Re-submission

**abiraterone acetate 250mg tablets (Zytiga®)**

SMC No. (764/12)

Janssen-Cilag Ltd

06 July 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a re-submission

**abiraterone acetate (Zytiga®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

**SMC restriction:** abiraterone is restricted to use in patients who have received only one prior chemotherapy regimen.

Abiraterone plus prednisone was associated with significantly improved overall survival compared with placebo plus prednisone in patients with mCRPC previously treated with docetaxel.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of abiraterone. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**
**Indication**
With prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

**Dosing Information**
1,000mg (four 250mg tablets) as a single daily dose that must not be taken with food. The tablets should be swallowed whole with water at least two hours after eating and no food should be eaten until at least one hour later. Abiraterone acetate is to be taken with low dose prednisone or prednisolone (recommended dose is 10mg daily).

**Product availability date**
9 September 2011

**Summary of evidence on comparative efficacy**

Abiraterone acetate is a prodrug of abiraterone, an androgen biosynthesis inhibitor. It specifically inhibits the enzyme cytochrome P450 17 (CYP17), which is involved in the production of testosterone, and blocks androgen synthesis in the adrenals, testes and prostate tumours. Abiraterone is administered orally.

Abiraterone has a marketing authorisation for use in men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. The submitting company has proposed that the Scottish Medicines Consortium (SMC) considers this product when positioned for use in patients who have received only one prior chemotherapy regimen.

The evidence to support the use of abiraterone acetate in prostate cancer comes from the results of one pivotal, randomised, double-blind, phase III study. Eligible patients were men aged ≥18 years with histologically or cytologically confirmed prostate cancer who had received one or two different cytotoxic chemotherapy regimens (one containing docetaxel). They had disease progression as assessed by the investigator using prostate-specific antigen (PSA) progression (according to PSA Working Group criteria), or radiographic progression in soft tissue or bone with or without PSA progression. Additional inclusion criteria were ongoing androgen deprivation (serum testosterone ≤50ng/dL) and Eastern Co-operative Oncology Group (ECOG) performance status score ≤2. Eligible patients were randomised in a ratio of 2:1 to receive abiraterone acetate (1,000mg daily) plus a corticosteroid (prednisone or prednisolone [5mg twice daily]) (n=791) or placebo plus a corticosteroid (prednisone or prednisolone [5mg twice daily]) (n=394) until disease progression. Randomisation was stratified by ECOG performance status, worst pain over previous 24 hours (measured on the Brief Pain Inventory Short Form [BPI-SF]), number of prior chemotherapy regimens and type of evidence of disease progression (PSA only or radiographic ± PSA).

The primary endpoint was overall survival, assessed in all randomised patients who received the study drug. An interim analysis, planned after 67% (534/797) of the total events had occurred (cut-off date 22 January 2010), ascertained that the results showed significant survival benefit, crossing the pre-specified stopping boundary. The double-blind phase of the study was therefore terminated and patients in the placebo group who were still receiving study medication...
or were in the long-term survival follow-up could receive abiraterone. This interim analysis is the primary analysis and further updated survival has also been reported. No patients had crossed-over from placebo to abiraterone by the time of the updated analysis.

At this primary analysis, after a median follow-up of 12.8 months and median treatment durations of 8 months in the abiraterone and 4 months in the placebo group, there had been 333 deaths in the abiraterone and 219 deaths in the placebo group (42% versus 55% respectively). The median overall survival was significantly longer in the abiraterone than in the placebo group: 14.8 months versus 10.9 months respectively, corresponding to a hazard ratio (HR) of 0.65 (95% confidence interval [CI]: 0.54 to 0.77), \( p<0.001 \). The treatment effect of abiraterone over placebo on overall survival was consistent across all subgroups, significantly favouring abiraterone, with the exception of patients with ECOG performance status of 2.\(^1,^2\)

