

**6.08 ENZALUTAMIDE
capsules, 40 mg,
Xtandi®, Astellas.**

1 Purpose of Application

1.1 Restricted Benefit listing for enzalutamide for treatment of metastatic castration-resistant prostate cancer (mCRPC) in those who have not had prior docetaxel.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ENZALUTAMIDE Capsules, 40 mg, 112	1	2	\$ [REDACTED]	Xtandi® Astellas

Authority required
For the treatment of patients with metastatic castration-resistant prostate cancer.
Clinical criteria:
The treatment must not be used in combination with chemotherapy,
AND
Patient must not have had prior docetaxel,
AND
Patient must have a WHO performance status of 2 or less,
AND
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.

[REDACTED]

2.1 The requested basis for listing is cost-effectiveness versus watchful waiting, abiraterone and docetaxel.

2.2 The current (post-docetaxel) and proposed (pre-docetaxel) restrictions are identical in terms of maximum quantities, script numbers, and published price. However, the submission proposed a [REDACTED] % discount from the current effective price applied at the DPMQ level, [REDACTED]

2.3 The current PBS listing for enzalutamide includes a clinical criteria stating patients must have failed docetaxel or be unsuitable for docetaxel. This submission has proposed wording for an 'additional' PBS listing which differs from the current PBS listing by including the clinical criteria, "Patients must not have had prior docetaxel". However, the current PBS listing could be broadened to allow use in the proposed earlier line of treatment if docetaxel was no longer mentioned as part of the restriction. This would not require two separate listings. The Pre-Sub-Committee Response (p. 1) re-stated the preference for having two separate listings in order to avoid potential confusion with other PBS medications and therefore avoid prescriber error.

- 2.4 The PBAC noted the submission's preference for having two separate PBS listings for enzalutamide treatment before docetaxel (new proposed listing) and post-docetaxel (current PBS listing) in order to avoid potential confusion with other PBS medications and therefore avoid prescriber error. The PBAC noted further consideration of the restriction wording may be required to determine whether there are objective ways to define the two proposed suitable patient groups (asymptomatic and symptomatic) for earlier treatment based on progression and/or symptoms.

3 Background

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of ESC consideration, the clinical evaluation report and TGA Delegates Overview were available. The Delegates Overview suggests that the indication is likely to be "for the treatment of patients with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated."
- 3.2 The PBAC has not previously considered enzalutamide for the treatment of chemotherapy-naïve patients with mCRPC.
- 3.3 Enzalutamide is currently PBS-listed for mCRPC where the patient:
- has failed treatment with docetaxel due to resistance or intolerance; OR
 - is unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel.
- Abiraterone currently has an identical listing, and each of the listings include wording precluding use of one after the other.
- 3.4 The PBAC has previously considered and rejected a submission for abiraterone requesting use in a similar population (Abiraterone PSD, July 2014).

4 Clinical place for the proposed therapy

- 4.1 Metastatic castrate resistant prostate cancer (mCRPC) is advanced cancer of the prostate gland that has spread to the lymph nodes, bones or other organs of the body and is no longer sensitive to hormonal castration (surgical or medical). The first-line of treatment for mCRPC is docetaxel provided chemotherapy is suitable, followed by enzalutamide or abiraterone and/or cabazitaxel after failure with docetaxel therapies (or predicted intolerance to docetaxel for enzalutamide or abiraterone).
- 4.2 This submission proposed use of enzalutamide for the treatment of mCRPC prior to treatment with docetaxel.
- 4.3 The ESC noted that although the current National Comprehensive Cancer Network (NCCN) Guidelines suggest initial treatment of mCRPC with abiraterone or enzalutamide, it also highlights that the evidence base is in the setting of men who had no or minimal symptoms. Additionally, docetaxel is especially recommended for those with rapidly progressing disease or visceral metastases despite lack of

symptoms. On the PBS, docetaxel has an unrestricted listing and may be currently used early in the treatment algorithm in order to access later line therapies that are only available after docetaxel. Additionally, ESC noted that trials (as cited in Crawford et al 2015¹) have evaluated the use of docetaxel pre-castrate resistance (i.e. with androgen deprivation therapy (ADT)) as a means of delaying castrate resistance and prolonging survival.

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

5 Comparator

- 5.1 The submission nominated (i) watchful waiting (■%), (ii) abiraterone (■%) and (iii) docetaxel (■%) as comparators on the basis of subgrouping the requested chemotherapy naïve population according to symptoms and progression and the results of a clinician survey.
- 5.2 In its consideration of the abiraterone submission requesting use in chemotherapy naïve men, "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." (Abiraterone PSD July 2014).
- 5.3 The PSCR (pp. 1-2) highlighted that watchful waiting does not mean no therapy but incorporates continued hormonal therapy. The PSCR further reiterated that the Specialist Survey included in the submission suggested that ■% of oncologists would alter the way in which watchful waiting patients are currently treated if enzalutamide (and abiraterone) were available on the PBS before chemotherapy.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the changing treatment paradigm for asymptomatic men with disease progression. The goal of earlier treatment with the novel hormonal therapies (enzalutamide or abiraterone) was discussed as delaying symptom development and chemotherapy toxicities, rather than improving survival.
- 6.2 The PBAC considered that the hearing was informative as it provided a clinical perspective on the purpose of treating mCRPC with enzalutamide earlier in the disease pathway and assisted the PBAC in identifying two patient populations for whom earlier enzalutamide treatment may be justified: asymptomatic patients, for whom placebo, or watchful waiting, is the appropriate comparator; and symptomatic

