

6.04 ENZALUTAMIDE, Capsule 40 mg, Xtandi[®], Astellas Pharma Australia Pty Ltd

1 Purpose of submission

- 1.1 The Category 2 submission requested General Schedule – Authority Required listing for enzalutamide for the treatment of non-metastatic castration resistant prostate cancer (m0CRPC).
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus darolutamide.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	m0CRPC
Intervention	Enzalutamide, 160 mg (4 x 40 mg capsules) as a once daily oral dose Medical castration with a LHRH analogue should be continued during treatment of patients not surgically castrated ^a
Comparator	Main comparator: Darolutamide, 600 mg (2 x 300 mg) as a twice daily oral dose (total daily dose = 1,200 mg) in combination with a GnRH analogue if patient has not received a bilateral orchiectomy ^b Near market comparator: Apalutamide, 240 mg (4 x 60 mg) as a once daily oral dose in combination with a GnRH if patient has not received a bilateral orchiectomy ^c
Outcomes	MFS, OS
Clinical claim	In patients with m0CRPC, enzalutamide is no worse than the main comparator, darolutamide, at improving MFS with a similar adverse event profile. In patients with m0CRPC, enzalutamide is no worse than the near market comparator, apalutamide, at improving MFS with a similar adverse event profile.

Source: Table 1.1-1, p4 of the submission

GnRH = gonadotrophin-releasing hormone; LHRH = luteinising hormone-releasing hormone; m0CRPC = non-metastatic castration resistant prostate cancer; MFS = metastasis-free survival; OS = overall survival; PI = product information

^a Enzalutamide PI; available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=pi&q=enzalutamide>

^b Darolutamide PI; available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-01276-1&d=20210906172310101>

^c Apalutamide PI; available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=pi&q=apalutamide>

2 Background

Registration status

- 2.1 Enzalutamide was TGA registered on 10 September 2019 for the treatment of patients with m0CRPC.
- 2.2 Other TGA indications include: the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC); the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) following failure of androgen

deprivation therapy in whom chemotherapy is not yet indicated; and the treatment of patients with mCRPC who have previously received docetaxel.

Previous PBAC consideration

- 2.3 In July 2021, the PBAC extended the restriction for enzalutamide for patients with mCRPC to remove the criterion that patients must have failed treatment with docetaxel due to resistance or intolerance.
- 2.4 Darolutamide was listed on the PBS for the treatment of mCRPC on 1 November 2021. Apalutamide was recommended for listing on the PBS with the same restriction on a cost-minimisation basis with darolutamide at the November 2021 PBAC meeting, but at the time of the PBAC's March 2022 meeting, was yet to proceed to listing.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ENZALUTAMIDE Capsule 40 mg, 112	1	5	Published: \$3,536.86 Effective:	Xtandi Astellas Pharma Australia Pty Ltd
Category/Program:	General Schedule			
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners			
Condition	Non-metastatic castration resistant carcinoma of the prostate			
PBS indication:	Non-metastatic castration resistant carcinoma of the prostate			
Restriction:	<input checked="" type="checkbox"/> Authority Required (immediate/real-time assessment by Services Australia)			
Treatment phase:	Initial			
Clinical criteria:	Treatment must be used in combination with androgen deprivation therapy AND Patient must have a PSA doubling time of 10 months or less AND Patient must have a WHO performance score of 0 or 1 AND Patient must not have received prior treatment with darolutamide or apalutamide OR Patient must have developed intolerance to darolutamide or apalutamide of a severity necessitating permanent treatment withdrawal AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug			
Prescriber criteria:	The PSA doubling time must have been calculated using at least three PSA values obtained during androgen deprivation therapy			
Administrative advice:	No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised			
Treatment phase:	Continuing			
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Treatment must be used in combination with androgen deprivation therapy AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug			
Administrative advice:	No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised			

- 3.1 The submission proposed that enzalutamide be listed on the PBS under a special pricing arrangement at the same price as the comparator, darolutamide. As the effective price of darolutamide is not available to the sponsor, only the published price was provided at the time of submission.
- 3.2 The submission proposed that the requested restriction align with that implemented for darolutamide.
- 3.3 The proposed restriction aligns with the approved TGA indication.
- 3.4 Flow on changes would be required to the current PBS restrictions for enzalutamide and abiraterone in the mCRPC setting to reflect the PBAC's previous advice preventing the sequential use of novel hormonal agents (NHAs; darolutamide, apalutamide,

enzalutamide and abiraterone), which due to cross resistance, were considered to be of uncertain benefit and cost effectiveness.

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

4 Population and disease

- 4.1 Castration resistant prostate cancer (CRPC) is defined as progressive disease despite castrate levels of testosterone. m0CRPC is where patients with prostate cancer present with biochemical progression (i.e. rising serum prostate specific antigen (PSA)) despite treatment with androgen deprivation therapy (ADT), but have no radiologically detectable metastases. Patients with m0CRPC who have a PSA doubling time of 10 months or less are considered to be at high risk of developing metastases. In the absence of treatment for m0CRPC beyond ADT with possible use of secondary hormonal therapies, it is expected that approximately one-third of m0CRPC patients will develop metastases within two years, with more than half becoming metastatic within three years. Once metastases have formed, the disease becomes incurable and median survival has been estimated to be 16 to 30 months.
- 4.2 The submission proposed that enzalutamide would be available for patients with m0CRPC as an alternative to darolutamide and, potentially, apalutamide (recommended by the PBAC in November 2021).
- 4.3 Enzalutamide is a second-generation, orally administered androgen receptor antagonist. It has the following Anatomical Therapeutic Chemical (ATC) code: L02BB04.

