derived from the clinical trial COU-AA-301. As there are no direct comparative data for AAP and MP, the base case model assumes MP offers no survival advantage over PP alone. Patients are assumed to receive abiraterone until disease progression, mitoxantrone for up to ten three-week cycles, and prednisolone until death. The model assumes a ten-year time horizon. See Appendix 1 for further details.

4.1.2. Results

Table 2 reports the base-case analyses, reflecting use in patients who have only had one prior docetaxel-based chemotherapy regimen, and assuming the implementation of the approved Wales Patient Scheme for access to medicines (WPS).

Table 2. Commercial in confidence data removed.

4.1.3 WMP critique

Strengths of the economic evidence include:

- The efficacy data used in the economic model for the comparison of APP against PP were derived mainly from a direct comparative study, although the base case model makes use of a subgroup analysis (70%) of the trial population.
- A systematic review was conducted in an effort to identify relevant clinical data to inform comparisons against MP and to identify published utility values in the target patient population.
- A wide range of sensitivity and scenario analyses have been performed to explore the impact of modelling assumptions.

Limitations of the economic evidence include:

- There are no comparative data available to inform the analyses of AAP versus MP. The company assumes that MP is no more effective than PP alone in the base case model, and sensitivity analyses indicate the model is sensitive to the assumed relative effectiveness of MP and PP.
- Treatment discontinuation was used as a proxy for PFS as the definitions of PFS used in the COU-AA-301 trial were considered to be inconsistent with those likely to be used in practice. The hazard ratios for the different PFS definitions used in the trial were consistent and greater than the treatment discontinuation hazard ratio assumed in the model, and this aspect has not been explored in sensitivity analysis.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of abiraterone in combination with prednisolone/prednisone in comparison to mitoxantrone in combination with prednisolone/prednisone or prednisolone/prednisone alone for the treatment of mCRPC in adult men after a docetaxel-based chemotherapy regimen.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Due to a lack of data on the incidence and prevalence of mCRPC in the UK and Wales, the company used the costing report for the NICE technology appraisal of docetaxel (2006)[5] to estimate prevalence of mCRPC in Wales. Based on these data the company estimates there would be 588 patients in 2011, and that this number is expected to increase to 604 in 2016. Based on company-sought expert opinion, the company assumes that 40% of these patients will be treated with docetaxel, increasing to 45% in 2012 and 50% during the following three years. Of these patients, the company anticipates 75% would be eligible for treatment with abiraterone. **Commercial in confidence data removed**

Table 3. Commercial in confidence data removed.

5.1.2 WMP critique

The company made reasonable efforts to estimate the budget impact. However, there is uncertainty about the number of eligible patients due to a lack of data on the incidence and prevalence of mCRPC in Wales. More recent estimates of the incidence of prostate cancer in Wales would, using the company's approach of estimating mCRPC, result in a substantially greater number of patients estimated to develop mCRPC (938 versus 588 estimated by the company) and, consequently, a greater potential budget impact from the use of abiraterone than has been presented in the company's submission. The company acknowledges the more recent estimates of prostate cancer incidence, but considers these could lead to an overestimate in mCRPC cases. The budget impact estimates are therefore subject to uncertainty.

5.2 Comparative unit costs

Table 4 includes example acquisition costs of drugs that may be used in patients with mCRPC in the UK. Three-week costs have been presented to align costs with the three-week treatment cycle used for mitoxantrone or taxane treatment. Mitoxantrone is not specifically licensed for use in patients with mCRPC in the UK, but is recognised as a potential comparator by NICE[11] and the applicant company. Cabazitaxel is licensed for use in hormone-refractory patients previously treated with a docetaxel regimen[17], and in patients who responded to first-line docetaxel, re-treatment with docetaxel may be an option[8].

Table 4. Examples of drug acquisition costs for the treatment of mCRPC in adult men after a docetaxel-based chemotherapy.

	Regimen*	Cost per three weeks
Abiraterone (Zytiga®▼) 250 mg tablets (with prednisolone)	Abiraterone 1000 mg daily (plus prednisolone 10 mg daily)	**Commercial in confidence data removed**
Prednisolone 1 mg, 5 mg and 25 mg tablets	Prednisolone 10 mg daily	£2
Mitoxantrone (non-proprietary) 20 mg vial (with prednisolone)	Mitoxantrone 12 mg/m^2 – assume 1 or 2 × 20 mg vials per dose (plus prednisolone 10 mg daily) every three weeks	£100 to £200 (+ £2)
Cabazitaxel (Jevtana®▼) 60 mg/1.5 ml vial (with prednisolone)	Cabazitaxel 25 mg/m^2 – assume 1 × 60 mg vial per dose (plus prednisolone 10 mg daily) every three weeks	£3696 (+ £2)
Docetaxel (non-proprietary) 20 mg/ml vial (with prednisolone)	Docetaxel 75mg/m^2 – assume 1 × 140 mg vial per dose (plus prednisolone 10 mg daily) every three weeks	£900 (+ £2)

Costs are based on BNF[15] and MIMS[18] list prices as of 7 Nov 2011, assuming body surface area 1.8 m^2 and vial wastage.
**NB: Abiraterone would be taken until disease progression; prednisolone would be taken indefinitely; mitoxantrone, cabazitaxel and docetaxel would be taken for up to ten three-week cycles. Abiraterone and taxanes are taken in combination with prednisolone.*
See all relevant SPCs for further details.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that abiraterone is not suitable for shared care within NHS Wales.

