

7.02 APALUTAMIDE, Tablet 60 mg, Eryland[®], Janssen-Cilag Pty Ltd

1 Purpose of submission

- 1.1 The resubmission requested a General Schedule Authority Required (Telephone) listing for apalutamide for treatment of patients with non-metastatic castration-resistant prostate cancer (m0CRPC) at high risk of distant metastases.
- 1.2 Although listing was requested on the basis of a cost utility analysis versus placebo, pre-PBAC response stated that following the recent listing of darolutamide on the PBS for the same indication, a cost minimisation approach might be more appropriate. The key components of the clinical issue were addressed as per the November 2020 resubmission with the exception that this resubmission amended its previous claim of superior effectiveness over darolutamide to non-inferior effectiveness. Previously it had claimed superior effectiveness based on an indirect comparison of metastasis free survival outcomes, however that claim was not accepted by the PBAC (paragraph 7.8, apalutamide Public Summary Document (PSD), November 2020).

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

Component	Description
Population	Patients with CRPC with no distant metastases and who are at high risk of developing distant metastases as defined by a PSADT of ≤10 months (high risk m0CRPC).
Intervention	Apalutamide is administered orally at a dose of 240 mg daily (as 4 x 60 mg tablets) in addition to background ongoing ADT.
Comparator	<u>Main comparator:</u> Watchful waiting which is comprised of ongoing ADT (with or without secondary hormonal therapy). <u>Supplementary near market comparator:</u> Darolutamide, which was considered by the PBAC in July 2020, March 2021 and July 2021 for the same population as requested for apalutamide.
Outcomes	MFS, OS, rPFS, sPFS, time to initiation of cytotoxic chemotherapy, PFS2 and AEs.
Clinical claim	Superior effectiveness and inferior safety versus watchful waiting Non-inferior effectiveness and safety versus darolutamide

Source: Table 1.1, p11 of the resubmission.

ADT = androgen deprivation therapy, AE = adverse event; m0CRPC = non-metastatic castration resistant prostate cancer, MFS = metastasis free survival; OS = overall survival, PFS2 = progression free survival on the first subsequent therapy, PSADT = prostate specific antigen doubling time; rPFS = radiographical progression free survival; sPFS = symptomatic progression free survival

2 Background

Registration status

- 2.1 Apalutamide was TGA registered on the 5th July 2018 for the treatment of patients with non-metastatic castration-resistant prostate cancer (m0CRCP).

Previous PBAC consideration

2.2 Apalutamide was previously considered by the PBAC in November 2018, July 2019 and November 2020. Following is a summary of the key concerns identified in the November 2020 PBAC submission and the response taken by the resubmission.

Table 2: Summary of key matters of concern and how the resubmission addressed them

	Matter of concern raised at the November 2020 PBAC meeting	How the current resubmission addresses concern
Restriction	The PBAC considered that restricting PBS subsidy to patients with a PSA level of at least 2 ng/mL would help limit apalutamide use to higher risk patients who are more likely to benefit from treatment.	The resubmission presented revised restriction wording adding in the clinical criteria "patients must have a PSA level of at least 2 ng/mL".
Base case economic model	The PBAC noted that not all requested changes were implemented in the November 2020 resubmission and that the ICER remained high and uncertain. The PBAC requested the following changes in the economic model: <ul style="list-style-type: none"> • adjust the dose intensity in the model to reflect that expected in clinical practice and including a price reduction to achieve ICER in the range of \$40,000 to \$45,000 per QALY, using OS unadjusted for treatment switching. 	A revised base case with an ICER of \$ [redacted] /QALY gained brought about by the following changes: <ul style="list-style-type: none"> • A lower effective DPMQ of \$ [redacted] (previously \$ [redacted]) • A higher dose intensity to reflect that submitted in the November 2018 submission of 89.94% for apalutamide (changed from 66.24% in the November 2020 resubmission), and 96.08% for placebo (changed from 71.1% in November 2020 resubmission). • Unadjusted OS data from ITT population from SPARTAN used. • Previous model changes based on the July 2019 PBAC recommendations retained. The pre-PBAC response, noting that darolutamide was listed on the PBS on 1 November 2021 for the same indication, considered it would be more appropriate to compare apalutamide to darolutamide based on a cost minimisation approach.
Financial estimates & risk share	The PBAC requested the following changes in the financial estimates: <ul style="list-style-type: none"> • update the financial estimates to reflect the dose intensity applied in the model and • include details of a RSA which appropriately addressed the uncertainty with the financial estimates. 	Revised financial estimates, incorporating above changes in the economics model using the: <ul style="list-style-type: none"> • lower effective DPMQ and • higher dose intensity for apalutamide The resubmission proposed a [redacted]% rebate over subsidisation caps (previously [redacted]% as per the Pre-PBAC response in Nov 2020). The subsidisation caps were reduced to [redacted] ² over 5 years (previously [redacted] ²) by assuming a shorter duration of treatment.