Results of an updated analysis (cut-off date 20 September 2010) after a median follow-up of 20.2 months and a total of 775 events (501 [63%] in the abiraterone group and 274 [69%] in the placebo group) reported median overall survival of 15.8 months and 11.2 months respectively, corresponding to a HR of 0.74 (95% CI: 0.64 to 0.86).\(^3\)

The company submission presented results of a post-hoc, subgroup analysis in patients who had received only one prior chemotherapy regimen (70% [832/1,195]). The median overall survival at the time of the updated analysis (20 September 2010) in this subgroup significantly favoured abiraterone: 17.1 months in the abiraterone group versus 11.7 months in the placebo group (HR 0.71 [95% CI: 0.59 to 0.85]).\(^4\)

Results for secondary endpoints, including time to PSA progression, time to radiological progression, PSA response rate and objective response rate, significantly favoured abiraterone. Symptom-related endpoints also significantly favoured abiraterone. These included time to 25% of patients experiencing a skeletal event which was 9.9 months versus 4.9 months in the abiraterone and placebo groups respectively and pain palliation rate (reduction of at least 30% in Brief Pain Inventory-Short Form [BPI-SF] worst pain intensity score assessed in patients with a baseline pain score \( \geq 4 \)) which was achieved by 44% and 27% of patients respectively. Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire was an exploratory endpoint which demonstrated small and similar mean changes from baseline in each treatment group.

From the study results, treatment discontinuation was considered by the company to be the most appropriate proxy for progression-free survival (PFS) and was therefore used in the economic case. The results for this endpoint significantly favoured abiraterone over placebo both in the primary analysis and in the updated analysis in the subgroup of patients who had received only one prior chemotherapy regimen.

*Other data were also assessed but remain commercially confidential.*
Summary of evidence on comparative safety

During the pivotal study, treatment emergent adverse events were reported in 99% (782/791) of abiraterone and 99% (390/394) of placebo patients and were considered to be drug-related in 76% (604/791) and 77% (303/394) of patients respectively. Serious treatment emergent adverse events were reported in 38% (297/791) of abiraterone and 41% (163/394) of placebo patients which were considered drug-related in 8.8% (70/791) and 9.9% (39/394) of patients respectively. Treatment emergent adverse events lead to discontinuation in 19% (148/791) and 22% (88/394) of patients respectively.\(^3\)

The most commonly reported adverse events were fatigue (44% in the abiraterone and 43% in placebo group), back pain (30% and 33% respectively), nausea (30% and 32% respectively), constipation (26% and 31% respectively), which were generally considered consistent with the natural history of advanced mCRPC, as well as arthralgia (27% and 23% respectively) and peripheral oedema (31% and 22% respectively).\(^1,3\)

Mineralocorticoid adverse events were more common in the abiraterone than the placebo group: hypokalaemia (17% versus 8%), hypertension (9% versus 7%), and fluid retention (25% versus 17%). These were considered to be related to its mode of action and were reduced by the use of concomitant prednisone. Cardiac disorders were reported in 13% (106/791) of abiraterone and 11% (42/394) of placebo-treated patients; these included tachycardia (3% versus 2% respectively), atrial fibrillation (2% versus 1% respectively), cardiac failure (2% versus 1% respectively) and myocardial infarction (0.8% in each group).\(^3\) However, when standardised for the different durations of treatment, the difference was five cardiac events per 100-patient-years (33 versus 28 respectively) which occurred in atrial fibrillation and tachycardia.\(^3\) Changes in liver function tests were reported in similar proportions of patients (10% and 8% respectively).\(^1\)

Summary of clinical effectiveness issues

Abiraterone acetate is the first androgen biosynthesis inhibitor to become available in the UK after undergoing accelerated assessment by the European Medicines Agency (EMA). Evidence from the pivotal study demonstrated significantly improved overall survival with abiraterone compared with placebo; this was described by the EMA as clinically significant and was supported by secondary and symptom-related endpoints. The submitting company has proposed that SMC considers abiraterone when positioned for use in patients who have received only one prior chemotherapy regimen. The company presented results of a post-hoc subgroup analysis in patients who had only received one prior chemotherapy regimen (70% of the study population) and this supported the economic case. Subgroup analysis in the pivotal paper also supports greater efficacy in this group.