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

5 Comparator

- 5.1 The submission nominated darolutamide as the main comparator. The submission justified this nomination as darolutamide belongs to the same pharmacological class as enzalutamide and was listed on the PBS for the treatment of m0CRPC on 1 November 2021. The nomination of darolutamide as the main comparator was appropriate.
- 5.2 Apalutamide was nominated as a near market comparator as it was being considered by the PBAC for the treatment of m0CRPC at the November 2021 PBAC meeting. This was appropriate. Apalutamide was recommended for PBS listing for the treatment of m0CRPC at the November 2021 PBAC meeting.
- 5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy

and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. At the time of this evaluation the relevant alternative therapy PBS listed for mOCRPC was darolutamide. If apalutamide was PBS listed it would also be a relevant alternative therapy.

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 Medical Oncology Group of Australia (MOGA) expressed its support for enzalutamide for the treatment of mOCRPC. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for enzalutamide, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with placebo in the PROSPER trial.

Clinical trials

6.3 A literature search conducted by the sponsor (described in Section 2.1 of the submission) did not identify any randomised-controlled trials (RCTs) directly comparing enzalutamide to either darolutamide or apalutamide. However, three multi-centre, double-blind RCTs were identified that enabled an indirect treatment comparison (ITC) using placebo as the common reference:

- PROSPER (N = 1,401), comparing enzalutamide and placebo;
- ARAMIS (N = 1,509), comparing darolutamide and placebo; and
- SPARTAN (N = 1,207), comparing apalutamide and placebo.

6.4 The three trials identified by the submission have been considered previously by the PBAC in its considerations of darolutamide and apalutamide.

6.5 Details of the trials presented in the submission are provided in the table below.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Public Summary Document – March 2022 PBAC Meeting

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PROSPER	Full clinical study report protocol MDV3100-14 (C343-1005)	8 Dec 2018
	Supplemental clinical study report protocol MDV3100-14 (C3431005)	2 Oct 2018
	Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer.	NEJM. 2018;378(26):2465-2474
	Stemberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic castration-resistant prostate cancer.	NEJM. 2020;382(23):2197-2206
	Saad F, Stemberg CN, Efstathiou E, et al. Prostate-specific antigen progression in enzalutamide-treated men with nonmetastatic castration-resistant prostate cancer: any rise in prostate-specific antigen may require closer monitoring.	Eur Urol. 2020;78(6):847-853
ARAMIS	Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic castration-resistant prostate cancer.	NEJM. 2019;380(13):1235-1246
	Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide.	NEJM;2020(11):1040-1049
	Uemura H, Matsushima H, Kobayashi K, et al. Efficacy and safety of darolutamide in Japanese patients with nonmetastatic castration-resistant prostate cancer: a subgroup analysis of the Phase III ARAMIS trial.	Int J Clin Onc. 2021;26(3):578-590
SPARTAN	Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer.	NEJM. 2018;378(15):1408-1418
	Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer.	Ann Onc. 2019;30(11):1813-1820
	Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer.	Eur Urol. 2021;79(1):150-158
	Smith MR, Mehra M, Nair S, et al. Relationship between metastasis-free survival and overall survival in patients with nonmetastatic castration-resistant prostate cancer.	Clin Genitourin Canc. 2019;18(2):e180-e189
	Uemura H, Satoh T, Tsumaura H, et al. Efficacy and safety of apalutamide in Japanese patients with nonmetastatic castration-resistant prostate cancer: a subgroup analysis of a randomized, double-blind, placebo-controlled, Phase 3 study.	Prostate Int. 2020;8(4):190-197
	Perez-Ruixo C, Ackaert O, Ouellet D, et al. Efficacy and safety exposure-response relationships of apalutamide in patients with nonmetastatic castration-resistant prostate cancer.	Clin Cancer Res. 2021;27(16):4460-4467
	Smith MR, Thomas S, Gormley M, et al. Blood biomarker landscape in patients with high-risk nonmetastatic castration-resistant prostate cancer treated with apalutamide and androgen-deprivation therapy as they progress to metastatic disease.	Clin Cancer Res. 2021;27(16):4539-4548

Source: 2.2-1, pp20-21 of the submission

6.6 The key features of the RCTs are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Enzalutamide vs. placebo					
PROSPER	Enz: N = 933 Pbo: N = 468 Total: N = 1,401	R, DB, MC/ RCT: 18.5 months; OL: 48 months	Moderate	m0CRPC patients with high risk of distant metastases (PSADT ≤ 10 months)	Primary: MFS Secondary: time to PSA progression, PSA response rate, TCC, OS, safety
Darolutamide vs. placebo					
ARAMIS	Daro: N = 955 Pbo: N = 554 Total: N = 1,509	R, DB, MC/ RCT: 17.9 months; OL: 29 months	Moderate	m0CRPC patients with high risk of distant metastases (PSADT ≤ 10 months)	Primary: MFS Secondary: time to pain progression, time to first skeletal-related event, OS, safety
Apalutamide vs. placebo					
SPARTAN	Apa: N = 806 Pbo: N = 401 Total: N = 1,207	R, DB, MC/ RCT: 20.3 months; OL: 52 months	Moderate	m0CRPC patients with high risk of distant metastases (PSADT ≤ 10 months)	Primary: MFS Secondary: PFS2, time to pain symptomatic progression, TCC, OS, safety