¹ Crawford, e. D. et al (2015) 'Treating Patients with Metastatic Castration Resistant Prostate Cancer: A Comprehensive Review of Available Therapies' *The Journal of Urology*, Review Article avail. online 18 July 2015

patients, for whom docetaxel would be the appropriate comparator. The purpose of treatment would be either delaying symptoms from developing and maintaining a better quality of life for longer or delaying the toxicities of chemotherapy in patients considered suitable for docetaxel. The clinician indicated that neither of these patient groups would be considered to benefit substantially in survival from the earlier treatment with novel hormonal therapies.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (12), health care professionals (3) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with enzalutamide without prior docetaxel treatment, including fewer and more manageable side effects, improved quality of life and mental wellbeing. It was suggested earlier enzalutamide treatment would delay docetaxel treatment by around 2 to 2.5 years. The PBAC noted that while the median time to initiation of cytotoxic chemotherapy in the PREVAIL trial was 28 months for enzalutamide, the placebo arm also experienced a delay of 10.8 months. This suggests some patients won't need treatment even when castrate resistant and early enzalutamide treatment would provide an additional 17.2 months without docetaxel, not 2 to 2.5 years. Further consumer comments also noted that this listing would provide Australian patients with best practice care as recently determined by regulatory authorities in European and North American settings. Finally, some comments also noted that the current preclusion of enzalutamide use after abiraterone (and vice versa) is inappropriate for meeting individual patients' clinical needs.
- 6.4 The PBAC noted the advice received from the Medical Oncology Group of Australia and the Urological Society of Australia and New Zealand clarifying the likely use of enzalutamide without prior docetaxel treatment in clinical practice. The PBAC specifically noted the advice that this listing is supported by high level clinical trial evidence, is in keeping with international best practice, and would provide patients with improved quality of life.

Clinical trials

- 6.5 The submission presented a direct comparison of enzalutamide versus placebo and two indirect comparisons of trials of enzalutamide versus abiraterone and docetaxel, referred to as "Analysis A", "Analysis B" and "Analysis C", respectively. The trial evidence used to inform the comparisons of enzalutamide against the each nominated comparator is:
- Analysis A (vs watchful waiting): PREVAIL;
 - Analysis B (vs abiraterone): PREVAIL and COU-AA-302; and
 - Analysis C (vs docetaxel): PREVAIL, Tannock 1996, Kantoff 1999, Berry 2002, TAX-327 and Ye 2013.
- The mitoxantrone trials (Tannock 1996, Kantoff 1999, Berry 2002) are not directly applied in the indirect comparison, but used to demonstrate that the mitoxantrone + prednisolone arm of the docetaxel trials (TAX-327 and Ye 2013) is equivalent to the placebo ± prednisolone arm of the PREVAIL trial.
- 6.6 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and key associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Enzalutamide ± prednisolone versus placebo ± prednisolone		
PREVAIL	PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy	Clinical Study Report (Data cutoff 16 Sept 2013); Clinical Study Report Addendum (Data cutoff [REDACTED])
	Beer et al. Enzalutamide in metastatic prostate cancer before chemotherapy.	<i>New England Journal of Medicine</i> 2014; 371: 424-433.
Abiraterone + prednisolone versus placebo + prednisolone		
COU-AA-302	Basch et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial.	<i>The Lancet Oncology</i> 2013; 14(12): 1193-1199.
	Ryan et al. Abiraterone in metastatic prostate cancer without previous chemotherapy.	<i>New England Journal of Medicine</i> 2013; 368(2): 138-148.
	Rathkopf et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302).	<i>European Urology</i> 2014; 66(5): 815-825.
	Ryan et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study.	<i>The Lancet Oncology</i> 2015; 16(2): 152-160.
Mitoxantrone + prednisolone versus prednisolone		
Berry 2002	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.	<i>Journal of Urology</i> 2002; 168(6): 2439-2443.
Kantoff 1999	Kantoff et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: Results of the cancer and leukemia group B 9182 study.	<i>Journal of Clinical Oncology</i> 1999; 17(8): 2506-2513.
Tannock 1996	Tannock et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points.	<i>Journal of Clinical Oncology</i> 1996; 14(6): 1756-1764.
Docetaxel + prednisolone versus mitoxantrone + prednisolone		
TAX-327	Tannock et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.	<i>New England Journal of Medicine</i> 2004; 351(15): 1502-1512.
	Berthold et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study.	<i>Journal of Clinical Oncology</i> 2008; 26(2): 242-245.
Petrylak 2014	<i>Practical guide to the use of chemotherapy in castration resistant prostate cancer.</i>	The Canadian Journal of Urology April 77-83.
Ye 2013	Ye et al. A randomized open-label study comparing the docetaxel plus prednisone regimen versus mitoxantrone plus prednisone regimen for metastatic hormone refractory prostate cancer in Chinese population.	<i>European Journal of Cancer</i> 2013; 49: S706.
Zhou et al. 2015	Zhou, T. et al. (2015). A Multicenter, Randomized Clinical Trial Comparing the Three-Weekly Docetaxel Regimen plus Prednisone versus Mitoxantrone plus Prednisone for Chinese Patients with Metastatic Castration Refractory	PLoS ONE 10(1).

	<i>Prostate Cancer.</i>	
Meta-analyses of direct randomised trials		
Collins 2006	Collins et al. A systematic review of the effectiveness of docetaxel and mitoxantrone for the treatment of metastatic hormone-refractory prostate cancer.	<i>British Journal of Cancer</i> 2006; 95(4): 457-462.