Source: paragraphs 3.6 and 7.17, p36 of the apalutamide PBAC Public Summary Document (PSD) November 2020

DPMQ = dispensed price for maximum quantity, ICER = incremental cost effectiveness ratio, ITT = intention to treat, OS = overall survival
PSA = prostate specific antigen, QALY = quality adjusted life years, RSA = risk sharing arrangement

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$200 million to < \$300 million

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
APALUTAMIDE Tablet, 60 mg	1	120	5	published price effective price
				Janssen-Cilag Pty Ltd

Category/ Program	GENERAL – General Schedule (GE)
Prescriber type	Medical Practitioners
Condition	Castration resistant carcinoma of the prostate
PBS indication	Castration resistant carcinoma of the prostate
Restriction:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment phase:	Initial
Clinical criteria:	Patient must not have distant metastasis on conventional imaging AND 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 PSA level of at least 2 ng/mL AND Patient must have a WHO performance score of 0 or 1 AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug
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 Patient must not develop radiographic disease progression while receiving PBS-subsidised treatment with this drug for this condition
Treatment phase:	Initial – grandfather patients
Clinical criteria:	Patient must have previously received non PBS-subsidised treatment with this drug for this condition prior to <date> AND Patient does not have distant metastasis on conventional imaging AND Treatment must be used in combination with androgen deprivation therapy AND Patient must have had a PSA doubling time of 10 months or less prior to receiving non-PBS-subsidised treatment with this drug AND Patient must have a PSA level of at least 2 ng/mL prior to receiving non-PBS-subsidised treatment with this drug AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug
Prescriber instruction:	The PSA doubling time must be calculated using at least three PSA values obtained during androgen deprivation therapy
Administrative advice:	Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised

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Source: Tables 1.5 and 1.6, pp22-23 of the resubmission.

- 3.1 The requested restriction was updated to include the changes proposed by the PBAC that “patient must have a prostate specific antigen (PSA) level of at least 2 ng/mL” prior to receiving subsidised or non-PBS-subsidised treatment with apalutamide.
- 3.2 The resubmission also agreed to include clinical criteria to precluding use of abiraterone (also the sponsor’s drug) in metastatic castration resistant prostate cancer (mCRPC) post apalutamide and suggested that the same would be required for enzalutamide. This was appropriate and reflected the PBAC’s previous advice of no sequential use novel hormonal agents (NHAs) on the PBS, which, due to cross resistance, were considered to be of uncertain benefit and cost effectiveness (see paragraphs 2.7, 4.7, 6.46, 7.4, 7.13, apalutamide PSD, November 2018; paragraphs 2.5, 2.6, 7.3, 7.4, apalutamide PSD, July 2019; and paragraphs 3.1, 7.4, darolutamide PSD, July 2020).
- 3.3 The resubmission maintained its request for a ‘grandfather’ transitioning arrangement given the sponsor’s intention to establish a patient familiarisation program (PFP) prior to PBS listing. The resubmission estimated that 52 patients would require movement to PBS-subsidised apalutamide (down from 294 previously estimated) by the time of PBS listing. At the time of this resubmission, the proposed PFP had not yet started. The Secretariat advised that ‘grandfather’ arrangements are only necessary where the usual restriction contains an entry clause that the patient cannot meet if read literally. This is not the case with the recommended restriction.
- 3.4 Noting that the July 2021 PBAC recommendation for darolutamide for the same indication was proceeding for PBS listing, the PBAC considered that the restriction for apalutamide should align with that recommended for darolutamide.

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

4 Population and disease

- 4.1 mOCRPC is a disease stage of prostate cancer where patients have rising levels PSA but no radiographic evidence of distant metastatic disease. Patients with mOCRPC are classified into two groups based on PSA doubling time (PSADT) – patients with PSADT > 10 months are at low risk while patients with a PSADT ≤ 10 months are classified as high risk.
- 4.2 Patients with mOCRPC are currently managed with androgen deprivation therapy (ADT) with possible use of secondary hormonal therapies. The PBS listing of apalutamide was requested for treatment of patients at high risk of distant metastases with mOCRPC. The PBAC noted that treatment of high risk mOCRPC patients with apalutamide is consistent with a trend in using active treatments earlier in the pathway (paragraph 7.3, apalutamide PSD, November 2018).

- 4.3 There is also a trend to use NHAs earlier in the treatment pathway in preference of chemotherapeutic agents. The PBAC recently recommended to amend the PBS listings of abiraterone and enzalutamide in mCRPC to remove the need for prior docetaxel. This decision was based on recent data provided by the DUSC Secretariat which indicated that in 2020, 69% of use of abiraterone and enzalutamide was in patients who had not received a prior supply of docetaxel. The PBAC thus considered this amendment would better align the restrictions for abiraterone and enzalutamide with how these drugs are being used in clinical practice and with their TGA indications (paragraphs 5.1 and 5.2, abiraterone and enzalutamide PBAC PSD, March 2021).

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

5 Comparator

- 5.1 The resubmission maintained watchful waiting (also termed placebo), comprised of ongoing ADT with or without the addition of secondary hormonal therapies, as the main comparator. The PBAC had previously accepted this to be appropriate (paragraph 7.5, apalutamide PSD, November 2018; and paragraph 7.5, apalutamide PSD, July 2019).
- 5.2 The resubmission also nominated darolutamide as a supplementary near market comparator. An indirect comparison with darolutamide was included as supplementary evidence in the November 2020 resubmission, using published data from the ARAMIS trial. The PBAC considered that this was appropriate.
- 5.3 The resubmission maintained that enzalutamide was not considered as a comparator as it has not been considered by the PBAC despite its TGA registration for this population. While enzalutamide is yet to submit to the PBAC for listing in high risk mOCRPC, it is also a potentially relevant comparator. The PBAC indicated that “enzalutamide is likely to enter the same market as apalutamide, based on the PROSPER study” (paragraph 7.5, apalutamide PSD, July 2019). Enzalutamide is already PBS listed for mCRPC and given recent PBAC recommendation to remove the need for prior docetaxel, it is possible that patients classified as mOCRPC in the apalutamide trial (SPARTAN) may be identified as mCRPC and treated with enzalutamide on the PBS, given that more sensitive imaging techniques currently used in Australia allow earlier detection of metastasis than conventional imaging in SPARTAN.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from a number of individuals and health care professionals, as well as organisations (8) via the Consumer Comments facility on the PBS website. The comments described a range of benefits associated with treatment with apalutamide including the potential for an improved life expectancy and improvements in quality of life.
- 6.3 The PBAC noted the advice received from the following prostate cancer support groups: Tamworth and District, Ocean Reef, South Eastern, Heidelberg, and Nepean/Blue Mountains, outlining the need for additional prostate cancer treatments. Support for the submission was also received from Movember and the Prostate Cancer Foundation of Australia.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the apalutamide in mOCRPC submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the SPARTAN trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for apalutamide, which was limited to 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)^[1], based on a comparison with placebo.¹

