

6.1 ABIRATERONE ACETATE, tablet, 250 mg, Zytiga®, Janssen-Cilag Pty Ltd

1 Purpose of Application

- 1.1 Authority required listing for abiraterone for treatment of metastatic castrate-resistant prostate cancer (mCRPC) after treatment failure with androgen deprivation therapy (ADT; ie, prior to treatment with docetaxel).

2 Requested listing

- 2.1 The following restriction was requested. The strikethroughs are recommended changes from PBAC (notwithstanding the decision to reject the submission).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
ABIRATERONE Tablet, 250 mg	1	5	Zytiga JC

Severity:	Castration resistant metastatic
Condition:	carcinoma of the prostate
Clinical criteria:	<p>The treatment must be in combination with prednisone or prednisolone</p> <p>AND</p> <p>Patient must have progressed following treatment with bicalutamide or flutamide or nilutamide androgen deprivation therapy,</p> <p>AND</p> <p>Patient must be asymptomatic (defined by the absence of cancer-related pain)</p> <p>AND</p> <p>Patients must have a PSA of 114ng/mL or less</p> <p>AND</p> <p>Patient must have a ECOG WHO performance status of 1 or less</p> <p>AND</p> <p>The treatment must not be used in combination with chemotherapy</p> <p>AND</p> <p>Patient must not receive PBS subsidised abiraterone if progression of disease develops while on abiraterone. have progressive disease whilst taking this drug.</p>
Administrative Advice	<p>Patients who have received PBS subsidised abiraterone under this restriction are not eligible to receive PBS subsidised abiraterone following treatment with docetaxel.</p> <p><i>Special Pricing Arrangements apply.</i></p>

- 2.2 The selection of the prostate-specific antigen (PSA) threshold of 114ng/mL is based on post hoc sub group analyses (Berthold 2008¹ ; Armstrong 2007)² based on the median PSA levels of patients enrolled in the TAX327 trial (Tannock 2004)³, which compared docetaxel with mitoxantrone in patients with mCRPC and is dependent on the patients enrolled in the trial only. ESC noted that PSA level is age specific and that progression of disease is usually with reference to PSA kinetics (i.e. doubling time). Clinically, PSA <114ng/mL appears to be an arbitrary threshold for a ‘no treatment’ decision. ESC is aware of support from the Medical Oncology Group of Australia MOGA for the restriction (Pre-Sub-Committee Response (PSCR)).
- 2.3 It is also unclear to the ESC whether patients classified as experiencing mildly symptomatic pain according to the Brief Pain Inventory Questionnaire (BPI-SF Q3) used in Trial 302 and proposed to be excluded from the proposed trial PBS population would be effectively excluded by physician-rated definitions of asymptomatic disease.
- 2.4 Listing was sought on a cost utility basis with abiraterone compared to watchful waiting (placebo).

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 Abiraterone was TGA registered on 1 March 2012 and is indicated (with prednisone or prednisolone) for the treatment of patients with metastatic castration resistant prostate cancer (mCRPC):
- Who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) or
 - Who have received prior chemotherapy containing a taxanes
- 3.2 Abiraterone has not previously been considered by the PBAC for this indication. Abiraterone was listed on the PBS, on 1 August 2013, for the treatment of patients with mCRPC whose disease has progressed following treatment with docetaxel.

4 Clinical place for the proposed therapy

- 4.1 Metastatic castration resistant prostate cancer arises when metastatic tumours continue to develop despite androgen deprivation therapy (ADT) that reduces circulating androgens to castration levels.
- 4.2 Abiraterone is proposed for treatment of metastatic castration resistant prostate cancer (mCRPC) after failure with secondary-androgen deprivation therapy (ADT) but before docetaxel in patients with ‘asymptomatic’ disease (defined as physician assessed absence of cancer pain, PSA ≤114ng/mL, and ECOG ≤1).

For more detail on PBAC’s view, see section 7 “PBAC outcome”

¹ Armstrong A et al (2007), A contemporary prognostic nomogram for men with hormone refractory metastatic prostate cancer: a TAX327 study analysis. *Clin Cancer Res*; 13(21):6396-6403.