Source: Tables B-3 to B-5, ppB-23 to B-31 of the submission

6.7 The key features of the direct randomised trials are summarised in Table 2.

Table 2: Key features of the included trials

Trial	N	Design/ follow-up	Bias OS	Patient population	Outcome(s)	Modelled evaluation
Enzalutamide ± prednisolone versus placebo ± prednisolone						
PREVAIL	1717	R, DB, PG, PC / ██████████ (final)	Low ^a	mCRPC; asymptomatic or mildly asymptomatic; chemotherapy naïve	1°: OS, rPFS	OS, TTD
Abiraterone + prednisolone versus placebo + prednisolone						
COU-AA-302	1088	R, DB, PG, PC / 49.2mths (final)	Low ^b	mCRPC; asymptomatic or mildly asymptomatic; chemotherapy naïve	1°: OS, rPFS	OS, rPFS
Mitoxantrone + prednisolone versus prednisolone						
Berry 2002	119	R, OL, PG / 21.8mths	Low/unclear	mCRPC; asymptomatic; chemotherapy naïve	2°: OS	-
Kantoff 1999	242	R, OL, PG / 2yrs	Low/unclear	mCRPC; asymptomatic or symptomatic; chemotherapy naïve	1°: OS	-
Tannock 1996	161	R, OL, PG / NR	Low/unclear	mCRPC; symptomatic; chemotherapy naïve	2°: OS	-
Docetaxel + prednisolone versus mitoxantrone + prednisolone						
TAX-327 ^d	672	R, OL, PG / 20 months	Low ^c	mCRPC; asymptomatic or symptomatic; chemotherapy naïve	1°: OS	OS, Median time on tx
Ye 2013 Zhou et al 2015	220	R, OL, PG / 39.13 months docetaxel; 28.45 months mitoxantrone	Low/unclear	mCRPC; symptomatic; NR	1°: OS	OS

Abbreviations: R = randomised; DB = double-blind; OL = open-label; PG = parallel group; PC = placebo-controlled; NR= not reported

^a placebo cross-over after interim analysis

^b placebo cross-over after second interim analysis

^c cross-over was permitted (20% of patients in mitoxantrone arm received docetaxel)

^d TAX-327 is 3-arm trial, only relevant arms presented. Patients were randomised to the trial between March 2000 and June 2002 and the trial was published in 2004

Source: compiled during the evaluation

6.8 All of the trials generally have a low risk of bias with respect to the outcome overall survival, although there were limited details available for Ye 2013 as it is reported as an abstract only. The manuscript associated with the Ye 2013 study was provided by the sponsor in the PSCR (Zhou et al, 2015). While limited information is provided in the protocol, the clinical trial regimen is stated to be based on the pivotal trial TAX-327. However, as noted by the submission (pB-102), overall survival results are impacted by cross-over to active therapies and use of subsequent active therapies. Although this is not relevant to Berry 2002, Kantoff 1999 or Tannock 1996, cross-over and subsequent therapy (detailed below) is important for the newer trials.

PREVAIL	<p>Patients were un-blinded after the interim analysis ([REDACTED]).</p> <p>[REDACTED]. The submission's clinical claims and modelled analyses (A, B and C) are based on the PREVAIL final analysis, although subsequent therapy is controlled for in the comparisons versus watchful waiting and docetaxel using the Inverse Probability of Censoring Weights (IPCW) method.</p>
COU-AA-302	<p>Patients were un-blinded after the second interim analysis (20 Dec 2011 data cut-off) and those randomised to placebo could cross over to abiraterone. By the third interim (22 May 2012 data cut-off) 64.2% of the placebo arm and 50.2% of the abiraterone arm had trialled at least one subsequent active therapy. The submission's clinical claim and modelled analysis versus abiraterone is based on the third interim analysis of the COU-AA-302 trial.</p>
TAX-327/ Ye 2013	<p>The submission's clinical claim against docetaxel is based on the pooled results of TAX-327 ITT and Ye 2013 ITT:</p> <ul style="list-style-type: none"> • 20% of the mitoxantrone control arm received subsequent docetaxel in TAX-327. As docetaxel was the only drug available with a demonstrated survival benefit at the time of the trial, subsequent therapy in the docetaxel arm is unlikely to influence survival. • there is insufficient information available to determine subsequent treatment in Ye 2013, but given the use of docetaxel in the trial, and potential availability of other agents given the recent date of publication, subsequent therapy is not unlikely. The manuscript provided with the PSCR (Zhou et al 2015) does not provide any further information regarding post-progression treatments.

Comparative effectiveness

- 6.9 Table 3 presents the indirect comparison of overall survival between enzalutamide and docetaxel in chemotherapy naïve patients. Overall survival in the mitoxantrone trials is also presented but is not used to conduct the indirect comparison but to demonstrate that the mitoxantrone + prednisolone arm of the docetaxel trials (TAX-327 and Ye 2013) is equivalent to the placebo ± prednisolone arm of the PREVAIL trial. The trials may not be sufficiently comparable to conduct an indirect comparison as no baseline or trial characteristics are reported in Ye 2013, and patients in TAX-327 appear to have more severe disease. The considerable difference in incremental survival between Ye 2013 (8.2 months) and TAX-327 (2.4 months) also suggests these trials may not be sufficiently comparable to support including these trials in a meta-analysis.
- 6.10 Updated data in the PSCR (pp. 3-4) shows that more patients had previously used chemotherapy in Ye 2013 (estramustine monotherapy), ethnicity data is missing (though the Ye 2013 study was only conducted in China sites), lymph node/liver/lung involvement is not reported in TAX-327 nor is time since diagnosis. The ESC considered there was still missing information on key prognostic factors, for instance, ECOG status in TAX-327, disease site distribution especially lymph node in TAX-327 and pain symptoms in Ye 2013 (note that the Ye 2013 study did not include asymptomatic patients, only patients that were stabilised on analgesia). Also, if it is assumed that the duration of prostate cancer reported in Ye 2013 equates to diagnosis time in PREVAIL, then the patients in Ye 2013 have much shorter duration of disease (approximately two years in Ye 2013 compared to five years in PREVAIL; note that no information is provided on this variable for TAX-327).
- 6.11 By the final analysis in the PREVAIL trial, many patients in the placebo arm had crossed-over to enzalutamide such that [REDACTED]% of patients in the placebo arm had

used a subsequent therapy with a demonstrated survival benefit compared with ██████% in the enzalutamide arm. The submission stated that to control subsequent therapies, the Inverse Probability of Censoring Weights (IPCW) method was used. In short, the IPCW method involves censoring patients upon treatment switch, and then controlling for this potentially informative censoring by weighting the follow-up information for patients who remain at risk for the event such that they account not only for themselves, but also for patients with similar characteristics (both baseline and time dependent) whose follow-up was censored by informative censoring. A very important limitation of the method is its reliance on the “no unmeasured confounders” assumption, that is, data must be available on all baseline and time dependent prognostic factors for mortality that independently predict informative censoring (switching).

