PUBLIC SUMMARY DOCUMENT
Product: Abiraterone, tablet, 250 mg (as acetate), Zytiga®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

The submission requested an Authority Required PBS listing for initial and continuing treatment of a patient with metastatic advanced prostate cancer (castration resistant prostate cancer) in patients whose disease progression has occurred following treatment with docetaxel, in combination with prednisone or prednisolone. The submission also requested that the PBAC consider whether the rule of rescue is applicable.

2. Background

This drug had not previously been considered by the PBAC.

The Rule of Rescue:
There are four factors, which when applied concurrently in exceptional circumstances, are called the 'rule of rescue' as follows.
• No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients.
• The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC.
• The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.
• The proposed drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by PBAC.

3. Registration Status

On 1 March 2012, abiraterone was registered by the TGA for the following indication:

- Abiraterone is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a taxane.

4. Listing Requested and PBAC's View

Authority Required
Initial treatment, in combination with prednisone/prednisolone, of a patient with metastatic advanced prostate cancer (castration resistant prostate cancer) in whom disease progression has occurred following treatment with docetaxel.

Continuing treatment, in combination with prednisone/prednisolone, of a patient with metastatic advanced prostate cancer (castration resistant prostate cancer) who has previously

received treatment with PBS subsidised abiraterone acetate and who does not have progressive disease.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Prostate cancer is the most common cancer in Australian men and the second leading cause of male deaths due to cancer. The initial treatment choice is hormone therapy. However, the disease often develops into metastatic castrate resistant prostate cancer (mCRPC) as the tumour no longer responds to hormonal therapies. Docetaxel is currently used first-line in the treatment of patients with mCRPC. Due to the nature of the disease, disease progression after initial chemotherapy treatment occurs frequently.

Treatment options for mCRPC include secondary hormonal manipulations, palliative radiotherapy, chemotherapy and best supportive care. Currently, mitozantrone may be given to patients who are fit for chemotherapy in the second-line setting.

The submission proposed that the place in therapy of abiraterone was as a second-line therapy for patients with metastatic prostate cancer in whom disease progression has occurred following treatment with docetaxel.

6. Comparator

The submission nominated placebo (prednisone/prednisolone plus other care) and mitozantrone (mitozantrone plus prednisone/prednisolone plus other care) as the main comparators, which the PBAC considered appropriate.

The submission nominated cabazitaxel as an additional comparator, which the PBAC also considered appropriate. However, the PBAC noted that although cabazitaxel is likely to replace mitozantrone as second line therapy in the treatment of (mCRPC) for patients who are candidates for cytotoxic chemotherapy, it is not clear whether abiraterone would replace cabazitaxel.

7. Clinical Trials

The submission presented one direct randomised trial comparing abiraterone with best supportive care (placebo; Trial 301), three trials comparing mitozantrone and best supportive care (placebo; Berry, Tannock, Kantoff) and one trial comparing cabazitaxel with mitozantrone (TROPIC).

The submission also presented indirect comparisons of abiraterone versus mitozantrone and cabazitaxel, using placebo as the common comparator in the former and assuming placebo and mitozantrone are equivalent in the latter.

The following trials had been published at the time of submission:

Trial ID / First author	Protocol title/ Publication title	Publication citation
Abiraterone		
COU-AA-301		
de Bono JS et al	Abiraterone and increased survival in metastatic prostate cancer.	The New England Journal of Medicine