The pivotal study excluded patients with uncontrolled hypertension and clinically significant heart disease, and the summary of product characteristics (SPC) notes that abiraterone should be used with caution in patients with a history of cardiovascular disease. The study population comprised patients with good ECOG performance status (90% of enrolled patients had ECOG performance status of 0 or 1); this may be higher than would be expected in patients likely to be treated in NHS Scotland and could potentially affect the response achieved in clinical practice.
In the pivotal study, the survival benefit did not reach statistical significance in the small number of patients with ECOG performance status of 2.

Abiraterone offers an alternative, orally administered hormonal treatment option to intravenous chemotherapy regimens for these patients, and is better tolerated with a different safety profile. The SPC recommends that serum transaminases should be measured before starting treatment, then every 2 weeks for 3 months and then monthly thereafter. Blood pressure, serum potassium and fluid retention should be assessed monthly.

Comparative data on the relative efficacy of abiraterone and mitoxantrone were not available and a systematic review failed to identify any studies to allow the submitting company to perform an indirect comparison.

SMC clinical experts have reported an unmet need in this area with very limited treatment options for men whose disease has progressed after a docetaxel-based chemotherapy regimen.

### Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis comparing abiraterone plus prednisolone to best supportive care with either prednisolone or dexamethasone for the treatment of mCRPC. A comparison was also performed with mitoxantrone plus prednisolone, and with docetaxel retreatment plus prednisolone. The base case used data from a subpopulation of the phase III trial for abiraterone in which patients had received one prior treatment with docetaxel.

A 10-year time horizon was used in the base case analysis. Progression free and overall survival estimates from the phase III trial were extrapolated using a constant hazard function (i.e. the exponential hazard function) to determine the time spent in progression-free survival (PFS) and post-progression states, and life years gained with abiraterone plus prednisolone versus prednisolone alone. PFS was not based on standard measures used in the clinical trials such as radiographic progression, but instead based on treatment discontinuation data from the clinical trial, as this was argued by the submitting company to represent a more clinically relevant measure of disease progression. Comparative data on the relative efficacy of abiraterone and mitoxantrone were not available, and an attempted indirect comparison failed to find sufficiently comparable studies. Hence, a simple assumption was used that mitoxantrone plus prednisolone has the same PFS and overall survival efficacy as prednisolone alone. The submitting company made the same assumption regarding PFS and overall survival for the comparison with docetaxel retreatment.

The utility of the PFS health state was derived from an exercise using a mCRPC database mapping the FACT-P quality of life instrument to the EQ-5D, whereas post-progression utility was based on published EQ-5D values for patients with end-of-life prostate cancer. An additional on-treatment utility benefit for abiraterone over prednisolone for on-treatment benefits of less pain, fatigue and improved functional status was included in the utility calculations. A net disutility for grade 3 and 4 adverse events was estimated for mitoxantrone relative to abiraterone based on a naïve indirect comparison of adverse events in the abiraterone trial and a 1st line trial for mitoxantrone.
Treatment duration estimates were based on data from clinical trials for each treatment. Drug costs for mitoxantrone were based on an assumed patient body surface area of 2.01m², assumed no vial re-use and an outpatient setting for drug administration. Resource use data for scheduled hospital and GP visits, nurse visits, diagnostic/imaging and other laboratory tests and unscheduled events were estimated using Scottish clinical experts and analysis of data from the abiraterone clinical trial. Resource use based on clinical opinion/trial data and costs for grade 3 and 4 adverse events including the treatment of febrile neutropenia, concomitant medications, post-progression chemotherapy and terminal care was also estimated. For all these, a combination of trial data and Scottish clinical opinion was used to estimate the proportion of patients affected and resource use requirements.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price of abiraterone.