Clinical trials

- 6.5 No new clinical data was presented in the resubmission. The November 2020 resubmission had presented the results of final analyses from both the SPARTAN trial (for apalutamide) and the ARAMIS trial (for darolutamide). The median duration of follow up from SPARTAN and ARAMIS at final analyses were 52 months and 29 months respectively with no further clinical data expected.
- 6.6 Details of the SPARTAN and ARAMIS trials were unchanged from the November 2020 resubmission and are represented in the table below.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
SPARTAN	A study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer. Smith MR, Saad F, Chowdhury S et al. Apalutamide treatment and metastasis-free survival in prostate cancer.	September 2017 NEJM 2018; 378:1408-1418
ARAMIS	Fizazi K, Shore N, Tammela TL, et al. Darolutamide in non-metastatic castration-resistant prostate cancer.	NEJM 2019; DOI: 10.1056/NEJMoa1815671

Source: Table 4, apalutamide PBAC PSD, November 2020.

- 6.7 The key features of SPARTAN and ARAMIS (unchanged from November 2020) are presented 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

Table 4: Key features of the included evidence: Apalutamide + ADT vs. placebo + ADT

Trial	N	Design/duration	Patient population	Outcome(s)	Use in modelled evaluation
SPARTAN	Apalutamide: N = 806 Placebo: N = 401 Total: N = 1,207	R, DB, MC; 52 months (FA)	m0CRPC with high risk of distant metastases (PSADT ≤ 10 months)	Primary: MFS Secondary: PFS2, time to symptomatic progression, TTC, OS	Used
ARAMIS	Darolutamide: N = 954 Placebo: N = 554 Total: N = 1,508	R, DB, MC; 9.1 months		Primary: MFS Secondary: time to pain progression, time to first skeletal-related event, OS	Not used

Source: Table 5, apalutamide PBAC PSD, November 2020.

ADT = androgen deprivation therapy; DB = double blind; FA = final analysis; MC = multi-centre; MFS = metastasis-free survival; m0CRPC = non-metastatic castration resistant prostate cancer; OS = overall survival; PFS2 = progression free survival for first subsequent therapy; PSADT = prostate specific antigen doubling time, R = randomised, TTC = time to cytotoxic chemotherapy

6.8 Of the 46% of patients in the apalutamide arm who received subsequent therapy, 84.1% received abiraterone and 39.3% received enzalutamide. This high proportion of abiraterone treatment in the trial is not consistent with the PBS restriction precluding abiraterone treatment after apalutamide and limits the applicability of the trial to the Australian setting.

Comparative effectiveness

6.9 Key clinical evidence from the SPARTAN final analysis is summarised in below.

Table 5: MFS and OS Apalutamide vs. Placebo, SPARTAN trial

MFS results	Apalutamide vs. Placebo; HR (95% CI)
Investigator assessed	
ex-USA regulatory definition for censoring	0.25 (0.21, 0.31); p < 0.0001
USA regulatory definition for censoring*	0.27 (0.22,0.33); p < 0.0001
BICR-assessed	
ex-USA regulatory definition for censoring	0.30 (0.24, 0.36); p < 0.0001
USA regulatory definition for censoring*	0.28 (0.23, 0.35); p < 0.0001
OS results	Apalutamide vs. Placebo; HR (95% CI)
ITT IA1 (median follow up 20.3 months, no treatment switching)*	0.70 (0.47, 1.04); p = 0.074
ITT IA2 (median follow up 41 months, 19% switched#)^	0.75 (0.59; 0.96); p = 0.0201
FA (median follow up 52 months, 19% switched#):	
ITT (unadjusted for switching)	0.78 (0.64, 0.96); p = 0.0164
ITT (censored at switch)	0.69 (0.56, 0.84); p = 0.0003
RPSFTM (unadjusted for baseline covariates)	0.72 (0.55, 0.94); p = 0.0164
RPSFTM (adjusted for baseline covariates)	0.74 (0.57, 0.95); p = 0.0191
IPCW	0.68 (0.55; 0.84); p = 0.0003

Source: Table 7, apalutamide PSD, November 2020.