		2011; 364(21):1995-2005
Mitozantrone		
Tannock et al	Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative endpoints.	Journal of Clinical Oncology 1996; 14(6):1756-1764.
Dowling AJ et al	A retrospective analysis of the relationship between changes in serum PSA, palliative response and survival following systemic treatment in a Canadian randomized trial for symptomatic hormone-refractory prostate cancer.	Annals of Oncology 2001; 12(6): 773-778.
Osoba D et al	Health related quality of life in men with metastatic prostate cancer treated with prednisone alone or mitoxantrone and prednisone.	Journal of Clinical Oncology 1999; 17 (6):1654-1663.
Bloomfield DJ et al	Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic hormone-resistant prostate cancer: Based on a Canadian randomized trial with palliative endpoints.	Journal of Clinical Oncology 1998; 16(6): 2272-2279.
Bloomfield DJ et al	Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic hormone resistant prostate cancer based on a Canadian randomized trial with palliative endpoints [Abstract 1130].	Proceedings of the American Society of Clinical Oncology 1997; 16:317
Tannock I et al	Chemotherapy with mitoxantrone (M) and prednisone (P) palliates patients with hormone resistant prostate cancer (HRPC): results of a randomized Canadian trial.	Proceedings of the Annual Meeting of the American Society for Clinical Oncology 1995; 14: 653
Berry et al	Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer.	Journal of Urology 2002; 168: 2439-2443.
Gregurich M et al	Phase III study of mitoxantrone/low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone-refractory carcinoma of the prostate [Abstract 1321].	Proceedings of the American Society of Clinical Oncology 2000; 19:336
Kantoff et al	Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B9182 study.	Journal of Clinical Oncology 1999; 17(8):2506-2513
Cabazitaxel		
TROPIC de Bono JS et al	Prednisone plus cabazitaxel or mitoxantrone for metastatic castration resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial.	The Lancet 2010; 376: 1147-1154.
	Cabazitaxel plus prednisone/prednisolone significantly increases overall survival compared to mitoxantrone plus prednisone/prednisolone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel: Final results with updated overall survival of a multinational Phase III trial (TROPIC).	Poster presented at 35th ESMO, Milan, Italy, October 8-12, 2010.

8. Results of Trials

In the pivotal Trial 301, patients were randomly assigned in a 2:1 ratio, stratified by baseline ECOG (0 - 1 versus 2), presence or absence of pain, prior chemotherapies (1 versus 2) and documented type of prostate cancer (PSA progression only versus radiographic progression

in bone or soft tissue with or without PSA progression) to receive either abiraterone or best supportive care (placebo).

Trial 301 was powered to detect a difference between abiraterone and placebo and one interim analysis was planned (after 534 deaths were observed; 67% of the 797 total events). Median survival was statistically significantly longer for patients treated with abiraterone (14.8 months) than for those treated with placebo (10.9 months); resulting in an incremental overall survival of 3.9 months ($p<0.0001$). The hazard ratio was 0.646 (95% CI: 0.543, 0.768) in favour of abiraterone, corresponding to a 35.4% reduction in risk of death.

The indirect comparison of abiraterone and mitozantrone demonstrated a HR of 0.66 (95% CI: 0.51, 0.86 median overall survival) and the indirect comparisons of cabazitaxel and mitozantrone (TROPIC) showed a median overall survival for cabazitaxel of 15.1 months versus 12.7 months for mitozantrone, an incremental survival of 2.4 months (HR of 0.70 (95% CI: 0.59, 0.83). The indirect comparison of abiraterone and cabazitaxel demonstrated a HR of 0.93 (95% CI: 0.73, 1.19).

For PBAC's comments on these results, see Recommendation and Reasons.

Statistically significant differences in functional assessment of cancer therapy – prostate (FACT-P) scores between the abiraterone and placebo arms of Trial 301 were demonstrated. However, the magnitude of changes in the FACT-P Total Scores between the trial arms were small and changes in the subscale FACT-P scores were similar in both groups.

The overall safety of abiraterone was comparable with that of placebo.

9. Clinical Claim

The submission claimed:

1) abiraterone plus prednisone/prednisolone is superior in terms of comparative effectiveness and equivalent in terms of comparative safety over best supportive care (prednisone/prednisolone alone);
2) abiraterone plus prednisone/prednisolone is superior in terms of comparative effectiveness and superior in terms of comparative safety over mitozantrone plus prednisone/prednisolone alone;
3) abiraterone plus prednisone/prednisolone is non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over cabazitaxel plus prednisone/prednisolone alone.

Whilst the PBAC considered that there are uncertainties inherent from indirect comparisons, it accepted the clinical claims in the submission*, see Recommendation and Reasons.*

10. Economic Analysis

A stepped economic evaluation was presented. A decision analytic Markov model was used to estimate the incremental cost-effectiveness of abiraterone for mCRPC after disease progression with first-line docetaxel compared with best supportive care (mitozantrone plus prednisolone and prednisolone monotherapy).

The incremental cost/extra QALY (base case) gained (over 5 years) was estimated to be between $105,000 - $200,000.

Sensitivity analyses conducted during the evaluation, assuming all patients remained on abiraterone therapy until death, indicated that the model was most sensitive to the treatment effect associated with abiraterone, the price requested and the assumption that all patients discontinue abiraterone at disease progression rather than continuing treatment beyond disease progression until death.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost to the PBS was estimated by the submission to be between $30 – $60 million in Year 5 of listing. The estimate was considered uncertain because of the potential of extended use beyond disease progression given the safety profile and ease of administration of abiraterone.