6.12 The submission provided two adjustments to the enzalutamide trial data using the IPCW method:

- A. “Docetaxel is not a switch” - where subsequent therapy with a demonstrated effect on overall survival (cabazitaxel, abiraterone, sipuleucel-T, enzalutamide and radium-223), are censored as a switch. Docetaxel was not considered a switch in this analysis given it could be considered part of normal clinical practice; and
- B. “Docetaxel is a switch 2” – where the subsequent use of any of the therapies listed above, AND docetaxel, is censored.

6.13 The results of the IPCW adjustments to the PREVAIL ITT data are presented in Figure 1. Although both adjustments made a moderate overall difference to the enzalutamide arm of the PREVAIL trial, the impact on the placebo arm of the trial, particularly for the PREVAIL IPCW “docetaxel is a switch 2” analysis was substantial. The consequences of the IPCW adjustments were to decrease the HR (95% CI) from ██████ using the PREVAIL ITT (final analysis), to:

- ██████ using the PREVAIL IPCW “docetaxel is not a switch” (final analysis); and
- ██████ using the PREVAIL IPCW “docetaxel is a switch 2” (final analysis).

The submission based its comparison versus:

- “watchful waiting” on the PREVAIL IPCW “docetaxel is not a switch” data; indicating that, as docetaxel was considered part of normal practice, it did not require adjustment;
- abiraterone on the PREVAIL ITT data, indicating that the trials were similar with respect to subsequent therapies undertaken and therefore adjustments were not required; and
- docetaxel on the PREVAIL IPCW “docetaxel is a switch 2” analysis, indicating that “docetaxel” could not be in both arms of the comparison and that the incremental difference between enzalutamide and docetaxel was important. Although the method allowed for adjustment of subsequent therapies in the PREVAIL trial, the same adjustment was not conducted for the docetaxel trials, where:
 - 20% of those randomised to control in TAX-327 had subsequent therapy with docetaxel; and
 - there was insufficient information available to determine subsequent treatment in Ye 2013 and the updated manuscript for this study provided in the PSCR (Zhao et al 2015), but given the use of docetaxel in the trial, and potential

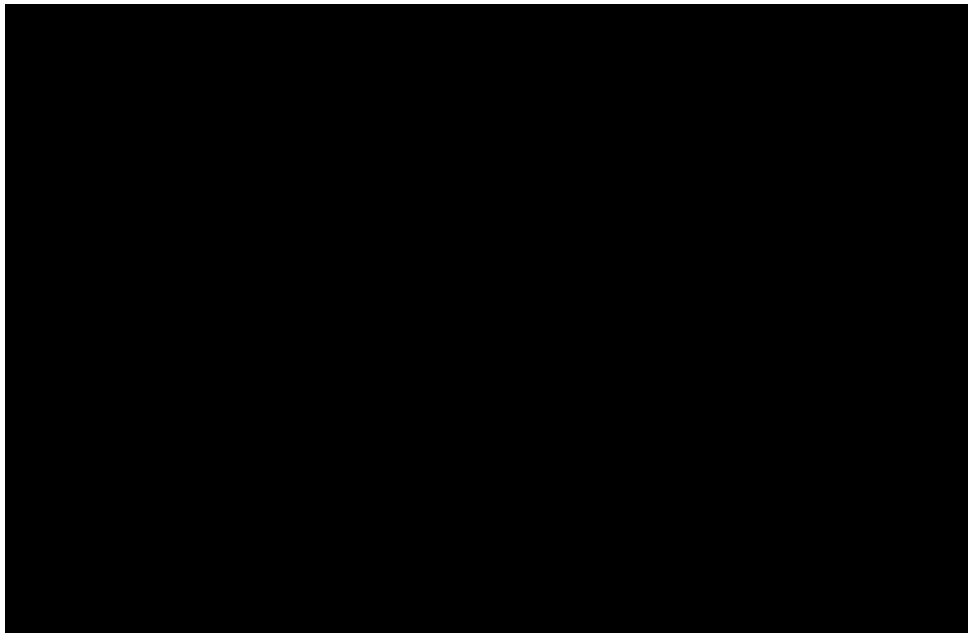
availability of other agents given the recent date of publication, subsequent therapy was not unlikely.

This approach favoured enzalutamide.