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.

GLOSSARY

Brief fatigue inventory (BFI)
This scale assesses fatigue level in cancer patients and identifies those patients with severe fatigue[19].

Brief pain inventory – short form (BPI-SF)
BPI-SF is an index of pain severity, pain relief, and the effects of pain on ability to function[20].

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[21].

Functional assessment of cancer therapy – prostate (FACT-P)
This questionnaire assesses symptoms and problems specific men undergoing prostate cancer therapy in order to evaluate quality of life[22].

Overall survival (OS)
The time from randomisation to death from any cause[12].

Progression-free survival (PFS)
The time interval from the date of randomisation to disease progression or death. Radiographic evidence of PFS was defined according to modified Response Evaluation Criteria in Solid Tumors (RECIST)[23], in which the baseline lymph node must be ≥ 2 cm to be considered a target lesion, or progression according to bone scans showing two or more new lesions not consistent with tumour flare.

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[6,8,10].

Time to PSA progression
In patients in whom the PSA level had not decreased, PSA progression was defined as a 25% increase over the baseline and an increase in the absolute-value PSA level by at least 5 nanogram/ml, which was confirmed by a second value. In patients in whom the PSA had decreased but had not reached response criteria (see PSA response rate), progressive disease would be considered to have occurred when the PSA level increased 25% over the nadir, provided that the increase was a minimum of 5 nanogram/ml and was confirmed. If at least a 50% decrease in the PSA level had been achieved, PSA progression would be an increase of 50% above the nadir at a minimum of 5 nanogram/ml[12].

PSA response rate
The proportion of patients with a ≥ 50% reduction in PSA concentration from the pretreatment baseline PSA value, which was confirmed after ≥ 4 weeks with an additional evaluation[12].

Time to first skeletal-related event (SRE)
The time interval to first SRE, which was defined as a pathological fracture, spinal cord compression, palliative radiation to bone or surgery to bone[9].

Pain palliation rate
The proportion of patients with a pain palliation response, which was defined as a patient with a ≥ 30% reduction from baseline in pain scores[13].

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Appendix 1. Additional health economic information

Table 1. Health economic model detail[9]

	Base case model	Appropriate?
Comparator(s)	Abiraterone in combination with prednisolone (AAP) compared to prednisolone alone (PP), and compared to mitoxantrone in combination with prednisolone (MP).	The company has included mitoxantrone in combination with prednisolone as a secondary comparator in the current submission; NICE has requested a comparison against mitoxantrone alone or in combination with prednisolone for a future technology appraisal[11].
Population	The base case model includes adult men with mCRPC who have had only one prior docetaxel-based chemotherapy regimen, representing a sub-set of the entire COU-AA-301 trial population (approximately 70%). A scenario analysis including all patients in the trial is also provided.	Yes. The licensed indication does not stipulate use only on those with experience of one prior docetaxel chemotherapy regimen, but the company indicates this will be the main use of the product. Use in patients with prior use of one or more docetaxel-based regimens (based on the all patients from the trial) is also considered in a scenario analysis.
Analysis type	A cost utility analysis (CUA) has been conducted using a survival-based simulation model consisting of three health states: progression-free state (PFS), post progression state (PPS) and dead state. Patients enter the model in PFS upon completion of docetaxel-based chemotherapy regimen. From the progression-free health state patients may proceed to the post-progression state then to death. The number of patients remaining in each health state at each model cycle was calculated directly from the PFS and OS curves from the clinical trial COU-AA-301.	CUA is the preferred type of analysis. The modelled pathway would seem appropriate.
Perspective	NHS Wales.	The analysis considered direct medical costs only.
Time horizon	The base case analysis assumes a ten-year time horizon. Sensitivity analysis considers four-, six- and eight-year time horizons.	Yes, a lifetime horizon of analysis (equivalent to ten years) is appropriate in the context of the course of the disease. Sensitivity analyses demonstrated that the model is not very sensitive to changes in time horizon.
Discount rate	A 3.5% p.a. discount rate is applied to both costs and outcomes. Sensitivity analysis considers 0% and 6% discount rates.	Yes. The model was not very sensitive to variation in discount rate between 0% and 6%.

Table 1 continued.