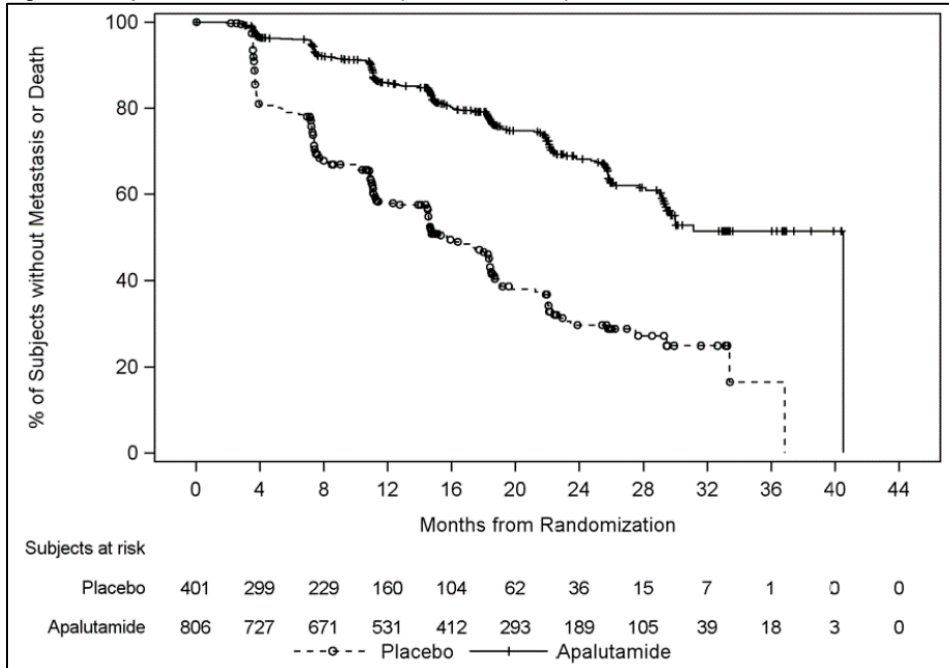
BICR = blinded independent central review; CI = confidence interval; FA = final analysis; HR = hazard ratio; IPCW = inverse probability of censoring weights; IA1 = interim analysis 1; IA2 = interim analysis 2; ITT = intent to treat; MFS = metastasis-free survival; OS = overall survival; RPSFTM = rank preserving structural failure time model; USA = United States of America

* Reported in Jul 2019 submissions,

^ Reported in the PSCR to Jul 2019 resubmission.

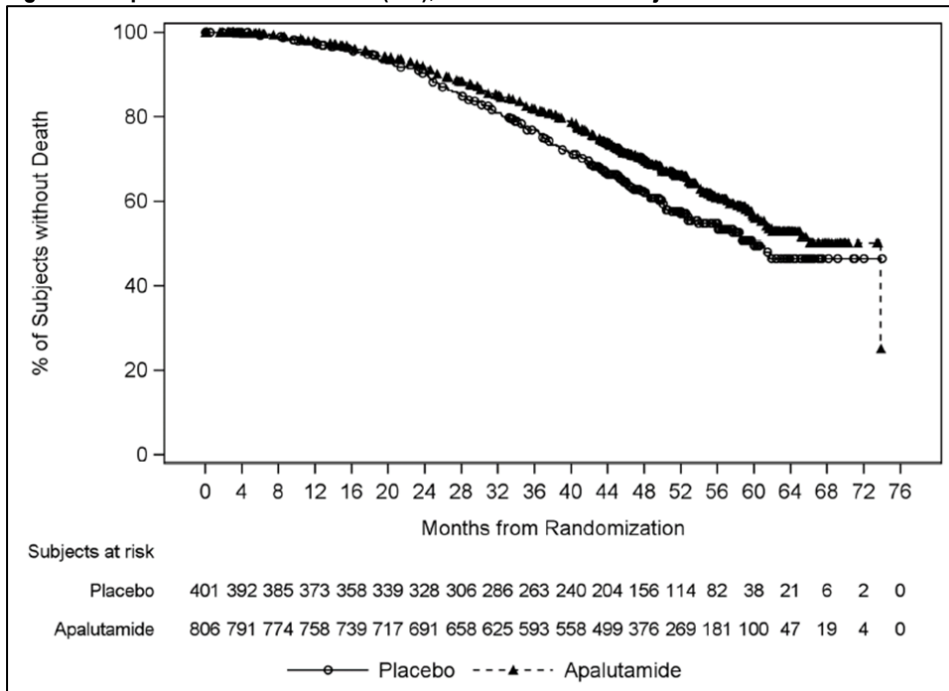
From placebo to apalutamide at treatment unblinding which happened after IA1.

Figure 1: Kaplan-Meier curve for MFS (BIRC-assessed), SPARTAN IA1



Source: Figure 1, apalutamide PSD, November 2020
 BIRC = blinded independent central review; IA1 = interim analysis 1; MFS = metastasis-free survival.

Figure 2: Kaplan Meier curve for OS (ITT), SPARTAN FA not adjusted for treatment switching



Source: Figure 2, apalutamide PSD, November 2020, Figure 2.1, p26 of the resubmission.
 FA = final analysis; ITT = intention-to-treat; OS = overall survival

6.10 The resubmission also noted that PBAC had previously considered that apalutamide was likely to be non-inferior compared to darolutamide in terms of efficacy and safety (paragraph 6.40, apalutamide PSD, November 2020). Results of the indirect comparison presented in the November 2020 resubmission comparing apalutamide and darolutamide using SPARTAN (interim analysis 1 for metastasis-free survival [MFS], and interim analysis 1 and final analysis for overall survival [OS]) and published results from the ARAMIS trial are presented below. While the resubmission’s analysis showed a significant MFS benefit for apalutamide compared to darolutamide, the PBAC noted “that the misclassification of patients in the ARAMIS trial may have impacted on the indirect comparison for MFS and that a sensitivity analysis excluding the misclassified patients resulted in a hazard ratio (HR) for darolutamide closer to results observed in SPARTAN (paragraph 6.39, apalutamide PSD, July 2021) and the difference were no longer statistically significant (paragraph 6.19, darolutamide PSD, March 2021). A much higher proportion of patients had crossed over from placebo to active treatment in the ARAMIS trial compared to SPARTAN (31% versus 19%).