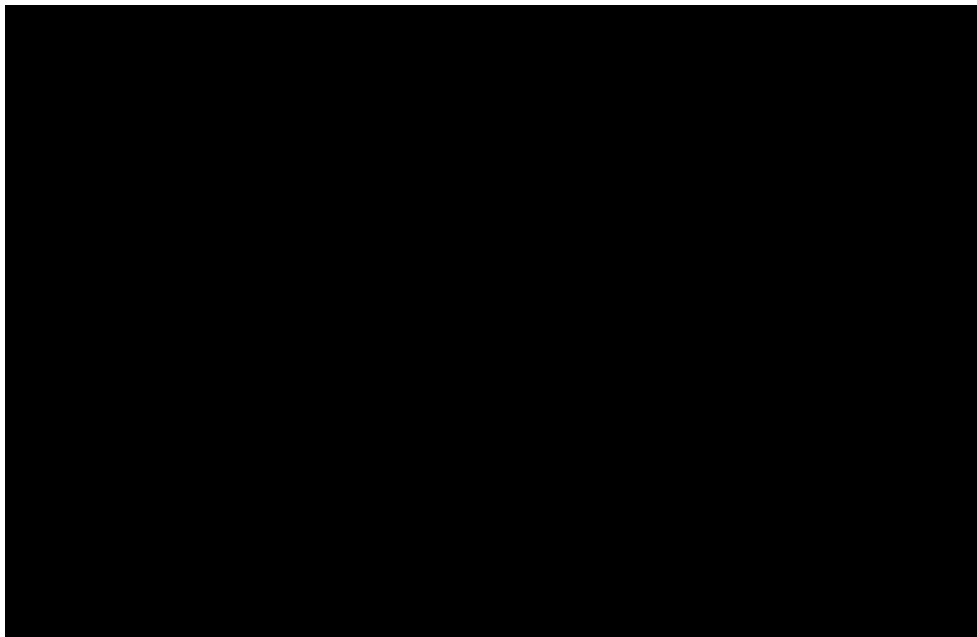
- 6.14 The ESC agreed with the Commentary conclusion that the effectiveness estimates were likely to be biased in favour of enzalutamide. This was because using the IPCW method on the docetaxel trials would be problematic as there was potentially missing information on key prognostic variables, even with the additional information on background characteristics of patients in the Ye 2013 study, provided in the PSCR (pp. 3-4). In particular, no clearer details about treatments post-progression were included in the updated clinical trial report provided with the PSCR (Ye 2013/Zhou et al 2015). The PSCR (p. 5) mentioned the impact of crossover to the active alternative docetaxel had been investigated for TAX327, concluding no apparent incremental benefit from switching/crossover for either arm. ESC did not consider removing Ye 2013 from consideration of this issue to be informative given the Ye 2013 study was conducted more recently and so likely better reflects contemporary therapies compared to the TAX-327 trial. These absences may violate the “no unmeasured confounders” assumption upon which the application of IPCW is fundamentally based.

Figure 1: Kaplan-Meier overall survival in PREVAIL final analysis (IPCW “docetaxel is not a switch”; A) and Kaplan-Meier overall survival in PREVAIL final analysis (IPCW “docetaxel is a switch 2”; B)

A



B



Source: Figure B-13, pB-131 and Source: Figure B-12, pB-130 of the submission

Table 3: Median overall survival in months (95% CI) in the enzalutamide trial (PREVAIL final analysis ITT, IPCW docetaxel is not a switch, and IPCW docetaxel is a switch 2), the mitoxantrone trials and the docetaxel trials

	Median months (95% CI)					HR (95% CI)	Indirect HR (95% CI)
	ENZ ± PRED	PBO ± PRED	PBO + PRED	MIT + PRED	DOC + PRED		
PREVAIL ITT (final analysis)							
PREVAIL IPCW (final analysis - docetaxel not a switch)	NR	NR					
PREVAIL IPCW (final analysis - docetaxel is a switch 2)	NR	NR					
Tannock 1996			10.8 (NR)	11.3 (NR)		0.91 (0.69, 1.20)	
Kantoff 1999			12.6 (NR)	12.3 (NR)		1.00 (0.80, 1.30)	
Berry 2002			19 (NR)	23 (NR)		1.13 (0.75, 1.70)	
TAX-327				16.5 (NR)	18.9 (NR)	0.76 (0.62, 0.94)	
Ye 2013				13.7 (NR)	21.9 (NR)	0.62 (0.45, 0.85)	
Meta-analysis (Tannock 1996, Kantoff 1999, Berry 2002)							
Meta-analysis (TAX-327 ^a , Ye 2013)							
ENZ ± PRED (ITT final analysis) vs DOC + PRED							
ENZ ± PRED (IPCW final analysis docetaxel not a switch) vs DOC + PRED							
ENZ ± PRED (IPCW final analysis docetaxel is a switch 2) vs DOC + PRED							

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Abbreviations: ENZ=enzalutamide; PRED=prednisolone; PBO=placebo; MIT=mitoxantrone; NR=not reported
^a patients were randomised to the trial between March 2000 and June 2002 and the trial was published in 2004
 Source: Tables B-50, B-51, B-52 and B-53 and Figures B-21 and B-22, ppB-152 to B-159 of the submission

6.15 The indirect comparison presented was based on hazard ratios. A meta-analysis of the median months of overall survival for docetaxel and subsequent indirect comparison based on median overall survival could not be conducted.

Comparative harms

6.16 Table 4 presents the adverse events reported in PREVAIL, and TAX-327.

Table 4: Summary of adverse events reported in PREVAIL and TAX-327

	PREVAIL (Interim analysis)		TAX-327	
	ENZ±PRED (N=871)	PBO±PRED (N=844)	DOC+PRED (N=335)	MIT+PRED (N=337)
Any AE	844 (96.9%)	787 (93.2%)		
SDR-AE				
Any grade ≥ 3 adverse event	374 (42.9%)	313 (37.1%)	46%	35%
Any serious adverse event	279 (32.0%)	226 (26.8%)		
AE - death	37 (4.2%)	32 (3.8%)	0.3%	1%
AE - tx discontinuation	49 (5.6%)	51 (6.0%)	11%	10%

Abbreviations: ENZ=enzalutamide; PRED=prednisolone; PBO=placebo; ABI=abiraterone; DOC=docetaxel; MIT=mitoxantrone; AE=adverse event; SDR=study drug related; tx=treatment
 Source: Tables B-42, B-43, B-49 and B-56, pB-136, pB-137, ppB-149 to B-150 and pB-162 of the submission

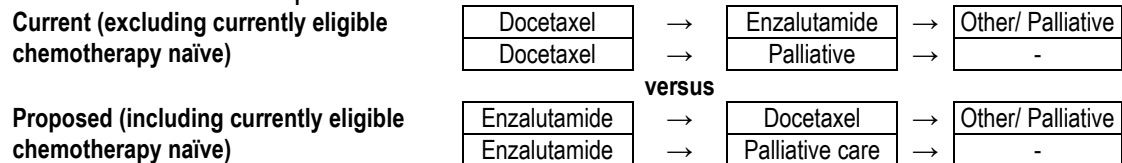
The most commonly reported adverse events with enzalutamide were fatigue, back pain, constipation, arthralgia, decreased appetite and hot flushes. Based on limited comparable data, the safety profiles of enzalutamide and abiraterone appeared generally similar. Docetaxel is known to cause fluid retention, cutaneous reactions including hand-foot syndrome and nail disorders, heart failure, myelosuppression, peripheral neuropathy and hypersensitivity. The submission stated the adverse event profiles of enzalutamide and docetaxel could not be formally compared.