² Berthold D et al (2008), Docetaxel plus prednisolone or mitoxantrone plus prednisolone for advanced prostate cancer: updated survival in the TAX327 study. *Journal of Clinical Oncology*; 26(2):242-245.

³ Tannock et al (2004). Docetaxel plus prednisolone or mitoxantrone plus prednisolone for advanced prostate cancer. *N Engl J Med*; 351:1502-1512

5 Comparator

- 5.1 The submission nominated watchful waiting (placebo) as the comparator. This required consideration as it is unclear to the ESC how many patients who are diagnosed with metastatic disease would opt for no treatment, particularly when (i) the use of docetaxel on the PBS is not precluded for 'asymptomatic' patients and (ii) a patient's fitness for chemotherapy is a consideration (treat patients earlier rather than later). Therefore, the Commentary stated that docetaxel and BSC (in those who are unable to undertake chemotherapy) are likely to be replaced. A mixed comparator of watchful waiting, docetaxel and BSC may be the appropriate comparator. The PSCR asserts that both European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend the use of docetaxel in patients with symptomatic mCRPC. For the small group of patients with rapidly progressing asymptomatic disease (i.e. with rapidly rising PSA doubling times or with hepatic metastases) the PSCR suggests these patients would not qualify for abiraterone as their PSA will have increased beyond the PBS eligibility criteria. The ESC noted that with a PBS restriction with five repeats it is feasible that abiraterone could be used for 6 months in patients with rapid doubling times of PSA (if low to start with) and still fall under the proposed PSA <114ng/mL.
- 5.2 The ESC noted docetaxel treatment will likely be reserved for those with pain or with rapid progression. The primary concerns with chemotherapy are with the myelosuppressive side effects and comorbidities. Pain confers poor prognosis and reduced OS, and may compromise further use of chemotherapy. Survival benefits from chemotherapy were seen in the TAX327 trial (docetaxel vs mitoxantrone) in symptomatic and asymptomatic patients. Collectively this evidence suggests that there is potential for mildly symptomatic patients or those with rapidly progressing disease to be treated currently with docetaxel. Docetaxel may therefore be an appropriate comparator.
- 5.3 The ESC considered that if the comparison is only in asymptomatic patients, without rapidly progressing disease, watchful waiting is the appropriate comparator. If it is likely that patients with mildly symptomatic disease or asymptomatic but rapidly progressing disease will be treated, then including docetaxel (and best supportive care in those ineligible for chemotherapy) may be appropriate. For the latter, the relative weighting of these treatment options would also need to be considered. No head-to-head trials comparing abiraterone and docetaxel or BSC are available.
- 5.4 The PSCR highlighted an analysis of a 10% sample of Medicare scripts, provided with the submission, which indicates that there is currently a substantial period of watchful waiting (a median time of [REDACTED]) between ceasing ADT and, if clinically suitable, initiating docetaxel.
- 5.5 A letter to the PBAC Secretariat was received from MOGA (7 May 2014) in response to the Secretariat's request for MOGA advice regarding the clinical place of abiraterone in patients with metastatic prostate cancer who have progressed following treatment with ADT. The letter stated "[the proposed extension to the PBS listing of abiraterone] will benefit those men who can never be considered for chemotherapy, and will delay the introduction of chemotherapy, and the associated toxicity, in those eligible for intravenous anti-neoplastic agents."

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (66), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with abiraterone including the ability to improve quality of life, postpone chemotherapy, and remain active in family life.