Source: Section 2 of the submission

Apa = apalutamide; DB = double blind; Daro = darolutamide; Enz = enzalutamide; m0CRPC = non-metastatic castration-resistant prostate cancer; MC = multi-centre; MFS = metastasis free survival; OL = open label; OS = overall survival; Pbo = placebo; PFS2 = progression-free survival for first subsequent therapy; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; R = randomised; TCC = time to cytotoxic chemotherapy

- 6.7 The PBAC has previously considered the risk of bias in the three trials to be moderate given the occurrence of adverse events in the active treatment arms such as rash and fatigue which would potentially results in unblinding (paragraph 6.6, darolutamide PDS, March 2021).
- 6.8 Overall, the trials recruited similar patients who had a PSA doubling time of 10 months or less and experienced disease progression whilst receiving treatment with ADT with no evidence of metastasis based on conventional imaging. Baseline demographic and clinical characteristics of patients in each of the three trials were broadly similar between the trials, with patients from PROSPER having a higher median PSA at baseline and a slightly shorter median PSA doubling time. More patients in ARAMIS have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 1, and patients in SPARTAN had a longer median time from diagnosis to randomisation.
- 6.9 Metastasis-free survival (MFS) was the primary outcome measure in all three trials, with overall survival (OS) and safety the most relevant secondary outcomes measured across the trials.
- 6.10 The PBAC has not previously identified any transitivity or heterogeneity issues between the trials which would compromise the results of the ITCs.
- 6.11 The PBAC has previously noted that the intention-to-treat analysis of MFS in the ARAMIS trial included patients who had been misclassified at baseline as not having metastases (5.2% of patients in the darolutamide arm and 7.0% of patients in the

placebo arm). The submission presented ITCs between the intention to treat (ITT) populations and censored for misclassified patients for MFS.

Comparative effectiveness

6.12 The submission presented ITCs, using the Bucher method, for MFS and OS – see Table 4.

6.13 The submission noted that as none of the three trials has OS data that was mature enough for analysis at the time of the primary analysis cut-off, the results of pre-specified analyses of the open-label extension studies were presented. During the open-label phases, switching to active treatment from the placebo arm was allowed after unblinding. Unadjusted results are presented below.

Table 4: Results of ITCs for enzalutamide vs. darolutamide and enzalutamide vs. apalutamide

Trial/comparison	Outcome	Active treatment n/N (%)	Placebo n/N (%)	HR (95% CI)
MFS (ITT)				
PROSPER: enzalutamide (18.5 months median follow-up)	Events	219/933 (23.5%)	228/468 (48.7%)	-
	Median months	36.6	14.7	0.29 (0.24, 0.35)
ARAMIS: darolutamide (17.9 months median follow-up)	Events	221/955 (23.1%)	216/554 (39.0%)	-
	Median months	40.4	18.4	0.41 (0.34, 0.50)
SPARTAN: apalutamide (20.3 months median follow-up)	Events	184/806 (22.8%)	194/401 (48.7%)	-
	Median months	40.5	16.2	0.28 (0.23, 0.35)
Indirect comparison enzalutamide vs. darolutamide				0.71 (0.54, 0.93)
Indirect comparison enzalutamide vs. apalutamide				1.04 (0.78, 1.37)
MFS (censoring patients misclassified in ARAMIS)^a				
PROSPER: enzalutamide (18.5 months median follow-up)	Events	219/933 (23.5%)	228/468 (48.7%)	-
	Median months	36.6	14.7	0.29 (0.24, 0.35)
ARAMIS: darolutamide (29.1 months median follow-up)	Events	171/955 (17.9%)	177/554 (31.9%)	-
	Median months	40.5	22.1	0.36 (0.29, 0.44)
Indirect comparison enzalutamide vs. darolutamide				0.81 (0.61, 1.07)
OS (final analyses of ARAMIS, SPARTAN and PROSPER)				
PROSPER: enzalutamide (48.0 months median follow-up)	Dead	288/933 (30.9%)	178/468 (38.0%)	-
	Median months	67.0	56.3	0.73 (0.61, 0.89)
ARAMIS: darolutamide (29.1 months median follow-up)	Dead	148/955 (15.5%)	106/554 (19.1%)	-
	Median months	NE	NE	0.69 (0.53, 0.88)
SPARTAN: apalutamide (52.0 months median follow-up)	Dead	274/806 (34.0%)	154/401 (38.4%)	-
	Median months	73.9	59.9	0.78 (0.64, 0.96)
Indirect comparison enzalutamide vs. darolutamide				1.06 (0.77, 1.45)
Indirect comparison enzalutamide vs. apalutamide				0.94 (0.71, 1.24)