Table 6: MFS and OS in SPARTAN and ARAMIS

Analysis	Outcomes	SPARTAN		ARAMIS	
		Apalutamide N=806	Placebo N=401	Darolutamide N=955	Placebo N=554
MFS IA1	Progressed, n (%)	209 (25.9)	210 (52.4)	221 (23.1)	216 (39.0)
	Median MFS, months	40.51	15.7	40.4	18.4
	HR (95% CI)	0.30 (0.24, 0.36)		0.41 (0.34, 0.50)	
	Median follow-up	20.3 months		17.9 months	
	Indirect comparison HR (95% CI) apalutamide vs darolutamide	0.724 (0.548, 0.958)			
OS IA1	Deaths, n (%)	62 (7.7)	42 (10.5)	78 (8.2)	58 (10.5)
	Median OS, months	NR	39.03 (39.03, NR)	NR	NR
	HR (95% CI)	0.70 (0.47, 1.04)		0.71 (0.50, 0.99)	
	Median follow-up	20.3 months		17.9 months	
	Indirect comparison HR (95% CI) apalutamide vs darolutamide	0.986 (0.584, 1.665)			
OS FA	Deaths, n (%)	274 (34.0)	154 (38.4)	148 (15.5)	106 (19.1)
	Median OS, months	73.86	59.89	NR	NR
	HR (95% CI)	0.784 (0.643, 0.956)		0.69 (0.53, 0.88)	
	Median follow-up	52.0 months		29.1 months	
	Indirect comparison HR (95% CI) apalutamide vs darolutamide	1.136 (0.824, 1.568)			

Source: Table 2-1, p29 of the resubmission, Table 8, apalutamide PSD, November 2020.

CI = confidence interval; HR = hazard ratio; FA = final analysis; IA1 = interim analysis 1; ITT = intent-to-treat; MFS = metastasis-free survival; NR = not reported; OS = overall survival

Comparative harms

6.11 No new safety data were presented in the resubmission. Key differences in safety outcomes between apalutamide and placebo are summarised under Benefits/harms. Overall, the safety data are consistent with the claim of inferior safety of apalutamide versus placebo. As detailed in the November 2020 resubmission, the most common

adverse events (AEs) for apalutamide included skin rash, fall, fracture, hypothyroidism, ischaemic heart disease and seizures.

Benefits/harms

6.12 A summary of the comparative benefits and harms associated with apalutamide versus placebo is presented in Table 7 below. This was based on data presented in the November 2020 resubmission.

Table 7: Summary of comparative benefits and harms for Apalutamide and Placebo

Benefits						
Metastasis free survival (median duration of follow up 20.3 months)						
SPARTAN	Apalutamide N=803	Placebo N=554	Absolute Difference	HR (95% CI)		
Progressed, n (%)	209 (25.9)	210 (52.4)	-	0.297 (0.244, 0.362) P<0.0001		
Median MFS, months (95% CI)	40.5 (29.70, 40.5)	15.70 (14.55, 18.40)	24.45 months			
24-month event-free rate (95% CI)	68.2% (63.8, 72.2)	29.6% (23.5, 0.360)	38.6%			
36-month event-free rate (95% CI)	51.4% (44.3, 58.1)	16.5% (0.055, 0.327)	34.9%			
Overall survival (median duration of follow up 52.0 months)						
Deaths, n/N (%)	154 (38.4%)	274 (34.0%)	-	0.784 (0.643, 0.956) p=0.0161		
Median OS, months (95% CI)	59.89 (52.80, NE)	73.86 (61.21, NE)	-13.97 months			
5-year survival rate (95% CI)	49.4% (42.6, 55.9)	55.9 (51.1, 60.4)	-6.5%			
Harms						
SPARTAN	Apalutamide n/N	Placebo n/N	RR (95% CI)	Events/100 patients		RD (95% CI)
				Apalutamide	Placebo	
Skin rash	212/803	25/554	4.20 (2.83, 6.25)	26.4	6.3	0.20 (0.16, 0.24)
Falls	177/803	38/554	2.31 (1.66, 3.21)	22.0	9.5	0.12 (0.08, 0.17)
Fracture	145/803	30/554	2.40 (1.65, 3.48)	18.1	7.5	0.11 (0.07, 0.14)
Hypothyroidism	79/803	8/554	4.89 (2.39, 10.03)	9.8	2.0	0.08 (0.05, 0.10)
IHD	44/803	11/554	1.98 (1.04, 3.80)	5.5	2.8	0.03 (0.00, 0.05)
Seizure	1/803	0/554	1.49 (0.06, 36.46)	0.1	0	0.00 (-0.00, 0.01)

Source: Table 11, apalutamide PSD, November 2020.

CI = confidence interval; HR = hazard ratio; IHD = ischaemic heart disease; MFS = metastasis-free survival; NE = not estimable; OS = overall survival; RD = risk difference; RR = risk ratio

6.13 On the basis of evidence from the SPARTAN trial presented by the resubmission, for every 100 patients treated with apalutamide in comparison to placebo:

- Approximately 39 more patients would remain metastasis free after 24 months of treatment;
- Approximately 6 more patients would survive after 5 years of treatment;
- Approximately 20 additional patients would experience skin rash;
- Approximately 12 additional patients would experience a fall;
- Approximately 11 additional patients would experience a fracture;
- Approximately 8 additional patients would experience hypothyroidism; and
- Approximately 3 additional patients would experience ischaemic heart disease.

Clinical claim

- 6.14 The resubmission retained its previous claim and described apalutamide as superior in terms of effectiveness compared with placebo and inferior in terms of safety compared to placebo. The PBAC had previously accepted the claim of superior comparative effectiveness of apalutamide versus placebo, noting that the improvement in OS was modest (paragraph 6.37, apalutamide PSD, November 2020). The PBAC also considered apalutamide to have inferior safety to placebo.
- 6.15 The resubmission amended its previous claim of superior efficacy (based on MFS) versus darolutamide to the alternate claim of at least non-inferior efficacy and safety compared to darolutamide. The PBAC considered that the claims that apalutamide demonstrated non-inferior comparative effectiveness and safety compared to darolutamide were reasonable.