6.3 The PBAC noted the advice received from Medical Oncology Group of Australia (MOGA) clarifying the likely use of abiraterone in clinical practice. The PBAC specifically noted the advice that in patients who are fit for chemotherapy, abiraterone will be used to delay the use of chemotherapy. For patients who are not candidates for chemotherapy (on the basis of medical reasons or patient preference) abiraterone will be used as the mainstay of treatment following failure of ADT. The PBAC noted that in study COU-AA-302 chemotherapy was used subsequently to study treatment (abiraterone or placebo) in the majority of patients. Thus the evidence provided in the submission related to the group of patients who were suitable for chemotherapy rather than the group of patients who would never receive chemotherapy.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Clinical trials

6.4 The submission is based on one head-to-head randomised trial comparing abiraterone + prednisone/prednisolone with watchful-waiting (placebo) + prednisone/prednisolone:

- Trial COU-AA-302 (*referred to as “Trial 302” herein*).
- The details of Trial 302 are below (*the third interim analysis was used*).

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
COU-AAA-302 (<i>“Trial 302”</i>)	A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisolone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer. Ryan et al. Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. Basch et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Ryan et al. Interim analysis (IA) results of COU-AA-302, a randomized phase III study of abiraterone acetate (AA) in chemotherapy-naïve patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).	Clinical Trial Report The New England journal of Medicine 2013; 368:138-148 The Lancet Oncology 2013; 14(12):1193-1199 Journal of Clinical Oncology 2012; 30(Suppl;Abstr LBA4518)

Key features of Trial 302

N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
1088 ^a	R, DB 36 mths ^b	Low ^c	mCRPC, medical or surgically castration, chemotherapy-naïve, asymptomatic or mildly symptomatic ^d	1°: OS, rPFS 2°: time to opioid use, time to chemotherapy, time to first deterioration, time to PSA progression	OS + time to study treatment discontinuation are modelled

^a safety population = 1082; PBS-sub-group = [REDACTED]

^b results in the submission are presented based on the third interim analysis to 36 months; planned final follow-up is to 5 years.

^c low risk of bias up to the second interim analysis; treatment was un-blinded after the second interim analysis and cross-over recommended

^dmildly symptomatic patients are excluded from the 'PBS population'

6.5 The submission nominates a PBS-subgroup (BPI-SF Q3 pain score: 0-1, baseline PSA ≤114ng/mL, ECOG≤1) in Trial 302 (n=[REDACTED]) as being representative of the PBS population. The ITT population of Trial 302 is arguably more representative of the likely PBS population, given:

- Clinician assessment/classification of “asymptomatic pain” may encompass patient rated pain scores of 2-3 out of 10 on the BPI-SF Q3;
- Majority ([REDACTED]%) of patients in Trial 302 had a PSA <114ng/mL (median of [REDACTED]ng/mL); and
- All patients enrolled in Trial 302 had an ECOG ≤1.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Comparative effectiveness

Overall survival in the ITT, non-PBS and PBS subgroup populations of Trial 302 (third-interim analysis)

	ITT population*		Post-hoc subgroup analysis			
			non-PBS subgroup (PSA≥114ng/mL, BPI-SF Q3 score: 3-4)		PBS subgroup (PSA<114ng/mL, BPI-SF Q3 score: 0-1)	
	AB	PLA	AB	PLA	AB	PLA
Event	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Censored	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Median survival (months)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Abs. difference	[REDACTED]		[REDACTED]		[REDACTED]	
p-value	[REDACTED]		[REDACTED]		[REDACTED]	
HR (95%CI) ^b	[REDACTED]		[REDACTED]		[REDACTED]	
Treatment interaction			[REDACTED]			

Abbreviations: ITT=intention to treat, CI=confidence interval, NE = not estimable, AB = abiraterone + prednisone/prednisolone, PLA= placebo + prednisone/prednisolone

*this is the third interim analysis

[REDACTED]

6.6 The observed increase in median overall survival benefit in the ITT populations:

- Trial 302 (pre-docetaxel; results did not meet the pre-specified statistical significance level based on the O’Brien-Fleming efficacy boundary (nominal

significance level of 0.0035)): [REDACTED] over [REDACTED] follow-up, with a median treatment duration of [REDACTED]; versus

- Trial 301 (post docetaxel): 3.9 months over 12.8 months follow-up with a mean treatment duration of 8.4 months.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Comparative harms

- 6.7 A statistically significantly greater proportion of patients treated with abiraterone experienced treatment emergent adverse events (specifically hypertension and hepatotoxicity) and Grade 3-4 treatment emergent serious adverse events.
- 6.8 A summary of the comparative benefits and harms for abiraterone versus watchful waiting (placebo) is presented in the table below.