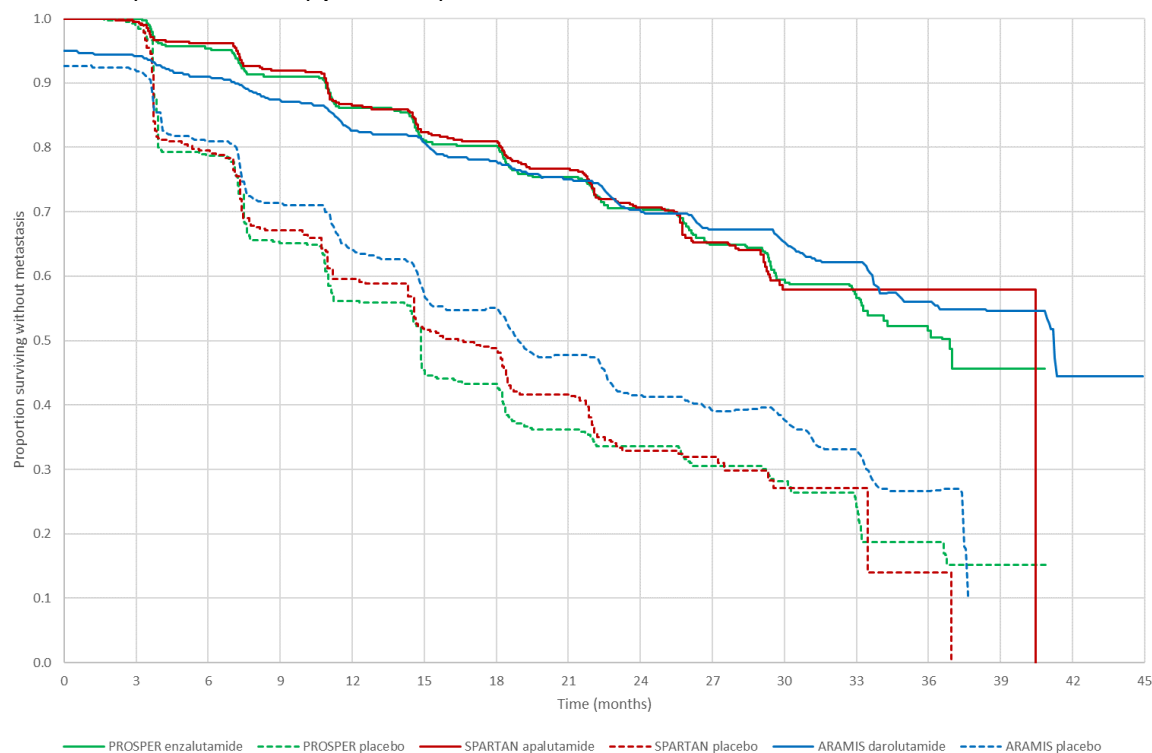
Source: Table 2.6-1, p53 of the submission

CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intention to treat; MFS = metastasis-free survival; NE = not estimable; OS = overall survival; **Bold** = statistically significant

^a It was reported that 50 patients had been misclassified and were found to have had metastases at baseline (Fizazi K. S. N., Nonmetastatic castration-resistant prostate cancer and survival with darolutamide, 2020, pp. S2,p.17). This has been noted by the PBAC (para 6.10, p.9, Darolutamide PSD July 2020).

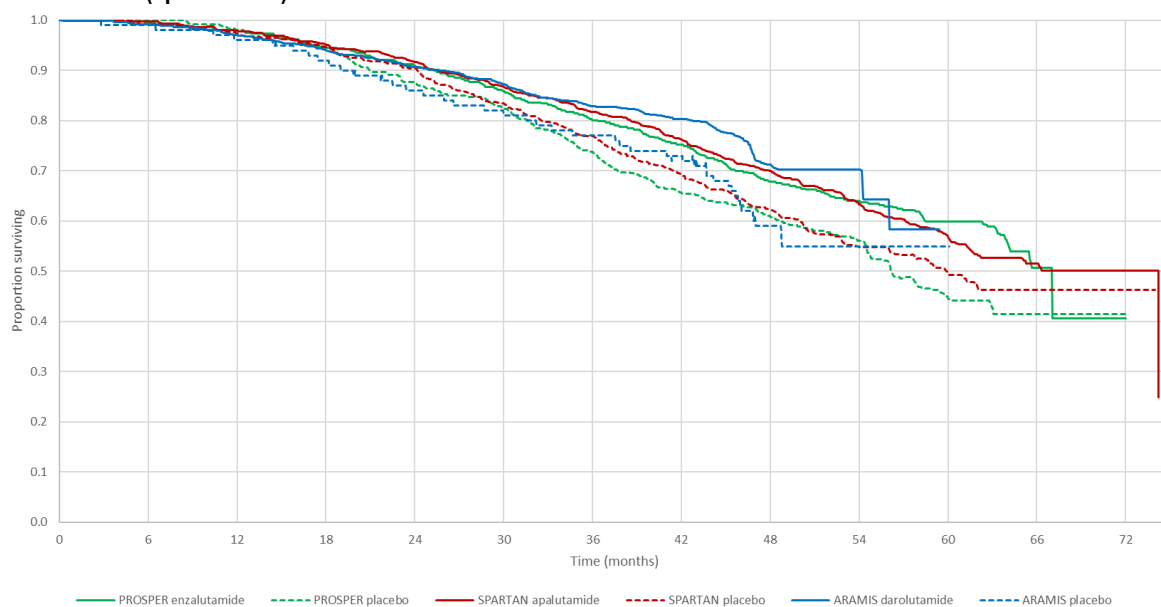
- 6.14 Although the ITC for MFS between enzalutamide and darolutamide statistically significantly favoured enzalutamide for the ITT population (HR = 0.71; 95% CI: 0.54, 0.93), when the population in ARAMIS was reclassified (see paragraph 6.9), the results were no longer statistically significant (HR = 0.81; 95% CI: 0.61, 1.07). There was no statistically significant difference between enzalutamide and apalutamide in terms of MFS (HR = 1.04; 95% CI: 0.78, 1.37).
- 6.15 ITCs for OS demonstrated no statistically significant differences between enzalutamide and darolutamide (HR = 1.06; 95% CI: 0.77, 1.45) or apalutamide (HR = 0.94; 95% CI: 0.71, 1.24). The submission noted that the OS results should be interpreted with care given the shorter median follow-up for patients treated with darolutamide and differences across the trials in terms of the proportion of patients free of metastases in the placebo arms who switched to active therapy in the open-label extension studies.
- 6.16 The submission presented digitised Kaplan-Meier plots for MFS (Figure 1) and OS (Figure 2) results from the PROSPER, ARAMIS and SPARTAN trials which were superimposed to allow ease of comparison.