12. Recommendation and Reasons

The PBAC noted that neither the TGA Clinical Evaluator's Report nor the Delegate's Summary had been received and that this would be helpful in determining the future place in therapy of abiraterone. The PBAC agreed that placebo (prednisone/prednisolone plus other care) and mitozantrone (mitozantrone plus prednisone/prednisolone plus other care) are the appropriate comparators. The PBAC also agreed that cabazitaxel is an appropriate additional comparator. However, the PBAC noted that although cabazitaxel is likely to replace mitozantrone as second line therapy in the treatment of mCRPC for patients who are candidates for cytotoxic chemotherapy, it is not clear whether abiraterone would replace cabazitaxel. The PBAC noted that the requested restriction does not preclude concomitant use of cabazitaxel and abiraterone nor does it preclude the use of abiraterone after cabazitaxel treatment. The PBAC considered there is also a risk that abiraterone could be used instead of docetaxel for patients who are not candidates for chemotherapy i.e. as first-line therapy. Therefore, the PBAC considered that there is considerable uncertainty regarding the clinical place in therapy of abiraterone.

The submission presented one direct randomised trial comparing abiraterone with best supportive care (placebo; Trial 301), three trials comparing mitozantrone and best supportive care (placebo; Berry, Tannock, Kantoff) and one trial comparing cabazitaxel with mitozantrone (TROPIC). There are also indirect comparisons of abiraterone versus mitozantrone and cabazitaxel, using placebo as the common comparator in the former and assuming placebo and mitozantrone are equivalent in the latter.

The PBAC noted that median survival was statistically significantly longer for patients treated with abiraterone (14.8 months) than for those treated with placebo (10.9 months); resulting in an incremental overall survival of 3.9 months ($p<0.0001$). The hazard ratio was 0.65 (95% CI: 0.54, 0.77) in favour of abiraterone, corresponding to a 35.4% reduction in risk of death. The PBAC agreed that it was reasonable to assume that there is no overall survival benefit for mitozantrone and that placebo and mitozantrone are equivalent. The indirect comparison of abiraterone and mitozantrone demonstrated a HR of 0.66 (95% CI: 0.51, 0.86) median overall survival) and the indirect comparisons of cabazitaxel and mitozantrone (TROPIC) showed a median overall survival for cabazitaxel of 15.1 months versus 12.7 months for mitozantrone, an incremental survival of 2.4 months (HR of 0.70 (95% CI: 0.59,

0.83). The indirect comparison of abiraterone and cabazitaxel demonstrated a HR of 0.93 (95% CI: 0.73, 1.19).

Whilst the PBAC considered that there are uncertainties inherent from indirect comparisons, it accepted the submission's clinical claims: 1) abiraterone plus prednisone/prednisolone is superior in terms of comparative effectiveness and equivalent in terms of comparative safety over best supportive care (prednisone/prednisolone alone); 2) abiraterone plus prednisone/prednisolone is superior in terms of comparative effectiveness and superior in terms of comparative safety over mitozantrone plus prednisone/prednisolone alone; 3) abiraterone plus prednisone/prednisolone is non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over cabazitaxel plus prednisone/prednisolone alone.

The PBAC noted that the economic model assumes that treatment with abiraterone and mitozantrone ceases upon disease progression and is highly sensitive to discontinuation of treatment. The PBAC considered that as abiraterone is given orally and has a relatively good safety profile, there is the potential that abiraterone may continue to be used well beyond disease progression and until death. The PBAC noted that sensitivity analyses were conducted during the evaluation, assuming all patients remained on abiraterone therapy until death. The results indicate that the model is most sensitive to treatment effect associated with abiraterone, the price requested for abiraterone and the assumption that all patients discontinue abiraterone at disease progression rather than continuing treatment beyond disease progression until death. The PBAC noted that the incremental cost/extra QALY (base case) gained (over 5 years) was estimated to be between $105,000 - $200,000, which was considered to be unacceptably high.

Regarding the rule of rescue, the PBAC agreed that the criteria are not intended to allow for the acceptance of extremely high incremental cost effectiveness for last line treatments of end-stage cancers. Therefore, the clinical place of abiraterone, as an additional treatment in a sequence of treatment options that do not considerably transform a patient's quality of life or extend survival substantially, does not qualify it as a drug for consideration under rule of rescue. Furthermore, there are alternative therapies available for the management of mCRPC, such as docetaxel retreatment, cyclophosphamide and carboplatin .