Summary of comparative benefits and harms for abiraterone+prednisone/prednisolone and watchful waiting (placebo)+prednisone/prednisolone

Benefits						
OS: Trial 302 (ITT population)						
	Abiraterone	Watchful waiting (placebo)	Absolute Difference		HR (95% CI)	
Survival*	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
Median (mths)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
radiographic progression-free survival (rPFS): Trial 302 (ITT population)						
rPFS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
Median rPFS (months)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
Harms						
	Abiraterone	Watchful waiting (placebo)	RR (95% CI)	RD (95% CI)	Event rate/100 patients	
					Abiraterone	Watchful waiting (placebo)
Adverse event (treatment emergent) of special interest in Trial 302 (safety population)						
Fluid retention	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Hypokalaemia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Hepatotoxicity	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Hypertension	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abiraterone = abiraterone + prednisone/prednisolone; Watchful waiting = placebo + prednisone/prednisolone

Abbreviations: NE = not estimable; PBO = placebo; RD = risk difference; RR = risk ratio

- 6.9 On the basis of direct evidence presented by the submission, the comparison of abiraterone + prednisolone/prednisone and placebo + prednisolone/prednisone resulted in an improvement of approximately 5 months overall survival and 8 months progression free survival for the ITT population. While this did not meet statistical significance based on the strict pre-specified significance criteria, this result may have been affected by the early termination and crossover observed in the trial. For every 100 patients treated with abiraterone, in comparison with placebo, approximately 7 additional patients experienced hepatotoxicity.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Clinical claim

- 6.10 The submission describes abiraterone as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over “watchful waiting (placebo)”. The claim regarding safety is adequately supported. There were differences in the rates of hypokalemia, hypertension and hepatotoxicity. However, with the exception of the increase in hepatotoxicity, these did not reach statistical significance after adjusting for treatment exposure. The claim with respect to effectiveness is adequately supported for the ITT population despite the differences in overall survival between abiraterone and placebo not meeting statistical significance according to the strict pre-specified statistical analyses planned for the trial. These results may have been affected by the early termination and crossover.
- 6.11 Although a statistically significant difference in overall survival was observed in the trial’s ‘PBS subgroup’ (BPI-SF Q3 score of 0-1, baseline PSA <114ng/mL and ECOG ≤1), this result may not apply to the likely PBS population. A comparison versus placebo (watchful waiting) may not be the only relevant comparison. Also, the PBS subgroup analysis was post-hoc and there was no statistically significant difference in the ITT population. The PSCR (p1) states that although this subgroup of was based on a combination of factors that were not pre-specified, subgroup analyses were pre-specified for the individual factors of PSA and pain score at baseline. This suggests that investigators did consider that these variables might be important as either prognostic factors or as modifiers of treatment effect.
- 6.12 The PSCR responded to the Commentary request (p6.1.COM.7) for the number of patients in Trial 302 who had a baseline PSA <114 ng/mL. These data are presented below;
- Total trial population (n= [redacted])
 - [redacted] of the [redacted] patients recruited to Trial 302 had a baseline PSA concentration of < 114 ng/mL
 - PSA<114 and pain <0-1: [redacted] (%)
 - PSA<114 and pain >0-1: [redacted] (%)
 - PSA>114 and pain <0-1: [redacted] (%)
 - PSA>114 and pain >0-1: [redacted] (%)
 - Australian Specific figures (n=132)
 - PSA<114 and pain <0-1: [redacted] (%)
 - PSA<114 and pain >0-1: [redacted] (%)
 - PSA>114 and pain <0-1: [redacted] (%)
 - PSA>114 and pain >0-1: [redacted] (%)

ESC considered it unclear how well the physician assessment of pain, as stated in the requested indication, aligns with the BPI-SF Q3. There is some chance that mildly symptomatic cancer pain could be included. PSA is a more objective measure. Given this uncertainty, if all PSA<114 are considered representative of the PBS population then this [redacted]% of the trial population represents the proposed PBS population. The ITT would therefore appear the most appropriate population to consider under the given restriction.