Economic analysis

- 6.16 The Pre-Sub-Committee Response (PSCR) and pre-PBAC response stated that the recent recommendation and subsequent listing on the PBS of darolutamide for the same indication meant it may be more appropriate to recommend apalutamide on a cost minimisation basis to darolutamide.
- 6.17 The ESC, noting that the PBAC had previously considered that apalutamide was non-inferior compared to darolutamide in terms of efficacy and safety (paragraph 7.08, apalutamide PSD, November 2020), considered that a cost minimisation approach between apalutamide and darolutamide would be appropriate. The ESC considered that the equi-effective doses would be:
- apalutamide 240 mg per day = darolutamide 1,200 mg per day
- 6.18 The ESC based the equi-effective doses on the recommended daily doses as per the relevant Product Information leaflets. The proposed equi-effective doses do not account for differences in compliance, treatment duration or differences in adverse event profiles, as these were not expected to differ between the two treatments.
- 6.19 In terms of the previous economic analysis, in November 2020 the PBAC noted (paragraphs 7.9 and 7.17, apalutamide PSD, November 2020) that not all requested modelling changes were implemented and considered that the incremental cost effectiveness ratio (ICER) remained high and uncertain. In November 2020, the PBAC advised that a future model would need to:
- adjust the dose intensity in the model (from 66.24%) to reflect that expected in clinical practice;
 - include a price reduction to achieve ICER in the range of \$40,000 to \$45,000 per quality adjusted life year (QALY), using OS unadjusted for treatment switching; and
 - apply OS unadjusted for treatment switching.

6.20 The ESC noted that the above changes were adopted by the resubmission, with the revised economic model resulting in a base case ICER of \$35,000 to < \$45,000 per QALY gained.

Drug cost/patient/month

Table 8: Intervention costs^a per patient across one month and model duration

	Apalutamide			Placebo		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose	219 mg/day	240 mg/day ^a	240 mg/day ^b	-	-	-
Mean duration	31.65 months ^c	39.25 months ^f	44.9 months	13.45 months	21.98 months	18.9 months
Cost/patient/month (\$)	-	██████████ ^d	██████████ ^d	-	\$0	\$0
Cost/patient/course (\$)	-	██████████ ^e	██████████ ^g	-	\$0	\$0
Cost/patient/month Nov.2020 model (\$)	-	██████████	██████████	-	\$0	\$0
Cost/patient/course Nov.2020 model (\$)	-	██████████	██████████	-	\$0	\$0

Source: Table 2.5, p34 of the resubmission, Excel workbook Partitioned survival model and financial estimates model.

DPMQ = dispensed price for maximum quantity; MFS = metastasis free survival; TTD = time to treatment discontinuation

^a The November 2020 economic model applied a dose intensity of 66.24% to apalutamide and 71.1% to placebo, while the corresponding dose intensities in the current revised model were 89.94% and 96.08%.

^b A dose intensity of 89.9% was applied to apalutamide for the updated financial estimates.

^c Treatment duration is defined as the duration from the date of the first dose of study drug to the date of the last dose of study drug+1 divided by 30.4375.

^d effective DPMQ x 1.01 scripts per month x dose intensity i.e. \$██████████ x 1.01 x 89.94% = \$██████████ (based on calculations in the model)

^e discounted costs, undiscounted cost for apalutamide over 10 years is \$██████████.

^f in the economic model TTD was set to not exceed MFS.

^g calculated as \$██████████ x 44.9 months

6.21 The cost per patient per month of apalutamide was slightly increased from \$██████████ to \$██████████ and the average cost of apalutamide treatment over 10 years increased from \$██████████ to \$██████████ (discounted), driven by an increase in the assumed dose intensity for apalutamide (from 66.24% to 89.94%) and placebo (from 71.1% to 96.08%).

Estimated PBS usage & financial implications

6.22 This submission was not considered by DUSC. As for the November 2018 and July 2019 and November resubmissions, the resubmission applied an epidemiological approach to estimate the number of incident and prevalent patients treated with apalutamide.

6.23 The PBAC noted the revised financial estimates which applied a higher dose intensity, as per the economic model, and lower effective dispensed price for maximum quantity (DPMQ) for apalutamide. Given the methodology to calculate patients initiating apalutamide was unchanged the uncertainty identified in previous submission remained; however, the PBAC considered that apalutamide would share a portion of the market that had been agreed for darolutamide, thereby mitigating a number the previous concerns. The PBAC noted that if recommended on a cost minimisation basis

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to darolutamide, apalutamide would be cost neutral as its listing would not result in an incremental cost to the Government.

6.24 Table 9 provides a summary of the data sources used and assumptions made to estimate the usage and cost of the requested PBS listing of apalutamide, and the changes relative to the July 2019 and November 2020 resubmission.