Benefits/harms

6.17 Notwithstanding the potential exchangeability issues between the enzalutamide and docetaxel trials and between the docetaxel trials (due to differences in patients and treatments undertaken), the absolute difference in median survival reported in each of the trials, compared with “placebo” is:

- An additional [redacted] months (final analysis from ITT in PREVAIL) for enzalutamide; and
- An additional 2.4 months (TAX-327) to 8.2 months (Ye 2013) for docetaxel.

6.18 Of interest was a comparison of:



The submission did not (i) provide evidence to inform this comparison, nor (ii) provide any evidence that the order in which enzalutamide and docetaxel are used in a

treatment algorithm results in treatment modification to support the contention that enzalutamide → docetaxel is superior to docetaxel → enzalutamide.

- 6.19 It was noted that the absolute difference in median survival reported for enzalutamide compared with placebo in a post-docetaxel population was 4.8 months.

Clinical claim

- 6.20 The submission claimed that, with respect to overall survival, enzalutamide demonstrated:

- superior efficacy and similar safety to placebo (Analysis A). The evaluator considered this was reasonably supported by the PREVAIL trial when considering the ITT results from the trial and when applying the IPCW adjustments to account for use of subsequent therapies;
- at least non-inferior effectiveness and safety when compared with abiraterone (Analysis B). The evaluator considered this was reasonable based on the data presented and was consistent with the current therapeutic relativity accepted in the post-docetaxel population; and
- superior efficacy and similar safety to docetaxel (Analysis C). The ESC considered this was not reasonable because the claim is based on (i) an indirect comparison with potential exchangeability issues; (ii) the differential adjustment for subsequent therapies for the PREVAIL trial, but not the docetaxel trials, which would favour enzalutamide.

- 6.21 However, the unadjusted trial results indicated an incremental survival benefit of [REDACTED] months and 4.8 months for enzalutamide compared with placebo in the pre- and post-docetaxel settings, respectively. This suggested that, for an estimated additional cost of shifting enzalutamide treatment to a pre-docetaxel setting of \$ [REDACTED] per patient, there would be an approximate reduction of [REDACTED] median overall survival. Furthermore, a comparison of the mean and 95% confidence intervals demonstrated that it would be unlikely that the difference of [REDACTED] [REDACTED] is clinically relevant.

- 6.22 The PSCR (p. 1) stated the pre- vs. post-docetaxel studies (incremental survival benefit of [REDACTED] and 4.8 months respectively) cannot validly be compared due to key differences between the studies and disease severity. The PBAC however considered that this interpretation whilst acknowledging all its limitations serves to highlight the minimal impact of earlier enzalutamide treatment on overall survival.

- 6.23 Overall, the PBAC considered the claims versus overall survival to be less relevant than delayed symptom progression and improvement in quality of life.

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

Economic analysis

- 6.24 The submission presented three modelled economic analyses of enzalutamide versus:

- Placebo/watchful waiting (Analysis A)
- Abiraterone (Analysis B)

- Docetaxel (Analysis C).

6.25 Analysis C required consideration of (i) a claim of superiority of enzalutamide compared with docetaxel based on the results of an indirect comparison of hazard ratios, noting that the incremental median overall survival compared with “placebo” reported in the PREVAIL ITT trial was [redacted] months compared with 2.4 months (TAX-327) to 8.2 months (Ye 2013) for docetaxel; and (ii) that the differential methods used to account for treatment with subsequent therapies in the enzalutamide and docetaxel trials was reasonable.

6.26 Table 5 provides a summary of the model structure.

Table 5: Summary of model structure and rationale

Time horizon	10 years in the model base case versus median 31 months follow-up in PREVAIL
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Cycle length	1 week
Half-cycle correction	Yes
Transition probabilities	Refer to Section D.4
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: constructed during the evaluation

6.27 Table 6 summarises the key drivers of the model.

Table 6: Key drivers of the model (Analysis C)

Description	Method/Value	Impact
Incremental progression-free survival	Based on the time to treatment discontinuation (TTD) in the PREVAIL and median cycles in TAX327 trials. The ESC considered median number of cycles of treatment with docetaxel cannot be used as a proxy for progression-free survival as treatment with docetaxel is finite and limited to a maximum of 10 cycles; time on treatment cannot inform PFS and is likely to be underestimated. This resulted in the time in the PFS health state for enzalutamide being ~[redacted] weeks compared with ~[redacted] weeks in the docetaxel arm. It is noted that median “pain control progression-free survival” on docetaxel in Ye (2013) was reported as 12.7 months.	High, favours enzalutamide The model is driven by incremental PFS
Incremental overall survival	Based on the PREVAIL IPCW final analysis docetaxel is a switch 2 for enzalutamide and placebo, with a HR=[redacted] applied to the placebo arm (IPCW final analysis docetaxel is a switch 2) to derive OS for docetaxel. This results in an estimated overall survival of ~[redacted] weeks in the docetaxel arm.	Low (in isolation)/ High (combined with PFS), favours enzalutamide

Source: compiled during the evaluation

6.28 The submission did not make a clinical claim regarding progression-free survival between enzalutamide and docetaxel. Therefore to present a model driven almost completely by an assumed difference in progression-free survival was inappropriate.

