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

1. Purpose of Application

The re-submission sought a review of the March 2012 PBAC decision that cabazitaxel was the main comparator to abiraterone and that abiraterone be recommended on a cost-minimisation basis against it. In addition the re-submission also sought a review of the approach to the estimation of the overall costs associated with the adverse event profile associated with cabazitaxel.

2. Background

This was the fourth consideration of abiraterone by the PBAC. It was previously considered as a major submission at the November 2011 PBAC meeting and subsequently as minor submissions at the March 2012 and July 2012 meetings. The PBAC had previously recommended abiraterone for listing at both the March 2012 and July 2012 meetings but the sponsor did not to proceed with listing.

A copy of the Public Summary Document from the November 2011 meeting, including addendums for the March 2012 and July 2012 meetings, is available at:
http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/abiraterone

3. Registration Status

Abiraterone was TGA registered on 1 March 2012 with 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

The sponsor requested the restriction recommended at the July 2012 PBAC meeting.

Authority Required
Castration resistant metastatic carcinoma of the prostate.

- The treatment must be in combination with prednisone or prednisolone;
- The treatment must not be used in combination with chemotherapy;
- Patient must have failed treatment with docetaxel due to resistance or intolerance;
- Patient must have a WHO performance status of 2 or less; and
- Patient must not receive PBS-subsidised abiraterone if progressive disease develops while on abiraterone.

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

5. Clinical Place for the Proposed Therapy

The re-submission proposed that abiraterone was an additional treatment option to best

supportive care, mitozantrone and cabazitaxel for patients with prostate cancer who have failed treatment with docetaxel.

The re-submission proposed that patients with metastatic castrate resistant prostate cancer (mCRPC) who have progressing disease after treatment with docetaxel can be divided into two groups – (i) patients who would be considered candidates for further cytotoxic chemotherapy; and (ii) patients who would not be considered candidates for further chemotherapy. The re-submission proposed that abiraterone is an alternative treatment option for both patient groups, and claimed that cabazitaxel would only be used in patients suitable for further cytotoxic chemotherapy.

6. Comparator

The re-submission presented a mixed comparator of mitozantrone in 25% of patients and best supportive care in 75% of patients for the scenario where cabazitaxel is not available on the PBS. This scenario was presented in the November 2011 submission. At the time this re-submission was prepared (lodged in July 2012), cabazitaxel had a positive PBAC recommendation to list but was not yet listed on the PBS.

The re-submission also presented an alternative scenario in which cabazitaxel is available on the PBS. The alternative scenario assumed that cabazitaxel is the comparator for 50% of patients (i.e. patients suitable for cytotoxic chemotherapy following progression of disease after treatment with docetaxel) and best supportive care for the remaining 50% of patients whom would not be considered for further chemotherapy.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The re-submission did not present any new clinical trial data to that presented in previous submissions. Publication details have previously been reported in the November 2011 Public Summary Document.

8. Results of Trials

Refer to the Public Summary Document from the November 2011 meeting. No additional trial data were presented.

9. Clinical Claim

The clinical claims presented in the re-submission were unchanged from those presented in the previous three submissions. *Refer to previous abiraterone Public Summary Documents.*

10. Economic Analysis

The basis of the economic claim in the submission was a modelled economic evaluation based on the claim of superior efficacy versus mitozantrone and best supportive care and superior safety versus cabazitaxel and mitozantrone.

The re-submission presented an incremental cost effectiveness ratio (ICER) of between $45,000 and $75,000 per quality adjusted life years gained (QALY) for abiraterone versus the current scenario (assuming 75% best supportive care and 25% mitozantrone in the comparator arm), based on taking treatment discontinuation rates and time from

discontinuation to death from the trial, and extrapolating to 7 years duration (from 12.8 months in the trial) and applying utility weights from Sandblom et al (2004). In March 2012, the PBAC had previously considered that the proportion of patients receiving best supportive care was very small and therefore it was problematic to include a comparison against best supportive care as part of a cost-minimisation (or cost utility analysis).

The re-submission presented an ICER of between $45,000 and $75,000 per QALY for abiraterone versus the alternate scenario (assuming 50% best supportive care and 50% cabazitaxel in the comparator arm), based on assuming the same discontinuation and death rates for cabazitaxel compared to abiraterone.

The re-submission also provided a direct comparison of abiraterone and cabazitaxel. Treatment for febrile neutropenia associated with cabazitaxel in addition to the cost of an intravenous infusion were included as cost-offsets. The re-submission's cost estimates were based on an average of 6 cycles of cabazitaxel treatment. The costs of administering granulocyte colony-stimulating factor (G-CSF) to prevent and treat febrile neutropenia were based on Australian-Refined Diagnosis Related Group (AR-DRG) data.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated with abiraterone was unchanged from the July 2012 re-submission.

The submission's revised estimated overall net cost to the PBS for cabazitaxel and abiraterone was between $10 - $30 million per year in year 5.

12. 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 and a cost-effectiveness basis when compared with best supportive care.