Table 9: Data sources and parameter values applied in the utilisation and financial estimates

	July 2019	November 2020	Current resubmission
Epidemiology			
Prevalence data	Five-year prostate cancer prevalence data - Cancer in Australia 2017 publication from AIHW. Male population growth – ABS-projected male population growth (50+ years) between 2012 and 2019. The November 2018 submission had used estimates based on all ages (0-85+ years). Proportion of prevalent patients that are m0CRPC – based on Liede (2013), sourced from a patient flow model using international registry data. Proportion of m0CRPC patients at high risk – ePAD CRPC clinical registry data.	Unchanged. The DUSC considered the assumptions and data informing the estimates of incidence and prevalence of m0CRPC could not be fully verified (paragraph 6.43, apalutamide, PSD, November 2018). This statement remains applicable as the methodology to estimate the number of m0CRPC patients was unchanged.	The current resubmission did not change the methods to estimate the incidence and prevalence of eligible patients. In November 2020, PBAC considered that these values remained highly uncertain (paragraph 7.14, apalutamide, PSD, November 2020).
Incidence data	Patients treated with ADT sourced from PBS data (10% PBS sample data analysis by Prospecption) with ePAD CRPC clinical registry data used to estimate patients with m0CRPC and at high risk of distant metastases.		
Utilisation			
Uptake rate	Sponsor assumption: Prevalent population: 50% in Year 1, 40% in Year 2, 10% in Year 3; incident population: 50% in Year 1; 70% in Year 2; 90% in Years 3-6.	Unchanged. These uptake rates may be overestimated. Given that apalutamide patients are precluded from abiraterone and enzalutamide treatment after progression to mCRPC in the updated restriction, some patients may not initiate apalutamide.	Uptake of apalutamide was reduced (sponsor assumption) to: Prevalent population: 50% in Year 1, 30% in Year 2, 10% in Year 3; incident population: 50% in Year 1; 55% in Year 2; 60% in Year 3, 65% in Year 4, and 70% in Years 5-6.
Transition of patients	Applying data from the economic model, patients transition through three states – m0CRPC, mCRPC and death.	Updated extrapolations in the economic model. The resubmission used the OS and TTD extrapolations to estimate the number of apalutamide patients on treatment. This is appropriate.	Unchanged

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	July 2019	November 2020	Current resubmission
Number of scripts per month	1.01 scripts/month as one script provides 30 days treatment.	Unchanged.	Unchanged
Dose intensity	66.24% sourced from the SPARTAN trial based on tablet counts. This was a decrease from the 89.94% applied in the November 2018 estimates.	Unchanged.	Apalutamide dose intensity was increased to 89.94%, which was the value applied in November 2018.
Usage of abiraterone in mCRPC	Assumed to be 100%. This was a shift from the November 2018 estimates where treatment in mCRPC was based on 68% enzalutamide and 32% abiraterone.	Subsequent abiraterone use after apalutamide is removed.	Unchanged
Cost of medicines			
Apalutamide	\$ [REDACTED] per script	\$ [REDACTED] per script	\$ [REDACTED] per script
ADT	\$222.63 average cost per month as calculated for the economic model.	\$221.96 average cost per month as calculated for the economic model.	\$301.37 average cost per month as calculated for the economic model.
Patient co-payment	Average co-payment for prednisolone, mometasone and levothyroxine was applied (\$17.08).	Average co-payment for prednisolone, mometasone and levothyroxine was applied (\$18.56). PBS=\$18.95, RPBS=\$5.43 (PBS/RPBS split= 97.1%/2.9%)	Average co-payment for prednisolone, mometasone and levothyroxine was applied (\$18.89). PBS=\$19.24, RPBS=\$4.92 (PBS/RPBS split=97.5%/2.5%)
Impact on other medicines			
Subsequent therapy for mCRPC	Assumed that the only agent used will be abiraterone.	Docetaxel and cabazitaxel assumed to be the only agents used in the mCRPC setting after apalutamide.	Unchanged. However, the proportion of docetaxel and cabazitaxel used was halved in the apalutamide group.
Treatment of AEs	Type of agents and time on treatment sourced from SPARTAN and the economic model.	Unchanged. The resubmission did not include the cost of treatments for IHD, which was updated as a TEAE.	Unchanged.
MBS usage and costs			
MBS items applied to AEs	GP visits were included for management of AEs with the rate of AEs based on SPARTAN and the economic model.	Unchanged. The resubmission did not include the cost of medical services for IHD, which was updated as a TEAE.	Unchanged
MBS items for monitoring	Usage was based on the economic model.	Unchanged	Unchanged

ABS = Australian Bureau of Statistics; ADT = androgen deprivation therapy; AE = adverse event; AIHW = Australian Institute of Health and Welfare; CRPC = castration resistant prostate cancer; GP = general practitioner; IHD = ischaemic heart disease; m0CRPC = non-metastatic castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; TEAE = treatment-emergent adverse event; TTD = time to treatment discontinuation
Source: Section 4, pp.46-58 of the resubmission. Section 4, pp114-128 of the November 2020 resubmission; Section 9.3.1 to Section 9.3.6.5, p129-148 of the July 2019 resubmission

6.25 Table 10 summarises the estimated changes in script volume and total cost to the government budget as presented in the resubmission and the November 2020 resubmission.

Table 10: Financial estimates from the current resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 1-6
Estimated extent of use							
Apalutamide patient initiations	■ ^{b,1}	■ ^{c,1}	■ ¹	■ ¹	■ ¹	■ ¹	■ ²
Apalutamide scripts	■ ³	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁵
Estimated financial implications of apalutamide							
Cost to the PBS/RPBS less co-payment (effective price)	■ ⁶	■ ⁷	■ ⁷	■ ⁷	■ ⁸	■ ⁸	■ ⁹
Change in cost of other medicines to PBS/RPBS*	-■ ¹⁰	-■ ¹¹	-■ ¹¹	-■ ¹¹	-■ ¹¹	-■ ¹¹	-■ ¹²
Change in cost for the MBS	-■ ¹⁰	-■ ¹⁰	-■ ¹⁰	-■ ¹⁰	-■ ¹⁰	-■ ¹⁰	-■ ⁶
Net cost for the health budget	■ ⁶	■ ¹³	■ ¹⁴	■ ¹⁴	■ ¹⁴	■ ¹³	■ ¹⁵
Nov 2020 submission	■ ⁶	■ ¹⁴	■ ¹⁴	■ ¹⁴	■ ¹⁴	■ ¹⁴	■ ¹⁵

Source: Table 4.3, p51; Table 4.14, p57 of the resubmission. Table 4.2, p119, Table 4.5, p121, Table 4.7, p123, Table 4.12, p126 Table 4.13, p126 of the November 2020 resubmission

DPMQ = dispensed price for maximum quantity

* assuming abiraterone and enzalutamide at same effective DPMQ of \$■ and the rest at published prices (there were very minor discrepancies in the published prices used (out by a few cents) compared to those published on the PBS website, unlikely to impact results).