	Base case model	Appropriate?
Efficacy	For the comparison of AAP versus PP, the OS and PFS data used in the model were derived from COU-AA-301 study. As PFS in the COU-AA-301 study was considered not to be consistent with the way that the progression of metastatic prostate cancer is defined in UK practice, survival curves for treatment discontinuation were used as a proxy for progression. Both OS and PFS data were extrapolated beyond the trial period by truncating actual Kaplan-Meier curves when 10% (for OS) and 5% (for PFS) of patients remained at risk, to account for different levels of censoring. Scenario analyses have explored the impact of different methods for extrapolating OS and PFS (area under the Kaplan-Meier curve and parametric Weibull curves). Due to a lack of comparative data for MP versus AAP and PP, it was assumed that OS and PFS for MP are equivalent to PP. Scenario analysis was conducted which assumed that MP has PFS benefit compared to PP.	The company suggests that the definitions of PFS used in the COU-AA-301 study were not consistent with that used in UK practice and so has instead used treatment discontinuation as a proxy for PFS. The hazard ratio for treatment discontinuation is lower (i.e. is more favourable for abiraterone versus prednisolone) than the hazard ratios for PFS observed in the trial. As patients in the PFS state accrue fewer costs and more benefits than patients in the PPS state, there is potential for the analysis to favour abiraterone. Although sensitivity analyses indicate that the model is not particularly sensitive to the methods of PFS and OS data extrapolation and modelling, these are based on treatment discontinuation data used as a proxy for PFS and no further exploration of PFS has been considered. The company acknowledges there is a lack of comparative survival data for MP compared with PP or AAP, which introduces considerable uncertainty in the MP analyses. **Commercial in confidence data removed.**
Adverse effects	Based on the COU-AA-301 study, the rate of grade 3/4 adverse events (AEs) was assumed to be the same for AAP and PP. Therefore, AEs were not included in this model. For the comparison of AAP versus MP, data from the TROPIC study[9] (MP versus cabazitaxel + prednisolone) were compared with data from the COU-AA-301 study, in order to estimate incremental differences in costs and utilities. **Commercial in confidence data removed.**	Differences in AE rates between MP and AAP or PP were based on an unadjusted indirect comparison. Sensitivity analyses conducted by the company explored the impact of disutility for grade 3/4 AEs and associated costs for the comparison of MP versus PP and AAP. These analyses indicate that the model was not very sensitive to variation in disutilities and costs for AEs.

Table 1 continued.

	Base case model	Appropriate?
Utility values	Utility values for the PFS state were derived from FACT-P (a disease-specific health-related quality of life questionnaire) that was administered to patients in the COU-AA-301 study. Results were mapped onto EQ-5D. Mapped values were compared with utilities reported in the literature. Utility values for the post-progression phase were derived from published estimates. Sensitivity analyses were conducted to address the differences between baseline utilities for mCRPC reported in literature, the uncertainty about utilities for post-progression mCRPC health state, and utilities for AEs.	Appropriate to use relevant trial-derived utility values where possible. The company acknowledges that its approach to mapping utility values in the PFS state is not yet validated, but considers these are robust being based on trial data. Sensitivity analyses using alternative values from the literature (0.85 to 0.538) indicate the model is sensitive to the assumed utility value for the progression-free health state. **Commercial in confidence information removed.** The model appears relatively insensitive to the utility values assumed for the PPS and AEs.
Resource use and costs	A panel of oncologists, nurses and pharmacists was used to obtain information about costs for each health state. These include scheduled outpatient visits, scans and blood tests, unscheduled event-related treatments, concomitant medication costs, AE-related costs and terminal treatment costs. The AAP regimen incurs additional costs related to tests conducted every two weeks for the first three months of treatment and monthly thereafter[1]. A number of assumptions have been made concerning the duration of treatments. It is assumed that patients will receive abiraterone until disease progression, mitoxantrone for a maximum of 30 weeks and prednisolone until death.	Appropriate items of resource use appear to be incorporated, and published costs applied. As resource use is based primarily on expert opinion, this would be subject to considerable uncertainty; however, sensitivity analyses indicate the model is relatively insensitive to the assumed scheduled and unscheduled costs in the range +/-50%. **Commercial in confidence information removed.**
Uncertainty and scenario analyses	**Commercial in confidence information removed.**	A wide range of analyses have been conducted; however, these exclude the proxy PFS data that are based on treatment discontinuation rates.
Model provided?	Yes.	Yes.
AAP: abiraterone with prednisolone; AEs: adverse events; CUA: cost utility analysis; EQ-5D: EuroQol-5 Dimension; mCRPC: metastatic castration-resistant prostate cancer; MP: mitoxantrone with prednisolone; NICE: National Institute for Health and Clinical Excellence; OS: overall survival; WPS: Wales Patient Scheme for access to medicines; PFS: progression-free survival/state; PPS: post-progression state; PP: placebo plus prednisolone; WMP: Welsh Medicines Partnership.		