The base case cost per quality adjusted life year (QALY) gained for abiraterone versus the various comparators are shown below:

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Cost per QALY with PAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC/prednisolone</td>
<td>£46,421</td>
</tr>
<tr>
<td>BSC/dexamethasone</td>
<td>£44,606</td>
</tr>
<tr>
<td>Mitoxantrone + prednisolone</td>
<td>£41,122</td>
</tr>
<tr>
<td>Docetaxel retreatment + prednisolone</td>
<td>£24,205</td>
</tr>
</tbody>
</table>

The submitting company also presented a selection of weighted average cost per QALY figures to reflect the mixed pattern of current treatment options. Assuming 70% of patients are currently treated with prednisolone alone, 20% docetaxel retreatment and 10% mitoxantrone, the weighted average cost per QALY was £41,641 with the PAS. If 45% of patients are currently treated with prednisolone alone, 35% with docetaxel retreatment and 20% with mitoxantrone, the cost per QALY was £34,717.

Sensitivity analysis demonstrated the incremental cost-effectiveness ratios (ICERs) were sensitive to the variations in PFS utilities, and scenarios assuming a greater relative efficacy for mitoxantrone and docetaxel retreatment. Assuming a PFS utility of 0.85 (the highest value reported in the literature review), produced the best ICERs for abiraterone vs prednisolone of £42.5K/QALY with PAS and £37.5K/QALY with PAS versus mitoxantrone plus prednisolone and £22K versus docetaxel retreatment. Assuming a PFS hazard ratio of 0.9 for mitoxantrone and docetaxel retreatment relative to prednisolone resulted in an increased with-PAS cost per QALY for abiraterone of £46,044/QALY in the mitoxantrone comparison and £27,808 in the docetaxel retreatment comparison. Applying the Weibull survival function to PFS and overall survival, assuming no additional ‘on treatment’ utility benefit for abiraterone, and assuming a lower body surface area for the comparison with mitoxantrone all increased the ICER for abiraterone.

An important issue regarding the cost-effectiveness of abiraterone was the high cost per QALY in the base case. Other issues were:

- There is uncertainty, in particular versus mitoxantrone and docetaxel retreatment, due to the limited analysis of relative effectiveness and adverse events performed for these comparisons. The results showed some sensitivity to assuming increased efficacy for
these comparator treatments.

- The one-way sensitivity analysis showed the ICERs were upwardly sensitive to a number of key variables such as the method of extrapolating overall and progression-free survival and the utility score for PFS. In general, however, the variation in the ICERs was less than 10%.

- The cost-effectiveness case is most favourable against docetaxel retreatment and the greater the % of this assumed in the weighted average, the more cost-effective the treatment becomes. However, SMC clinical experts have suggested that the level of use of docetaxel retreatment is variable, and in some areas is not as high as the company has suggested. In addition, the weighted average analyses results potentially underestimate the efficacy that would be associated with docetaxel retreatment or mitoxantrone and the sensitivity analysis showed that the ICERs had upward sensitivity when additional efficacy was assumed for these comparators.

- There remains some uncertainty regarding the use of treatment discontinuation as a proxy for PFS. However the company has presented reasons to support this being an appropriate measure given the way in which PFS was measured in the trial compared to how it would typically be assessed in clinical practice which seem broadly reasonable.

SMC considered the likely range of cost-effectiveness ratios and the uncertainties outlined above. SMC considered the application of decision modifiers and concluded that the criteria for improvement in life expectancy, improvement in quality of life and evidence that a sub-group of patients may derive specific or extra benefit and that the medicine can be targeted at this sub-group were all considered to apply. Although there were some limitations in the economic analysis, the committee agreed that the relatively high cost per QALY was acceptable given the expected benefits of the treatment and in the context of the decision modifiers.

*Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Edinburgh and Lothian Prostate Cancer Support Group
- Prostate Cancer Charity Scotland

Additional information: guidelines and protocols

The European Association of Urology (EAU) “Guidelines on Prostate Cancer” discuss various chemotherapeutic options for patients with advanced, relapsing and castration-resistant prostate cancer. In patients who are candidates for chemotherapy, docetaxel 75mg/m² every three weeks is the first-choice cytotoxic regimen as it confers a significant survival benefit. Docetaxel or mitoxantrone with prednisolone or hydrocortisone, are recommended for patients with symptomatic osseous metastases due to hormone-resistant prostate cancer. Docetaxel offers significant advantages in pain relief compared with mitoxantrone so is the preferred option. The 2012 update recommends that patients who relapse following first-line docetaxel should be considered for cabazitaxel or abiraterone as second-line treatment based on the results of prospective, randomised phase III studies. Docetaxel as a second-line option can be considered in patients who previously responded to docetaxel.
The European Society for Medical Oncology published “Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up” in 2010. In relation to castration-refractory metastatic disease, docetaxel given every three weeks is recommended for consideration for symptomatic patients. It also recommends mitoxantrone as an alternative if docetaxel is contraindicated, noting that mitoxantrone is inferior in palliation and does not prolong survival. In patients with painful bone metastases external beam radiotherapy, or radio-isotope therapy are recommended. Intravenous bisphosphonates are recommended for patients with bone pain resistant to radiotherapy and conventional analgesia.

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline 58, “Prostate cancer: diagnosis and treatment” in February 2008. The goals of treatment in hormone-refractory prostate cancer are to improve survival and quality of life and to control symptoms. Advice following a previous technology appraisal of docetaxel was adopted; that docetaxel is recommended as a treatment option in men with metastatic hormone-refractory prostate cancer if their Karnofsky performance status score ≥60%. The regimen was recommended up to 10 cycles, but should be stopped on the advent of severe adverse events or disease progression. Repeat cycles of treatment with docetaxel are not recommended.

### Additional information: comparators

Cabazitaxel was recently licensed for hormone refractory disease previously treated with a docetaxel-containing regimen but was not recommended for use by SMC. Some current treatment guidelines recommend repeated courses of docetaxel or mitoxantrone plus prednisolone (unlicensed).

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone* (plus prednisolone)</td>
<td>1,000mg orally once daily. Prednisolone 10mg orally daily.</td>
<td>2,054</td>
<td>N/A</td>
</tr>
<tr>
<td>Cabazitaxel (plus prednisolone)</td>
<td>25mg/m² intravenous infusion over 60 minutes every three weeks. Prednisolone 10mg orally daily.</td>
<td>3,699</td>
<td>36,986</td>
</tr>
<tr>
<td>Docetaxel (plus prednisolone)</td>
<td>75mg/m² intravenous infusion over 60 minutes every three weeks. Prednisolone 5mg orally twice daily.</td>
<td>903</td>
<td>9,026</td>
</tr>
<tr>
<td>Mitoxantrone** (plus prednisolone)</td>
<td>12mg/m² intravenous infusion over 15 to 30 minutes every three weeks. Prednisolone 10mg orally daily.</td>
<td>155</td>
<td>1,549</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs are taken from MIMS February 2012 except for prednisolone cost from eVadis on 18 April 2012. Costs are based on an adult with a body surface area of 1.8m² rounded to the nearest vial size, given ten cycles and does not include the cost of infusion fluids or pre-medication.

* Abiraterone (plus prednisolone) is given continuously but has been calculated as a 21 day cycle to allow comparison with other agents. Costs for 28 days are £2,735 and for 1 year are £35,551.

** Mitoxantrone is not licensed for the treatment of prostate cancer, and the dosage is based on a comparative study with cabazitaxel.
Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 144 in year 1 and 235 in year 5. Based on an estimated uptake of 80% in year 1 (115 patients) rising to 87% in year 5 (205 patients), the impact on the medicines budget was estimated at £2.7m in year 1 and £4.8m in year 5 without the PAS. The net medicines budget impact was estimated at £2.5m in year 1 and £4.5m in year 5 without the PAS.

*Other data were also assessed but remain commercially confidential.*
References

The undernoted references were supplied with the submission.


*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

This assessment is based on data submitted by the applicant company up to and including 15 June 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.
Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.