The PBAC recalled that this was consistent with its previous recommendation of July 2012. The PBAC noted the re-submission's argument that best supportive care should be a relevant comparator, and that abiraterone be listed on a cost-effectiveness basis compared with best supportive care (superior effectiveness and equivalent safety; 50%) and a cost-minimisation basis with cabazitaxel (non-inferior effectiveness and superior safety; 50%). However, the PBAC considered that estimating the number of patients unsuitable for cabazitaxel following treatment with docetaxel remained a source of much uncertainty, and that the exact proportion of comparator split is therefore unclear due the current changing market. The PBAC noted the clinical management algorithm provided by the Medical Oncology Group of Australia (MOGA) estimating that 50% of patients will be unfit for further chemotherapy following treatment with docetaxel. However, it was unclear to the PBAC what data this percentage figure was based on. In acknowledging this advice, the PBAC therefore considered that a pragmatic approach would be to accept an equal comparator split between best supportive care (50%) and cabazitaxel (50%).

The PBAC recalled that they had previously accepted that abiraterone has a better safety profile, and as an oral dosage form, is more convenient to administer than cabazitaxel. The PBAC also recalled that that they had previously considered it appropriate to include a cost offset for the intravenous administration of cabazitaxel, and that this remained unchanged from the July 2012 recommendation. The PBAC noted the re-submission's proposal (consistent with the July 2012 submission) that the costs associated with the administration of granulocyte colony-stimulating factor (G-CSF) to prevent and treat febrile neutropenia, occurring as a result of treatment with cabazitaxel, should be offset against the cost of abiraterone. The PBAC reaffirmed that G-CSF is not routinely administered in clinical practice and is not PBS subsidised for prostate cancer. However, the PBAC agreed that changes in the rate of utilisation of G-CSF would have implications for the dose intensity of cabazitaxel as patients may be more or less able to tolerate cabazitaxel and develop neutropenia, depending on whether G-CSF was used more or less frequently. The PBAC also recalled that the cost of some G-CSF usage, inevitable in real world practice, was taken into account in its recommendation to list cabazitaxel at its March 2012 meeting. Therefore, as the consideration of abiraterone was contemporaneous with the PBAC consideration of cabazitaxel, the Committee considered that a cost offset for G-CSF use with cabazitaxel of less than $500 for a complete course of treatment was appropriate, noting that the amount was significantly less than that proposed in the submission.

The PBAC noted that results of the key sensitivity analyses conducted during the evaluation indicate that the model is most sensitive to treatment duration for abiraterone and cabazitaxel and the point of discontinuing treatment. This causes uncertainty in the ICER, which ranges from a base case ICER in the range of $45,000 - $75,000 up to an ICER in the range of $105,000 - $200,000 if 100% of patients remained on abiraterone beyond disease progression, up until the point of death. The PBAC further noted that these ICERs relied on inappropriately high cost offsets for G-CSF and are therefore favourable to the sponsor. As previously noted, the proportion of patients on cabazitaxel in the comparator arm of the model, and costs of G-CSF were also significant.

The PBAC reaffirmed its concerns from July 2012, that there would be considerable risk of use of abiraterone in patients prior to using docetaxel. The PBAC also reaffirmed that there would be a high risk that patients may be treated with both abiraterone and cabazitaxel either sequentially or in combination, and that abiraterone may be continued beyond disease progression, potentially leading to a substantial increase in the ICER. The PBAC therefore reaffirmed its decision from July 2012 that a risk share agreement would be required to mitigate the financial risk to Government of treatment beyond progression and use in patients who had not previously been treated with docetaxel.

In considering that an equal comparator split between best supportive care (50%) and cabazitaxel (50%) was appropriate, the PBAC accepted that the implications would be that abiraterone and cabazitaxel will be competing for market share only in the 50% subset of patients who are fit for further chemotherapy following docetaxel failure. The PBAC therefore accepted that only 50% of predicted abiraterone use post docetaxel should be included in the same financial cap as cabazitaxel. The PBAC considered that the remaining 50% of predicted abiraterone use in patients who are considered unfit for chemotherapy

should be subject to an equal but separate risk share arrangement, with both risk share arrangements including a suitable rebate if the cap was exceeded.

The PBAC noted that the recommended NOTE in the restriction for abiraterone will have flow on effects to the NOTEs for the cabazitaxel and docetaxel listings at the time abiraterone's listing is implemented.

The PBAC recommended the 20 Day Safety Net Rule should apply.

The PBAC recommended abiraterone is not suitable for inclusion in the medicines for prescribing by nurse practitioners within collaborative arrangements.

Recommendation:
No changes to the restriction recommended at the July 2012 PBAC meeting were recommended. The PBAC's recommended changes relate to the basis of the recommendation and not to the restriction text.

13. 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.

14. Sponsor's Comment

Janssen-Cilag is pleased with various aspects of the PBAC's November 2012 recommendation.

Janssen-Cilag disagrees with the PBAC recommendation that the listing of abiraterone should be based partially on the basis of cost-minimisation with cabazitaxel. In addition, it is Janssen-Cilag's view that the PBAC's estimate of the total cost of treatment with G-CSF for patients experiencing febrile neutropenia when on cabazitaxel of less than $500 over 6 treatment cycles is a significant underestimate and is not reflective of drug costs, nor the costs of treating febrile neutropenia as an inpatient over a course of treatment.

Despite these concerns related to the recommendation by the PBAC, Janssen-Cilag believes that additional submissions would delay patient access. Janssen-Cilag is committed to listing abiraterone on the PBS as soon as possible and are moving forward with the listing of abiraterone.