

7.01 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 Listing was requested on the basis of a cost utility analysis versus placebo. The key components of the clinical issue addressed by the resubmission are presented in Table 1.

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

Component	Description
Population	Patients with CRPC with no distant metastases (m0CRPC) and who are at high risk of developing distant metastases as defined by a PSADT of ≤ 10 months
Intervention	Apalutamide 240 mg/day with background ADT
Comparator	<u>Main comparator:</u> Watchful waiting (referred to as placebo) comprised of ongoing ADT, with or without secondary hormonal therapy. <u>Supplementary near market comparator:</u> Darolutamide, which was rejected by the PBAC for the same population at its July 2020 meeting. A clinical comparison of apalutamide versus darolutamide was presented as supplementary analysis.
Outcomes	MFS, OS, rPFS, sPFS, time to initiation of cytotoxic chemotherapy, PFS2, and AEs.
Clinical claim	<ul style="list-style-type: none"> On the basis of SPARTAN FA data, that apalutamide when used in addition to background ADT demonstrated superior effectiveness versus placebo as assessed by statistically and clinically significant improvements in (MFS, rPFS, sPFS, PFS2 and OS) but inferior safety. On the basis of indirect comparison versus darolutamide (using published data from ARAMIS for darolutamide), apalutamide provides superior comparative effectiveness based on MFS and non-inferior comparative effectiveness based on OS and time to first cytotoxic chemotherapy and non-inferior safety.

Source: Table 1.1, p13 of the resubmission.

ADT = androgen deprivation therapy; AE = adverse event; CRPC = castration resistant prostate cancer; m0CRPC = non-metastatic castration resistant prostate cancer; MFS = metastasis free survival; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; 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.

Previous PBAC consideration

2.2 This was the third submission for apalutamide. Apalutamide was considered by the PBAC in November 2018 and July 2019. Table 2 presents a summary of the key concerns identified in the July 2019 PBAC consideration and the response taken by this resubmission.

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

Component	Matter of concern in July 2019	How the resubmission addresses it
Restriction	The PBS restriction should not allow abiraterone to be used after apalutamide paragraph 7.3, apalutamide, PSD, July 2019).	The resubmission accepted to preclude use of abiraterone after apalutamide.
Clinical benefit	The PBAC considered that it was likely that apalutamide provided an OS benefit, however the magnitude of this benefit remained uncertain as the data were immature (paragraph 7.7, apalutamide, PSD, July 2019).	The resubmission presented updated OS data from the final analysis (FA) of SPARTAN, with a median follow-up of 52 months (compared to 32 months in the July 2019 resubmission and 41 months (IA2) in the PSCR).
Base case economic model	The PBAC advised the following changes were required to the base case economic model: <ul style="list-style-type: none"> - use of BICR-assessed MFS; - use of a 10-year time horizon; - include updated TTD data; and - use unadjusted OS results (i.e. do not include any adjustments for treatment switching) given the uncertain magnitude of the OS gains (paragraph 7.13, apalutamide, PSD, July 2019). 	The resubmission updated the base case economic evaluation with: <ul style="list-style-type: none"> - BICR-assessed MFS; - 10-year time horizon; - updated TTD data (from SPARTAN FA) However, OS data in the base case were adjusted for treatment switching. The resubmission argued that SPARTAN FA data with a longer duration of follow up had considerably reduced the uncertainty in the magnitude of OS benefit and therefore use of OS adjusted for treatment switching in the base case was justified. This may not be appropriate as uncertainty in extrapolated OS remains (see Economic Analysis section below).
ICER	The PBAC required an ICER in the range of \$40,000 to \$45,000 per QALY using the base-case model outlined in paragraph 7.13 (paragraph 7.17, apalutamide, PSD, July 2019).	The ICERs presented in the base case (using OS data adjusted for treatment switching) ranged from \$ [redacted] to \$ [redacted]/QALY. The ICER using the unadjusted OS data was \$ [redacted]/QALY. The resubmission noted that removing the costs associated with subsequent abiraterone treatment from the apalutamide arm of the model resulted in ICERs within the PBAC's requested range. These analyses are considered uncertain (see Economic Analysis section below).
Ex-manufacturer price	The PBAC considered a price reduction would be required to achieve the requested ICER range (paragraph 7.17, apalutamide, PSD, July 2019).	No change to the ex-manufacturer price of apalutamide (\$ [redacted]) was proposed.
Financial estimates	The financial estimates should be updated to remove the assumption that abiraterone can be used after apalutamide (paragraph 7.17, apalutamide, PSD, July 2019).	The use of abiraterone following apalutamide treatment was removed from the financial estimates. These results are considered uncertain (see Financial analysis section below).

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Component	Matter of concern in July 2019	How the resubmission addresses it
Risk share agreement	The PBAC considered that a risk sharing arrangement with ■■■% rebates for expenditure above the caps would be necessary to address uncertainties regarding the number of incident and prevalent patients, uptake of apalutamide and dose intensity in clinical practice (paragraphs 6.50 and 7.15, apalutamide, PSD, July 2019).	The resubmission did not consider a ■■■% rebate appropriate because the financial estimates did not assume ■■■% uptake of apalutamide in high risk m0CRPC. The resubmission proposed a ■■■% rebate (increased to ■■■% in the pre-PBAC response) beyond the caps.