Figure 1: Superimposed digitised Kaplan-Meier plots of MFS from PROSPER (enzalutamide), ARAMIS (darolutamide) and SPARTAN (apalutamide)



Source: Figure 2-4, p42 of the submission
MFS = metastasis-free survival

Figure 2: Superimposed digitised Kaplan-Meier plots of OS from PROSPER (enzalutamide), ARAMIS (darolutamide) and SPARTAN (apalutamide)



Source: Figure 2-8, p45 of the submission
OS = overall survival

Comparative harms

6.17 The most common adverse events reported at the time of the primary analysis for the PROSPER, ARAMIS and SPARTAN trials are presented below.

Table 5: Summary of key adverse events in the trials

	PROSPER 18.5 months median follow-up		ARAMIS 17.9 months median follow-up		SPARTAN 20.3 months median follow-up	
	Enzalutamide N = 933	Placebo N = 468	Darolutamide N = 955	Placebo N = 554	Apalutamide N = 806	Placebo N = 401
Any AE	808 (86.9%)	360 (77.4%)	794 (83.2%)	426 (76.9%)	775 (96.5%)	371 (93.2%)
Any serious AE	226 (24.3%)	85 (18.3%)	237 (24.8%)	111 (20.0%)	199 (24.8%)	92 (23.1%)
Grade 5 AE	NR	NR	37 (3.9%)	18 (3.2%)	NR	NR
AE leading to discontinuation	87 (9.4%)	28 (6.0%)	85 (8.9%)	48 (8.7%)	85 (10.6%)	28 (7.0%)
AE leading to death	32 (3.4%)	3 (0.6%)	NR	NR	10 (1.2%)	1 (0.3%)
Most common (≥ 5%)						
Fatigue	303 (32.6%)	64 (13.8%)	115 (12.1%)	48 (8.7%)	244 (30.4%)	84 (21.1%)
Hot flush	121 (13%)	36 (7.7%)	50 (5.2%)	23 (4.2%)	NR	NR
Nausea	106 (11.4%)	40 (8.6%)	48 (5.0%)	32 (5.8%)	145 (18.1%)	63 (15.8%)
Diarrhoea	91 (9.8%)	45 (9.7%)	66 (6.9%)	31 (5.6%)	163 (20.3%)	60 (15.1%)
Hypertension	111 (11.9%)	24 (5.2%)	63 (6.6%)	29 (5.2%)	199 (24.8%)	79 (19.8%)
Fall	106 (11.4%)	19 (4.1%)	40 (4.2%)	26 (4.7%)	125 (15.6%)	36 (9.0%)
Constipation	85 (9.1%)	32 (6.9%)	60 (6.3%)	34 (6.1%)	NR	NR
Dizziness	91 (9.8%)	20 (4.3%)	43 (4.5%)	22 (4.0%)	65 (8.1%)	8 (2.0%)
Arthralgia	78 (8.4%)	32 (6.9%)	77 (8.1%)	51 (9.2%)	128 (15.9%)	30 (7.5%)
Asthenia	82 (8.8%)	28 (6.0%)	NR	NR	NR	NR
Decreased appetite	89 (9.6%)	18 (3.9%)	NR	NR	NR	NR
Back pain	73 (7.8%)	33 (7.1%)	84 (8.8%)	50 (9.0%)	NR	NR
Headache	85 (9.1%)	21 (4.5%)	NR	NR	NR	NR
Haematuria	62 (6.7%)	36 (7.7%)	NR	NR	NR	NR
UTI	38 (4.1%)	30 (6.5%)	47 (4.9%)	28 (5.1%)	NR	NR
Weight loss	55 (5.9%)	7 (1.5%)	34 (3.6%)	12 (2.2%)	129 (16.1%)	25 (6.3%)
Urinary retention	20 (2.2%)	28 (6.0%)	33 (3.5%)	36 (6.5%)	NR	NR
AE's of special interest						
Major adverse CV event	48 (5.2%)	13 (2.8%)	NR	NR	NR	NR
Mental impairment disorders	48 (5.2%)	9 (1.9%)	5 (0.5%)	7 (1.3%)	2 (0.2%)	0
Hepatic impairment	11 (1.2%)	9 (1.9%)	NR	NR	NR	NR
Neutropenia	9 (1.0%)	1 (0.2%)	NR	NR	NR	NR
Convulsion	3 (0.3%)	0	2 (0.2%)	1 (0.2%)	NR	NR

Source: Tables 2.5-3, 2.5-4 and 2.5-5, pp46-48 of the submission

AE = adverse event; CV = cardiovascular; NR = not reported; UIT = urinary tract infection

6.18 The submission noted that each of the NHAs (plus ADT) was associated with a higher likelihood of any adverse event, any serious adverse event and adverse events leading to discontinuation than placebo (plus ADT). The NHAs were particularly associated with higher risks of fatigue, falls, hypertension, dizziness and weight loss.

6.19 The submission stated that the data were inadequate for drawing definitive conclusions in regard to comparative toxicity, but that it was generally considered that there was a similar risk of adverse events between enzalutamide, darolutamide and apalutamide. This was reasonable.