- 6.13 The PBAC considered the ITT analysis to be the most relevant trial data. The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.14 The PBAC considered that the claim of inferior comparative safety was reasonable.

- 6.15 However, the PBAC did not accept the comparator of “watchful waiting” and therefore these claims are not a sufficient basis for consideration of cost-effectiveness. See paragraph 7.3.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Economic analysis

- 6.16 The submission presents a modelled economic analysis.

Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 3 years in trial
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Health states	1) “Free of progression”; 2) “Progressing disease”; 3) “Dead”
Cycle length	30 days
Transition probabilities	Trial 302 with extrapolation

Source: compiled during the evaluation

Key drivers of the model

Description	Method/Value	Impact
Population modelled (effect size)	Base case ICER based on the results of the PBS subgroup in Trial 302.	High, favours abiraterone There is uncertainty as to whether the wording of the requested restriction is sufficient to limit use of abiraterone on the PBS to patients with comparable characteristics of those included in this subgroup. ITT population may be more representative.

Source: compiled during the evaluation

- 6.17 Some errors were detected in the model. The results presented below are those with these errors amended.

Results of the stepped economic evaluation

Step and component	Abiraterone + prednisolone	Prednisolone	Increment
Step 1: ITT population trial-based costs and outcomes			
Costs			
LYs			
Incremental cost/extra life-years gained over 3 years			
Step 2: ITT population trial-based costs and pre-modelling (life years converted into quality adjusted life years)			
Costs			
QALYs			
Incremental cost/extra QALY gained over 3 years			
Step 3a: ITT modelled evaluation (model extrapolated from 3 to 10 years with <u>log-logistic</u> and <u>gamma</u> functions[^])			
Costs			
LYs			
Incremental cost/extra LY gained over 10 years			
Incremental cost/extra QALY gained over 10 years			
Step 3b: ITT modelled evaluation (model extrapolated from 3 to 10 years with <u>exponential</u> and <u>weibull</u> functions[#])			
Costs			
LYs			
QALYs			

Incremental cost/extra LY gained over 10 years					
Incremental cost/extra QALY gained over 10 years					
Step 4: PBS subgroup modelled evaluation (model population changed from the ITT to PBS population@)					
Costs					
LYs					
QALYs					
Incremental cost/extra LY gained over 10 years					
Incremental cost/extra QALY gained over 10 years					
Results for the economic evaluation presented for the post-docetaxel population (November 2012)					
Costs					
LYs					
QALYs					
Incremental cost/extra LY gained over 7 years					
Incremental cost/extra QALY gained over 7 years					

[REDACTED]

- 6.18 The key driver of the differences in the total cost of abiraterone in the current and post-docetaxel models is the mean duration of treatment - [REDACTED] estimated in the current model versus [REDACTED] observed in the post-docetaxel setting. The model estimates an overall survival benefit of [REDACTED] compared with placebo in the pre-docetaxel and [REDACTED] compared with 50:50 cabazitaxel:BSC in the post-docetaxel settings [REDACTED].
- 6.19 To analyse the ITT population, the submission utilised a log-logistic and gamma function to extrapolate “free of progression” and “overall survival”. As shown in Figure C.2.2.3 (p44) of the Commentary, the application of these functions leads to an anomaly of negative patients in the “Progressing Disease” health-state by Year 4. The evaluation attempted to correct for this using exponential and Weibull functions for “free of progression” and “overall survival”.
- 6.20 The ESC also noted that the ICER accepted by PBAC for use of abiraterone in the treatment of metastatic prostatic cancer post chemotherapy was approximately \$45,000 - \$75,000/QALY. The ESC therefore questioned why a substantially higher ICER should be accepted in the current submission as being cost-effective. Thus, sensitivity analyses on the ICER for the ITT population were performed to assess what price for abiraterone would be required to achieve an ICER between \$45K-\$75K/QALY, assuming that PBAC is prepared to accept the analysis based on a non-statistically significant difference in overall survival for the ITT population in the trial.