- 6.29 The PSCR (p. 4) provided an additional publication (Petrylak 2014), which reported time to progression of 7.9 months for the TAX327 trial. When this result was incorporated in the model, the PSCR claimed the ICER to be \$45,000/QALY – \$75,000/QALY (compared with the base case of \$45,000/QALY – \$75,000 /QALY). The PSCR also argued that a published version of Ye 2013 (Zhou et al 2015) suggested a median “disease progression-free survival” of 3.42 months. Although the paper provided insufficient detail to define this end point, when incorporated in the model, the ICER would be \$15,000/QALY - \$45,000/QALY.
- 6.30 The ESC noted the outcome “disease progression” was not defined nor discussed in Zhou et al 2015 or in the online supplementary material. Median time to “tumour progression”, “pain progression” and “PSA progression” in the docetaxel arm of Zhou et al 2015 was reported as 12.19 months, 12.71 months and 12.71 months respectively (see Table 7 below).

Table 7: Progression-free survival results reported in Zhou 2015

Outcome	Definition	Median progression-free survival Months (95% CI)		
		Docetaxel	Mitoxantrone	p-value
Tumour progression	In tumour assessment, progressive disease defined as a “20% increase in the sum of the longest diameter of target lesions” (Table S1, online supplementary material).	12.19 months (8.05, 13.76)	9.13 months (6.93, 10.71)	0.0118
Pain progression	“Defined as an increased of ≥ 1 point in the PPI scale from its nadir noted on two consecutive visits three weeks apart, or $\geq 25\%$ increase in the daily analgesics score compared with the baseline score and noted on two consecutive visits three weeks apart, or requirement for local palliative radiotherapy” (Table S1, online supplementary material).	12.71 months (9.53, 15.47)	5.55 months (3.61, 8.44)	0.0002
PSA progression	“In PSA non-responders: progression was defined as a 25% increase over the nadir value (provided that the rise is a minimum of 5 ng/ml) and confirmed by a second value at least one week later. In PSA responders: progression was defined as a 50% increase over the nadir value (provided that the rise is a minimum of 5 ng/ml) and confirmed by a second value at least one week later.” (Table S1, online supplementary material) (Note: PSA response was “defined as a PSA decline of $\geq 50\%$ and confirmed at least three weeks later)	12.71 months (7.65, 17.51)	5.55 months (3.48, 8.90)	0.0001
Disease progression	Not reported.	3.42 months (2.79, 4.96)	2.14 months (1.61, 2.76)	0.0029

Source: Zhou et al 2015: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0117002>

- 6.31 Table 8 summarises the results of the modelled economic evaluation. The italicised text in Table 8 are due to a discrepancy between the submission’s claim regarding which extrapolation distributions were used for progression-free survival (PFS derived from time to treatment discontinuation data), Gamma as stated in Section C of the submission, and Weibull used in the base case ICER presented in the submission. The results are those generated from the use of the former.

Table 8: Results of the modelled economic evaluation (Analysis C)

	ENZ → DOC	DOC → ABI	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

corrected enzalutamide PFS extrapolation distribution from Weibull to Gamma as stated in Section C.

Source: Tables D-13, D-14 and D-15, pD-34 p D-38 of the submission

- 6.32 Although the model estimated a moderate benefit in overall survival with enzalutamide compared to docetaxel, progression-free survival at the start of the model was assumed to be significantly greater with enzalutamide compared with docetaxel ([REDACTED]), therefore, large incremental utilities accrue in the first health state “stable disease”, which drives the result of the model.
- 6.33 The submission may have significantly underestimated progression-free survival on first-line docetaxel ([REDACTED] weeks, based on median number of cycles of treatment, when pain-free progression was reported as 12.7 months in Ye 2013). Progression-free survival for docetaxel was not reported, and on the basis that the submission did not base its claim of superior efficacy on PFS, when progression-free survival on first-line docetaxel in the docetaxel arm is set equal to the progression-free survival to first-line enzalutamide in the enzalutamide arm, the ICER increased to more than \$200,000/QALY.

Drug cost/patient/year

- 6.34 \$ [REDACTED] assuming an effective DPMQ of \$ [REDACTED] and [REDACTED] scripts per year. This compared with up to \$ [REDACTED] for docetaxel (up to [REDACTED] cycles accounting for drug cost only).
- 6.35 When considering the median duration of treatment, the cost was \$ [REDACTED] (assuming an effective DPMQ of \$ [REDACTED] and [REDACTED] months [scripts] of treatment) in the pre-docetaxel setting. This estimate did not include any cost-offset associated with a reduction in use of enzalutamide or abiraterone post-docetaxel. This is compared with \$ [REDACTED] for enzalutamide in the post-docetaxel setting (assuming \$ [REDACTED]/script and [REDACTED] months [scripts] of treatment).

Estimated PBS usage & financial implications

- 6.36 The submission was considered by DUSC.
- 6.37 The submission presented a mixed epidemiological and market-share approach to estimate the cost to government of the proposed listing of enzalutamide in chemotherapy naïve patients with mCRPC. The submission estimated utilisation for all drugs prescribed for mCRPC under two scenarios: 1) assuming the current listing of enzalutamide (including use in currently eligible chemotherapy naïve patients) and 2) assuming the proposed listing of enzalutamide (all chemotherapy naïve patients); the difference between which is the incremental cost of listing.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Scripts ^a					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to Medicare Australia	\$	\$	\$	\$	\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

Source: Table E.6-4, pE-47 of the submission

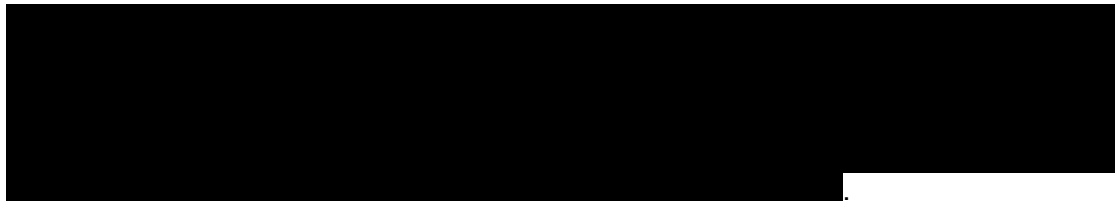
The redacted table above shows that the number of patients treated with enzalutamide is estimated to be less than 10,000 per year at a net cost to the PBS of \$10 - \$20 million in Year 1 to \$30 – 60 million in Year 5.