Benefits/harms

6.20 As the submission presented ITCs and claims of non-inferiority, the benefits and harms table is not presented.

Clinical claim

6.21 The submission claimed that enzalutamide was non-inferior, in terms of both effectiveness, as assessed by MFS and OS, and safety, when compared to both darolutamide and apalutamide when used in the management of patients with mOCRPC.

6.22 The submission stated that the claims were consistent with the PBAC's advice from March 2021 when in consideration of darolutamide, the PBAC considered that:

- 'overall, the efficacy of darolutamide would likely be non-inferior compared to apalutamide and enzalutamide' (paragraph 6.30, darolutamide Public Summary Document (PSD), March 2021); and
- 'the claim that darolutamide was non-inferior in terms of safety compared to apalutamide and enzalutamide was reasonable' (paragraph 6.31, darolutamide PSD, March 2021).

6.23 The PBAC considered that the claims made by the submission in terms of efficacy and safety were reasonable, were supported by the evidence presented and aligned with previous PBAC decisions.

Economic analysis

6.24 Based on the clinical claim that enzalutamide is non-inferior to darolutamide in terms of efficacy and safety, a cost-minimisation approach to the economic evaluation was presented by the submission (see Table 6).

6.25 The sponsor for enzalutamide noted that darolutamide was listed on the PBS under the terms of a confidential Special Pricing Arrangement (SPA). As the effective price of darolutamide was therefore unknown, the cost-minimisation approach was presented using the published price of darolutamide. The sponsor stated that it was prepared to consider PBS listing of enzalutamide at the same effective price as that of darolutamide. As the effective and published prices of apalutamide were unknown at the time of submission, no cost minimisation comparison versus apalutamide was presented.

Public Summary Document – March 2022 PBAC Meeting

Table 6: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, enzalutamide was assumed to be non-inferior to darolutamide and apalutamide.
Therapeutic claim: safety	Based on evidence presented, enzalutamide was assumed to be non-inferior to darolutamide and apalutamide.
Evidence base	ITC of the primary endpoint of MFS (and the secondary outcome of updated OS) for enzalutamide versus darolutamide and enzalutamide versus apalutamide.
Equi-effective doses	Enzalutamide 160 mg per day = darolutamide 1,200 mg per day = apalutamide 240 mg per day
Direct medicine costs	The same cost per day is sought for enzalutamide as for darolutamide. The sponsor of enzalutamide understands that the effective dispensed price of darolutamide will be lower than the published dispensed price and is prepared to consider listing of enzalutamide at the same SPA price as that agreed for darolutamide.
Other costs/cost offsets	None

Source: Table 3.1-1, p60 of the submission

ITC = indirect treatment comparison; MFS = metastasis-free survival; OS = overall survival; SPA = Special Pricing Arrangement

6.26 The equi-effective doses of enzalutamide, darolutamide and apalutamide were based on the recommended regimens specified in the respective Product Information documents for each treatment, which are the same as was administered in the three key trials. The submission proposed that the equi-effective doses were:

Enzalutamide 160 mg per day (administered as 4 x 40 mg capsules once daily) =

Darolutamide 1,200 mg per day (administered as 2 x 300 mg tablets twice daily) =

Apalutamide 240 mg per day (administered as 4 x 60 mg tablets once daily)

6.27 The submission noted that each NHA is administered as a fixed regimen until disease progression, with the management of adverse events being the only reason for varying dose. As there were no significant differences in efficacy or safety the submission assumed that, given the same daily cost of treatment, the total cost of a course of treatment will also be the same. This was reasonable, as compliance, treatment duration and differences in adverse events were not expected to differ between the three treatments.

6.28 The submission presented a cost-minimisation using the published dispensed price for maximum quantity (DPMQ) of darolutamide.

Table 7: Cost-minimisation between enzalutamide and darolutamide

Row	Parameter	Value	Source / Reference
A	Darolutamide days of therapy	28	PBS
B	Darolutamide AEMP	\$3,375.64	PBS ex-manufacturer prices
C	Darolutamide daily price	\$120.56	B/A
D	Enzalutamide days of therapy	28	Proposed item
E	Enzalutamide cost-minimised AEMP	\$3,375.64	C x D

Source: Table 3.4-2 of the submission

AEMP = approved ex-manufacturer price; PBS = Pharmaceutical Benefits Scheme

Drug cost/patient/course

Table 8: Drug cost per patient for enzalutamide

	Enzalutamide Trial dose and duration
Dose	160 mg/day
Median duration of treatment	36.6 months
DPMQ	\$3,536.86
Cost/patient/month ^a	\$3,844.87
Cost/patient/course	\$140,722

Source: Created during evaluation based on Table 3.4-2, p64 of the submission

DPMQ = dispensed price for maximum quantity

a 1 month = 30.4375 days

6.29 The cost of treatment for enzalutamide was calculated to be \$140,722 for 36.6 months of treatment. This was based on a DPMQ of \$3,536.86 per 28-day supply and a median MFS of 36.6 months in the PROSPER trial.

Estimated PBS usage & financial implications

6.30 This submission was not considered by DUSC.

6.31 The submission noted that if enzalutamide is recommended on the basis of the cost-minimisation approach versus darolutamide, the products would directly substitute for each other and the listing of enzalutamide would be cost neutral.

6.32 However, noting that darolutamide was listed on the PBS on 1 November 2021 and no market share data was available at the time of preparation of the submission, a mixed epidemiological/market-share approach to estimating the utilisation and financial impact of enzalutamide was presented.

6.33 A summary of the data sources used, and assumptions made to estimate the usage and cost of the requested PBS listing of enzalutamide is presented below.