Results of the modelled economic evaluation

	<i>Modelled evaluation (Step 3b: ITT population; 10 year extrapolation using exponential and weibull functions) – corrected during the evaluation to not get the anomaly of negative patients</i>			<i>Modelled evaluation (Step 3a: ITT population; 10 year extrapolation using log-logistic and gamma functions) – submission’s approach with the anomaly of negative patients</i>		
	<i>AB</i>	<i>PLA</i>	<i>Increment</i>	<i>AB</i>	<i>PLA</i>	<i>Increment</i>
<i>Costs</i>						
<i>LYs</i>						
<i>QALYs</i>						
<i>Incremental cost/LY</i>						
<i>Incremental cost/QALY</i>						

Sensitivity analyses (ex-man price for abiraterone)

Abbreviations: ITT=intention to treat, CI=confidence interval, NE = not estimable, AB = abiraterone + prednisone/prednisolone, PLA= placebo + prednisone/prednisolone

[Redacted]

6.21 No medical management or downstream pharmaceutical costs were included in the model. Given the survival advantage of the abiraterone arm, the omission of these costs favours abiraterone.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Estimated PBS usage & financial implications

6.22 The submission was considered by the Drug Utilisation Sub-Committee (DUSC). The main issues identified by the DUSC include the following:

- The number of patients who have failed PBS androgen deprivation therapy (ADT) has been underestimated in the submission.
- The proportion of prevalent patients who have failed ADT and would be eligible for abiraterone according to the proposed criteria is not known. The submission uses the proportion of patients in Trial 302 who would meet the proposed PBS criteria. The DUSC considered that this approach is flawed as the clinical trial participants are a select group that would not characterise the prevalent mCRPC population.
- There is very high potential for mildly symptomatic patients to be treated with abiraterone outside of the proposed listing. Patients are likely to try an oral treatment before moving to chemotherapy.
- Abiraterone may substitute for ADT resulting in longer durations of abiraterone treatment; may be used post progression in patients unsuitable for chemotherapy; or may be used again post-docetaxel.

6.23 The estimated PBS usage and financial implications are presented below.

Estimated use and financial implications of abiraterone post-ADT

	2015	2016	2017	2018	2019
Estimation of use and costs of the proposed drug					
Total patients eligible for abiraterone post-ADT					
Patients treated with abiraterone post-ADT					
Abiraterone scripts					
Net cost of abiraterone scripts (post-ADT) to PBS/RPBS					
Estimation of changes in use and cost of other drugs					
Prednisolone scripts					
Net cost of prednisolone scripts (post-ADT) to PBS/RPBS					
Estimated patients treated with abiraterone (post-docetaxel)					
Patients in DOA abiraterone (post-docetaxel)					
Change in patients treated with					

	2015	2016	2017	2018	2019
abiraterone (post-docetaxel)					
Net cost of abiraterone (post-docetaxel) to the PBS/RPBS	████████	████████	████████	████████	████████
Estimated financial implications for the PBS/RPBS					
Net cost of abiraterone to the PBS/RPBS	████████	████████	████████	████████	████████
Estimated financial implications for government health budgets					
Net cost of abiraterone to the health budget	████████	████████	████████	████████	████████