The PBAC therefore rejected the submission on the basis of an unacceptably high incremental cost-effectiveness ratio and due to uncertainty regarding the clinical place in therapy.

Recommendation:
Reject

13. Sponsor's Comment – November 2011

The sponsor has no comment.

ADDENDUM

Product: Abiraterone, tablet, 250 mg (as acetate), Zytiga®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: March 2012

Purpose of Application:
The resubmission requested an Authority Required listing for the initial and continuing treatment, in combination with prednisone or prednisolone of patients with metastatic advanced prostate cancer (castration resistant prostate cancer) in whom disease progression has occurred following treatment with docetaxel.

Listing Requested and PBAC's View:
Authority Required
Initial treatment, in combination with prednisone/prednisolone, of a patient with metastatic advanced prostate cancer (castration resistant prostate cancer) in whom disease progression has occurred following treatment with docetaxel.

Continuing treatment, in combination with prednisone/prednisolone, of a patient with metastatic advanced prostate cancer (castration resistant prostate cancer) who has previously received treatment with PBS subsidised abiraterone acetate and who does not have progressive disease as defined below.

Definition of progressing disease:
PSA progression and radiographic progression and clinical symptoms.

Note:
Abiraterone is not to be used in combination with cytotoxic chemotherapy.
Docetaxel will not be PBS reimbursed following use of abiraterone.
Once abiraterone has been discontinued, retreatment with abiraterone will not be PBS subsidised.

For PBAC's view, see Recommendation and Reasons.

Comparator:
The PBAC had previously accepted placebo (prednisone/prednisolone plus other care) and mitozantrone (mitozantrone plus prednisone/prednisolone plus other care) as the appropriate comparators. The PBAC also agreed that cabazitaxel was an appropriate additional comparator, as noted previously.

Summary of Resubmission:
The resubmission sought to address the following PBAC concerns associated with the rejection of the original submission:

- uncertainty in relation to the clinical place of abiraterone relative to cabazitaxel;
- uncertainty in relation to the clinical place of abiraterone relative to docetaxel;
- potential use beyond progression; and
- a high and unacceptable ICER.

Details are presented below.

Uncertainty in relation to the clinical place of abiraterone relative to cabazitaxel:
The re-submission proposed a revision to the restriction to include a note which precludes the concomitant use of abiraterone with any cytotoxic chemotherapy.

In addition, the resubmission proposed to work with clinicians and clinician groups to educate prescribers on the clinical positioning of abiraterone relative to cabazitaxel.

Uncertainty in relation to the clinical place of abiraterone relative to docetaxel:
The resubmission suggested that the risk of use of abiraterone prior to docetaxel is likely to be mitigated as a number of trials investigating new therapies in this clinical setting are currently underway.

In order to address the PBAC's concerns that docetaxel may be prescribed and be used in the post-abiraterone progression setting, the resubmission proposed a revision to the proposed restriction which precludes further therapy with docetaxel following treatment with abiraterone. In addition, the re-submission proposed restriction wording to limit treatment with abiraterone to one single treatment course, such that once progression has occurred, no further PBS-subsidised treatment with abiraterone would be permitted.

The resubmission also proposed the education of clinicians regarding the appropriate clinical positioning of abiraterone relative to docetaxel.

Potential use beyond progression:
The resubmission proposed restriction wording to preclude the use of abiraterone in combination with cytotoxic chemotherapy as a way of limiting use beyond progression.
In addition, the re-submission proposed to provide education to clinicians regarding the need to discontinue treatment with abiraterone at progression.

High and unacceptable ICER:
The re-submission offered a revised price.

Economic Analysis
A revised base-case estimate of the incremental cost-effectiveness of abiraterone was presented. No structural changes were made to the model used in the November 2011 submission, however a number of inputs were varied. The ICER in the revised base-case was between $45,000 and $75,000.

Estimated PBS Usage and Financial Implications:
The re-submission estimated the likely number of patients per year to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of between $10 - $30 million in Year 5.