Public Summary Document – March 2022 PBAC Meeting

Table 9: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Epidemiology		
Incident and prevalent prostate cancer populations	Incidence of all prostate cancer, 2020 = 16,471 Prevalence of all prostate cancer, 2020 = 89,703 Cancer Australia data Population growth = 3% Based on ABS population data.	Uncertain. The assumptions and data informing the calculation of the prevalent prostate cancer population after Year 1 could not be verified.
% of all prostate cancer patients who undergo castration	55% Based on data from the Prostate Cancer Outcome Registry – Victoria (Wang, 2018). It was assumed that castration includes prostatectomy, chemical castration, and high-dose brachytherapy.	Reasonable.
% who have m0CRPC	19.2% Based on Freeland, 2005, a retrospective study which identified patients who had developed a biochemical recurrence, defined as a single postoperative PSA of ≤ 0.2 ng/mL.	Uncertain. Although 19.2% of patients in Freeman 2005 developed a biochemical recurrence, only 8.1% had a rising PSA, defined as 2 rising PSA values ≤ 3 months apart and a PSA of ≤ 0.2 ng/mL.
% with PSADT ≤ 10 months (i.e. high risk)	42% Based on Freeland, 2005.	Reasonable.
Utilisation		
Uptake rate	Year 1 = 80%; Year 2 = 85%; Years 3-6 = 90% Based on Wang, 2018, which assumed that approximately 10% of patients would decline or discontinue treatment. The uptake rate was assumed to be lower in Years 1 and 2.	Likely overestimated. Given then m0CRPC patients are unable to receive NHAs after progression to mCRPC, some patients may choose not to initiate treatment in the m0CRPC setting.
Duration of treatment	36.6 months Median MFS observed in the PROSPER trial	Appropriate.
Number of prescriptions per year	13.04	Appropriate.
Compliance	92% Table 17, darolutamide PSD, March 2021.	Reasonable. Accepted for darolutamide.
Costs		
Enzalutamide cost in m0CRPC	Effective DPMQ = \$█ for 28-day supply Effective DPMQ in mCRPC	Reasonable.
Copayments	PBS = \$11.56; RPBS = \$4.55	Appropriate.

Source: Section 4 of the submission

ABS = Australian Bureau of Statistics; DPMQ = dispensed price for maximum quantity; m0CRPC = non-metastatic castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; MFS = metastasis-free survival; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time

6.34 The table below provides a summary of the estimated utilisation and financial impact of listing enzalutamide on the PBS.

6.35 For the financial estimates the submission assumed an effective DPMQ for enzalutamide of \$█, which was the effective DPMQ for enzalutamide in mCRPC.

Table 10: Estimated use and financial implications of listing enzalutamide on the PBS/RPBS

	2022	2023	2024	2025	2026	2027
Estimated extent of use						
Number of patients treated	1 ¹	1 ¹	1 ¹	1 ¹	1 ¹	1 ¹
Number of prescriptions dispensed ^a	2 ²	4 ⁴	6 ⁶	7 ⁷	9 ⁹	11 ¹¹
Estimated financial implications of enzalutamide						
Cost to PBS/RPBS (less co-payments)	\$3 ³	\$5 ⁵	\$5 ⁵	\$8 ⁸	\$10 ¹⁰	\$12 ¹²

Source: Table 4.2-1, p71, Table 4.2-2, p72 and Table 4.2-6, p73 of the submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming duration of treatment = 36.6 months; 13.04 prescriptions per year; and 92% compliance.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 50,000 to < 60,000

³ \$60 million to < \$70 million

⁴ 80,000 to < 90,000

⁵ \$100 million to < \$200 million

⁶ 100,000 to < 200,000

⁷ 60,000 to < 70,000

⁸ \$80 million to < \$90 million

⁹ 40,000 to < 50,000

¹⁰ \$50 million to < \$60 million

¹¹ 30,000 to < 40,000

¹² \$40 million to < \$50 million

6.36 In the situation that darolutamide was not listed on the PBS, the submission estimated that enzalutamide would cost the PBS/RPBS \$60 million to < \$70 million in Year 1, \$40 million to < \$50 million in Year 6, and \$500 million to < \$600 million over the first 6 years of listing.

6.37 The utilisation and financial impact estimates are likely overestimated due to uncertainty in the proportion of patients with mOCRPC, the high uptake rate assumed and as the submission did not incorporate cost offsets due to decreased use of enzalutamide and abiraterone in the mCRPC setting.

6.38 The submission stated that as the proposed listing for enzalutamide in the mOCRPC setting is identical to that proposed for darolutamide, there would be no impact on the processing of prescriptions for the Department of Health Services. In addition, the submission stated that there would be no impact on the MBS.

Financial Management – Risk Sharing Arrangements

6.39 The submission notes that if a Risk Sharing Arrangement (RSA) exists for darolutamide for use in the mOCRPC setting, if enzalutamide was recommended for listing, it would be required to join the existing RSA.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of enzalutamide for the treatment of patients with non-metastatic castration resistant prostate cancer (mOCRPC). The PBAC was satisfied

that enzalutamide was non-inferior in terms of efficacy and safety compared to darolutamide, the primary comparator. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost minimisation approach between enzalutamide and darolutamide was acceptable and that the listing would be cost neutral to Government.