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC rejected the submission to extend the PBS listing of abiraterone because the comparator was inappropriate, the sub-group analysis was not considered the most relevant patient group for PBS eligibility, the ICER was too high and the total PBS cost of treatment with abiraterone shifting from post-docetaxel to post-ADT was uncertain.
- 7.2 The PBAC noted the advice received from MOGA and the consumer comments that the proposed change to the abiraterone PBS restriction would provide a treatment option for patients who have not received chemotherapy.
- 7.3 The PBAC also noted comments from clinicians that for a small number of patients the current abiraterone restriction, requiring failure of, or intolerance to, docetaxel is a hurdle in gaining access to treatment where a single administration of docetaxel would inevitably demonstrate the patient was intolerant to docetaxel. PBAC considered a solution may be to amend the current restriction to allow PBS subsidised abiraterone where a patient is considered “unsuitable for docetaxel treatment on the basis of demonstrated or predicted intolerance to docetaxel”. PBAC considered this to be a minor change that may provide access to a small number of patients who are currently disadvantaged by the requirement to demonstrate intolerance. The proposed amendment of the restriction would not expand the market and would be adequately dealt with under existing risk share arrangements.
- 7.4 The PBAC did not consider “watchful waiting” to be an appropriate comparator for abiraterone to establish cost-effectiveness in the new treatment setting, after failure of ADT. Clinicians and patients make a decision on whether to wait and see or whether to treat. Once a decision to treat is made, the choice would be either abiraterone or docetaxel. The PBAC noted that there are now a number of new effective agents for metastatic prostate cancer and therefore the treatment algorithm for this disease will continue to evolve over the short to medium term.
- 7.5 The PBAC acknowledged that radium-223 injection is currently being assessed by MSAC for the treatment of patients with symptomatic castrate resistant prostate cancer with skeletal metastases. Should radium-223 be MBS listed this therapy would become a relevant comparator.
- 7.6 For the proposed restriction, PSA is clearly a more objective clinical criterion than pain scale. However the selection of the PSA threshold of 114ng/mL was based on a post-hoc sub group analysis of Trial 302. Clinically, PSA <114ng/mL appears to be an arbitrary threshold for a ‘no treatment’ decision and does not reflect the

importance of the rate of change of PSA as an indication of need for treatment. In addition, if all patients with PSA<114ng/mL in Trial 302 are considered representative of the PBS population, this equals █% of the trial population. The PBAC therefore agreed with the ESC that the ITT population is the most appropriate clinical data to consider. Furthermore, the PBAC considered that including PSA thresholds in the drug restriction would have the potential to impact adversely on clinical decision making.

- 7.7 The hazard ratio for overall survival in the post-hoc sub group for the proposed PBS population was █. The ITT results for Trial 302 showed an improvement in OS of █ months over 3 years follow-up, with median treatment duration of █ months. The hazard ratio for OS in the ITT population was █. The PBAC agreed with the pre-PBAC response (p2) that despite not meeting the strict pre-specified statistical level (p=0.0035), the conclusion that abiraterone is associated with a gain in overall survival in the ITT population is reasonable.
- 7.8 The ICER presented in the submission, based on the post-hoc sub group analysis was within the range of \$45,000 - \$75,000/QALY. The PBAC did not consider this sub group was as relevant as the ITT population and therefore this cost-effectiveness analysis was not acceptable. The ICER based on the ITT population was within the range \$105,000 - \$200,000/QALY. The PBAC considered this ICER unacceptably high.
- 7.9 The PBAC agreed with DUSC about the uncertainties in the financial estimates, particularly in relation to identifying patients who fit the post-hoc subgroup and the duration of therapy. Additionally, PBAC considered the use of “watchful waiting” as the comparator contributed to this uncertainty.
- 7.10 The PBAC therefore rejected the submission for the following reasons:
- “watchful waiting” was not considered an appropriate comparator for establishing cost-effectiveness in this setting;
 - the post-hoc subgroup analysis for defining the PBS eligible population was inadequately justified;
 - the ICER for both the post-hoc sub group and particularly the more appropriate ITT population were unacceptably high; and
 - the total PBS cost of treatment with abiraterone shifting from post-docetaxel to post-ADT was uncertain.

Outcome:

Rejected

8 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.

9 Sponsor’s Comment

Janssen is disappointed that the PBAC could not recommend abiraterone for patients who have metastatic castration resistant prostate cancer which has progressed

following treatment with androgen deprivation therapy based on the benefit observed in asymptomatic patients without pain who have a low PSA. Janssen are considering how best to interact with the PBAC in order to achieve a listing for abiraterone in this patient population.