- 6.38 DUSC considered the estimates presented in the submission did not adequately inform the budget impact estimates. The main issues were:
- The clinical place of enzalutamide is unclear. The proposed TGA indication "...in whom chemotherapy is not yet indicated..." implies that enzalutamide could potentially be used in the pre-chemotherapy setting (i.e. substitute for other anti-androgens) in addition to substitution within the chemotherapy setting.
 - The financial estimates model was poorly structured and not all of the inputs and results could be verified or followed. One example to illustrate this point was that the submission's estimate for the number of patients who would be treated with first-line therapy was higher than the number of patients eligible.
 - The prevalent population was derived using an epidemiological approach to adjust the incident population by a survival estimate. The survival assumption used to convert the incident figures to prevalent (14 months) was substantially lower than the survival observed in the PREVAIL trial (■ months). As such, this step was likely to underestimate the eligible population.
 - The assumptions for the treated population in the chemotherapy and post-chemotherapy settings relied on the results of clinician surveys undertaken by the sponsor. The reliability of the survey findings were uncertain due to the low participation rates, potential selection bias and the survey questions did not fully address the context of the requested listing.

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

Financial Management – Risk Sharing Arrangements

6.39



6.40



7 PBAC Outcome

7.1 The PBAC decided not to recommend extending the PBS listing of enzalutamide to include treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients who have not had prior docetaxel in the two patient populations for whom earlier enzalutamide treatment may be justified: asymptomatic patients, for whom placebo, or watchful waiting, is the appropriate comparator; and symptomatic patients, for whom docetaxel would be the appropriate comparator.

7.2 In light of the input from clinicians and consumers the PBAC agreed that the purpose of treatment would be to maintain a better quality of life for longer by either:

- In asymptomatic patients – delaying symptoms from developing, or
- In symptomatic patients considered suitable for docetaxel – delaying the toxicities of chemotherapy.

Neither of these patient groups would be considered to benefit substantially in survival from the earlier treatment with novel hormonal therapies. This is in contrast to the entire basis of the submission which was focused on a claim of overall survival advantage.

7.3 The PBAC considered that the clinical outcomes to demonstrate the effectiveness and thus the clinical value of enzalutamide would also vary across the two proposed subpopulations. When comparing enzalutamide and watchful waiting for asymptomatic patients, the relevant outcomes relate to delaying symptoms from developing, so relevant trial outcome measures should focus on differences in the time to development of these symptoms. In this regard, the PBAC noted that time to FACT-P degradation was longer for enzalutamide compared to watchful waiting (11.3 vs 5.6 months). When comparing enzalutamide and docetaxel for symptomatic patients, the relevant outcomes relate to quality of life from delaying the toxicities of chemotherapy. So relevant trials outcomes should focus on adverse event profiles of the therapy options. In this regard, the PBAC noted the median time to initiation of cytotoxic chemotherapy in PREVAIL was 28.0 months in the enzalutamide group versus 10.8 months in the placebo group, a median difference of 17.2 months ([REDACTED]). Any significant consequences for quality of life should also be factored into the cost effectiveness of enzalutamide treatment.

7.4 The PBAC noted the three analyses of the clinical data presented in the submission and, having identified the two relevant patient populations defined above, were particularly interested in the head-to-head trial of enzalutamide versus placebo, or watchful waiting, from Analysis A (PREVAIL), and the indirect comparison with docetaxel in Analysis C (PREVAIL, Tannock 1996, Kantoff 1999, Berry 2002, TAX-327 and Ye 2013).

7.5 The PBAC considered the ITT analyses of PREVAIL to be the most relevant given the use of subsequent therapies in the trial, including docetaxel, reflected proposed future clinical practice and adjusting for switching would therefore not be appropriate. The PBAC noted and agreed with the ESC's concerns regarding the indirect

comparison with docetaxel, particularly that the trials may not have been exchangeable, the IPCW adjustment to PREVAIL but not to the docetaxel trials favoured enzalutamide, and the absolute benefits in OS were small and similar; with an additional ■ months (final analysis from ITT in PREVAIL) for enzalutamide, and an additional 2.4 months (TAX327) to 8.2 months (Ye 2013) for docetaxel.

- 7.6 The overall survival gain of ■ months for enzalutamide in the PREVAIL trial also did not represent a significant gain in survival compared to enzalutamide in the post-docetaxel setting (4.8 months from the AFFIRM trial). Given the differences in study designs and disease severity of the patients, this interpretation was only considered for the purpose of highlighting the minimal impact of earlier enzalutamide treatment on overall survival. The PBAC considered the impact on quality of life from delaying disease symptoms (such as pain, fractures, and spinal cord compression) and delaying or reducing time with toxicities from chemotherapy were of most relevance to this patient population.
- 7.7 The PBAC noted the economic models were driven by assumptions about PFS that were not justified. The PBAC did not consider the submission models for Analysis A and Analysis C to appropriately reflect the value of early enzalutamide treatment and encouraged a resubmission to evaluate the potential gains in quality of life based on the patient populations and outcomes described above.
- 7.8 The PBAC noted the uncertainty with relation to the estimated PBS usage and financial estimates and recommended these estimates be revised by the sponsor in a future submission with consideration of the issues raised by DUSC.

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

Astellas is disappointed not to have secured an extended PBS listing for patients with mCRPC who have not had prior docetaxel, but is grateful to the PBAC for their helpful feedback and advice.