- 7.2 The PBAC noted that the Medical Oncology Group of Australia supported the listing of enzalutamide on the PBS for the treatment of mOCRPC.
- 7.3 The PBAC considered that the proposed place in therapy, as an alternative to darolutamide, and the nominations of darolutamide as the primary comparator and apalutamide as a near-market comparator were appropriate.
- 7.4 The PBAC recalled that it had previously considered the key clinical trials presented in the submission (PROSPER: enzalutamide versus placebo; ARAMIS: darolutamide versus placebo; and SPARTAN: apalutamide versus placebo) when considering darolutamide and apalutamide for the same indication.
- 7.5 The PBAC noted that an indirect treatment comparison was presented using placebo as the common reference.
- 7.6 The PBAC recalled that it had previously considered that enzalutamide, darolutamide and apalutamide were likely non-inferior in terms of efficacy and safety (paragraphs 6.30 and 6.31, darolutamide PSD, March 2021). The PBAC considered that these claims remained reasonable and were supported by the ITC presented in the enzalutamide submission.
- 7.7 The PBAC considered that the equi-effective doses were:
Enzalutamide 160 mg daily = darolutamide 1,200 mg daily = apalutamide 240 mg daily
- 7.8 The PBAC noted that the equi-effective doses did not account for differences in compliance, treatment duration or differences in adverse event profiles, and considered that these were not expected to differ on average between the treatments.
- 7.9 The PBAC noted that the submission presented utilisation and financial estimates based on a mixed epidemiological/market-share approach as no utilisation data for darolutamide were available at the time of submission. The PBAC considered that as enzalutamide was recommended on the basis of the cost minimisation versus darolutamide, the products would directly substitute for each other and the listing of enzalutamide would be cost neutral and not result in an incremental cost to Government.
- 7.10 The PBAC advised that enzalutamide should be listed on the PBS with the same restriction as darolutamide for mOCRPC. Noting that sequential treatment with novel hormonal agents is not intended on the PBS, the PBAC advised that flow-on changes would be required to the enzalutamide and abiraterone restrictions.

Public Summary Document – March 2022 PBAC Meeting

- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because enzalutamide is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over darolutamide, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.12 The PBAC noted that this submission was not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add indication (Castration resistant non-metastatic carcinoma of the prostate) on a separate prescribing rule to the existing indication (Castration resistant metastatic carcinoma of the prostate) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Available brands
ENZALUTAMIDE					
enzalutamide 40 mg capsule, 112	NEW	112	1	5	Xtandi
Early Supply Rule applies? Y					
Restriction Summary / Treatment of Concept:					
Category/Program: GENERAL – General Schedule (GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS authorities system)					
PBS indication: Castration resistant non-metastatic carcinoma of the prostate					
Treatment phase: [blank]					
Clinical criteria:					
The condition must have evidence of an absence of distant metastases on the most recently performed conventional medical imaging used to evaluate the condition.					
AND					
Clinical criteria:					
The condition must be associated with a prostate-specific antigen level that was observed to have at least doubled in value in a time period of within 10 months any time prior to first commencing treatment with this drug.					
AND					
Clinical criteria:					
Patient must have a World Health Organisation (WHO) or Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 1 prior to treatment initiation.					
AND					
Clinical criteria:					
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.					
AND					
Clinical criteria:					
Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or					

Public Summary Document – March 2022 PBAC Meeting

	Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation.
	Treatment criteria:
	Patient must be undergoing concurrent treatment with androgen deprivation therapy.
	Prescribing instructions: Prescribing instructions: Retain the results of all investigative imaging and prostate-specific antigen (PSA) level measurements on the patient's medical records - do not submit copies of these with this authority application. The PSA level doubling time must be based on at least three PSA levels obtained within a time period of 10 months any time prior to first commencing a novel hormonal agent for this condition. The third reading is to demonstrate that the doubling was durable and must be at least 1 week apart from the second reading.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply
	Administrative advice: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide (<i>pending</i>), (iii) darolutamide, (iv) enzalutamide.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

8.2 Amend darolutamide's restriction to appear as above.

8.3 Amend existing abiraterone listing for mCRPC as follows to exclude use following treatment with any of apalutamide (pending)/darolutamide/enzalutamide in mOCRPC:

Relevant extract of abiraterone Restriction summary / ToC:	
PB item codes: 11206T (abiraterone acetate 500 mg tablet, 60) 2698B (abiraterone acetate 250 mg tablet, 120)	
	Clinical criteria:
	Patient must not be undergoing treatment with this drug following treatment with any of: (i) darolutamide, (ii) enzalutamide; or
	Patient must have developed an intolerance to enzalutamide of a severity necessitating permanent treatment withdrawal
	Clinical criteria:
	<i>Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or</i>
	<i>Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation.</i>
	Administrative advice: <i>Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide (pending), (iii) darolutamide, (iv) enzalutamide.</i>

8.4 Amend existing enzalutamide restriction for mCRPC as follows to exclude use following treatment with any of apalutamide (pending)/darolutamide/enzalutamide in the mOCRPC setting:

Public Summary Document – March 2022 PBAC Meeting

Relevant extract of enzalutamide Restriction summary / ToC:	
PB item codes: 10174L (enzalutamide 40 mg capsule, 112)	
	Clinical criteria:
	Patient must not be undergoing treatment with this drug following treatment with any of: (i) darolutamide, (ii) abiraterone; or
	Patient must have developed an intolerance to abiraterone of a severity necessitating permanent treatment withdrawal
	Clinical criteria:
	Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or
	Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation.
	Administrative advice: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide (pending), (iii) darolutamide, (iv) enzalutamide.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Astellas Pharma Australia welcomes the PBAC decision to recommend the PBS listing of enzalutamide (Xtandi®) for men with non-metastatic castration resistant prostate cancer. We are working with the Department of Health to achieve the earliest possible PBS listing date.