^b including 3215 prevalent patients initiating

^c including 785 prevalent patients initiating

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ 40,000 to < 50,000

⁵ 200,000 to < 500,000

⁶ \$20 million to < \$30 million

⁷ \$50 million to < \$60 million

⁸ \$60 million to < \$70 million

⁹ \$300 million to < \$400 million

¹⁰ \$0 to < \$10 million

¹¹ \$10 million to < \$20 million

¹² \$80 million to < \$90 million

¹³ \$40 million to < \$50 million

¹⁴ \$30 million to < \$40 million

¹⁵ \$200 million to < \$300 million

Financial Management – Risk Sharing Arrangements

6.26 The resubmission proposed a risk sharing arrangement (RSA) which consisted of a single subsidisation cap beyond which rebates of ■% would be applied. The PBAC noted that there was no RSA in place for darolutamide in mOCRPC.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of apalutamide for the treatment of patients with non-metastatic castration resistant prostate cancer (mOCRPC). The PBAC was satisfied that apalutamide provides, for some patients, a moderate overall survival (OS) benefit

compared to standard of care (SOC) and was non-inferior in terms of efficacy and safety compared to darolutamide. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of apalutamide would be acceptable if it were cost-minimised to darolutamide.

- 7.2 The PBAC noted the comments from consumers, prostate cancer support groups and the Medical Oncology Group of Australia, all of which supported the listing of apalutamide on the PBS for the treatment of mOCRPC.
- 7.3 The PBAC recalled that in November 2020 it had considered that apalutamide resulted in superior comparative effectiveness and inferior comparative safety compared to SOC.
- 7.4 The PBAC also recalled that in November 2020 it had considered that apalutamide was likely to be non-inferior compared to darolutamide in terms of efficacy and safety, based on an indirect treatment comparison of apalutamide (SPARTAN trial) and darolutamide (ARAMIS trial) using placebo as the common comparator.
- 7.5 The PBAC noted that the resubmission addressed the key issues with the economic model; however, considered that the appropriate comparison was a cost minimisation approach relative to darolutamide.
- 7.6 The PBAC considered that the equi-effective doses were:

apalutamide 240 mg per day = darolutamide 1,200 mg per day
- 7.7 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 two treatments.
- 7.8 The PBAC noted that the resubmission presented updated financial estimates. The PBAC, noting that apalutamide would share a portion of the previously agreed darolutamide market, considered that the recommendation of apalutamide would be cost neutral as its listing would not result in an incremental cost to Government.
- 7.9 The PBAC advised that apalutamide should be listed on the PBS with the same restriction as darolutamide, but as the second drug for mOCRPC, the intent would be that sequential treatment with each drug not occur in the patient who tolerates the first drug. The darolutamide restriction should be updated to reflect this intent, as well as flow on changes to the enzalutamide and abiraterone restrictions to communicate that subsequent use of novel hormonal agents is not intended on the PBS.
- 7.10 The PBAC advised that apalutamide is not suitable for prescribing by nurse practitioners.
- 7.11 The PBAC advised that apalutamide should not be exempt from the Early Supply Rule.
- 7.12 The PBAC advised that, under Section 101(3BA) of the *National Health Act 1953*,

apalutamide should not be treated as interchangeable on an individual patient basis with any other drug.

- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because apalutamide 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.
- 7.14 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 new medicinal product (apalutamide) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Available brands
APALUTAMIDE					
apalutamide 60 mg tablet, 120	New	120	1	5	Erlyand
Restriction Summary / Treatment of Concept: [12398 edited] – as per darolutamide’s restriction as at 1 November 2021					
	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 treatment with one novel hormonal drug per lifetime				
	OR				

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Available brands
	Clinical criteria				
	<i>Patient must only receive treatment with a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation</i>				
	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 treatment with this drug 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: Special Pricing Arrangements apply				
	Administrative advice: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide				

Flow on changes:

- 8.2 Update darolutamide's restriction to appear identical to that displayed above.
- 8.3 Update abiraterone's restriction to exclude abiraterone use for metastatic disease following treatment with any of apalutamide/darolutamide (in non-metastatic disease) as follows.

Relevant extract of abiraterone Restriction summary 12353 / ToC: 12352 (current as at 1 November 2021)					
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 treatment with one novel hormonal drug per lifetime</i>				
	OR				
	Clinical criteria				
	<i>Patient must only receive treatment with 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: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide				

- 8.4 Update enzalutamide's restriction to exclude enzalutamide use for metastatic disease following treatment with any of apalutamide/darolutamide (in non-metastatic disease) as follows.

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Relevant extract of enzalutamide Restriction summary 12370 / ToC: 12371 (current as at 1 November 2021)	
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 treatment with one novel hormonal drug per lifetime
	OR
	Patient must only receive treatment with 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, (ii) darolutamide, (iv) enzalutamide

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

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

The sponsor had no comment.