Recommendation and Reasons:
The PBAC recommended listing abiraterone 250 mg tablets on the PBS as an Authority Required listing for the treatment, in combination with prednisone or prednisolone, of castration resistant metastatic carcinoma of the prostate in a patient who has failed treatment with docetaxel on a cost-minimisation basis with cabazitaxel. The equi-effective doses should take into account the differences in dosing schedule (abiraterone 1 g daily in combination with 10 mg prednisolone/prednisone monthly and cabazitaxel 25 mg/m^2 every 3 weeks in combination with 10 mg prednisolone/prednisone) and duration of therapy for cabazitaxel and abiraterone. The PBAC considered there was considerable risk of use in patients prior to using docetaxel. In addition, the PBAC was concerned that patients with castration resistant metastatic carcinoma may be treated with both cabazitaxel and abiraterone sequentially or in combination.

The PBAC noted that while no new clinical data were presented, a revised price was offered. The economic analysis was re-specified, based on less conservative sensitivity analyses from the original submission, and the source of utilities had changed (which has not previously been evaluated in a sensitivity analysis). The PBAC noted that the ICER was now estimated to be between $45,000 and $75,000 per QALY (compared with between $105,000 and $200,000 per QALY in the previous submission).

The PBAC considered that the proposed ICER for abiraterone is still too high. The PBAC acknowledged that abiraterone is non-inferior to cabazitaxel, but has a better safety profile and is more convenient to administer (oral administration) and that this should also be taken into consideration during pricing negotiations.

The PBAC considered that there are a number of assumptions in the abiraterone submission which overestimate the costs to Government:

1) the the proportion of patients receiving docetaxel as an inpatient (non PBS), which increases the number of patients eligible for abiraterone;
2) underestimation of the number of patients who do not take up second-line therapy;
3) high uptake of abiraterone and very little use of cabazitaxel. The PBAC considered that a 75:25 split (a market share approach) may be reasonable which takes into consideration that abiraterone is given orally and has a better side effect profile;
4) the number of scripts per treatment. Rather than a modelled number of scripts, the PBAC considered that the trial data should be used to estimate scripts per treatment.

The PBAC concluded that if the overestimates are accounted for, then the total projected expenditure would be about half that proposed in the submission.

The PBAC considered that "castration resistant metastatic carcinoma of the prostate" is the accepted description of the condition rather than "hormone resistant". The PBAC recommended the addition of several NOTES to ensure the appropriate use of abiraterone i.e. not in combination with chemotherapy, no use after progressive disease and no use of docetaxel after failure of abiraterone (or cabazitaxel). The PBAC also recommended that the restrictions for cabazitaxel and abiraterone be consistent.

In making this recommendation the PBAC noted the consumer comments on this item as well as advice from the Medical Oncology Group of Australia (MOGA).

The PBAC recommended that abiraterone is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements by nurse practitioners within a Shared Care Model.

Recommendation:
ABIRATERONE, tablet, 250 mg (as acetate)

Restriction: <u>Authority Required</u>
Treatment, in combination with prednisone or prednisolone, of castration resistant metastatic carcinoma of the prostate in a patient who has failed treatment with docetaxel due to resistance or intolerance and who has WHO performance status of 2 or less.

Note:
Abiraterone is not PBS-subsidised for use in combination with chemotherapy.

Patients who have received PBS subsidised abiraterone or cabazitaxel are not eligible for PBS subsidised docetaxel.

Patients who have progressive disease on abiraterone are no longer eligible for PBS-subsidised abiraterone.

Note:
Shared Care Model:
For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Note:
Special Pricing Arrangements apply

Max quantity: 120
Repeats: 2

14. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

15. Sponsor's Comment – March 2012

Janssen welcomes the PBAC's positive recommendation for abiraterone. However, Janssen disagrees with the parameters of the recommendation, specifically that abiraterone should be cost-minimised to cabazitaxel for all patients with metastatic castrate resistant prostate cancer who have failed docetaxel, and advises that it will not pursue listing on this basis.

Janssen believes that those patients who progress following docetaxel therapy can be classified into two groups:
1) patients in whom chemotherapy is unlikely to be tolerated or effective (for whom the sponsor considers the comparator is best supportive care); and
2) patients who are candidates to receive further chemotherapy (for whom the sponsor considers the comparators are mitoxantrone and cabazitaxel).

Janssen considers that patients in these two groups are managed differently with clinical decisions focused around the patient's functional status and ability to tolerate further chemotherapy.

Janssen will continue to work with the PBAC in order to achieve PBS listing for abiraterone.