Source: Table 1.3, pp16-18 of the resubmission; PSD =Public Summary Document; PSCR =Pre-sub-committee response

The redacted values correspond to the following ranges:

¹\$45,000 to <\$55,000/QALY gained

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

3 Requested listing

MEDICINAL PRODUCT	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Available brands
APALUTAMIDE apalumatimide60 mg tablet, 120	1	5	\$■■■■ published price \$■■■■ effective price	Eryland

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 type:	<input checked="" type="checkbox"/> Authority Required – (telephone/online)
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 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 Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug
Treatment phase:	Initial – grandfather patients

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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 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

Source: Table 1.4 and 1.5, pp22-23 of the resubmission.

- 3.1 The requested restriction was updated to include the clinical criteria “Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug”. The PBAC considered that this criteria could be deleted from the initial supply restriction.
- 3.2 The resubmission maintained its request for a grandfathering restriction given the sponsor’s intention to establish a patient familiarisation program (PFP) prior to PBS listing. The resubmission estimated that 294 patients would require grandfathering to PBS-subsidised apalutamide by the time of PBS listing. At the time of this resubmission, the proposed PFP had not started.
- 3.3 The PBAC has previously indicated that use of apalutamide in mOCRPC would preclude use of abiraterone and enzalutamide in mCRPC (paragraph 2.6, apalutamide Public Summary Document (PSD), July 2019). If apalutamide is recommended this would be reflected in flow-on changes to the abiraterone and enzalutamide restrictions.
- 3.4 Imaging methods are changing in Australia, with prostate-specific membrane antigen positron emission tomography (PSMA-PET) widely used to confirm absence or presence of metastasis and an MSAC application underway to formalise a listing of PSMA PET/CT imaging on the MBS¹. Therefore, the discussion in the Commentary document considered that it might be appropriate for the requested restrictions to also specify the type of imaging that should be used to determine whether patients are accurately staged as mOCRPC and the frequency of imaging required to rule out distant metastases. The Pre-Sub-Committee Response (PSCR) stated that conventional imaging, which includes bone scans, computed tomography (CT) and magnetic resonance imaging (MRI), is consistent with the SPARTAN trial evidence and

¹ MSAC application 1632 – PSMA PET/CT imaging for informing treatment of patients with prostate cancer, available from: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1632-public>, accessed 29 July 2020.

with clinical guidelines. In addition, the PSCR stated that the frequency of imaging of patients is a multifactorial decision which is dependent on disease characteristics, symptoms and patient characteristics, therefore best left to clinician judgement.

- 3.5 The ESC considered that PSMA-PET scanning, whilst not MBS subsidised, is an increasingly common staging modality for prostate cancer, and is standard of care in many centres in Australia. The ESC noted that PSMA-PET scanning is more sensitive compared to conventional imaging which would result in patients otherwise classified as mOCRPC being classified as having occult metastatic disease. The ESC considered, consistent with the SPARTAN trial, it would appropriate for patients with occult metastatic disease to be able to access apalutamide through the PBS. The PBAC considered use of the words “conventional imaging”, but without defining conventional imaging in the restriction, to be desirable as this builds flexibility in accommodating evolving medical practice.
- 3.6 The PBAC considered that PBS subsidy should be restricted to patients with a PSA level of at least 2 ng/mL, noting that PSA doubling time alone is not always an indicator of risk and a PSA level of at least 2 ng/mL was an inclusion criteria of the SPARTAN trial. 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.

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

4 Population and disease

- 4.1 Non-metastatic castrate resistant prostate cancer (mOCRPC) is a disease stage of prostate cancer where patients have rising levels of prostate-specific antigen (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 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 had 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).

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

5 Comparator

- 5.1 The resubmission again nominated watchful waiting (also termed placebo), which 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 ESC noted that the resubmission also nominated darolutamide as a supplementary near market comparator and included an indirect comparison between apalutamide and darolutamide (using published data from the ARAMIS trial).
- 5.3 The resubmission stated that enzalutamide was not considered as a supplementary comparator because it has not been considered by the PBAC for use in m0CRPC, despite its TGA registration for this population. Although enzalutamide is yet to submit to the PBAC for listing in high risk m0CRPC, it is a potentially relevant comparator. The PBAC previously noted 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 currently PBS listed for metastatic CRPC (mCRPC), including use prior to docetaxel chemotherapy in patients with a predicted intolerance.
- 5.4 As noted in paragraph 3.6 above, the ESC had previously considered that PSMA-PET screening is more sensitive compared to conventional imaging which could result in patients otherwise classified as m0CRPC being classified as having occult metastatic disease. The ESC noted that, in clinical practice, a patient with metastatic disease detected with PSMA-PET scanning would be eligible for PBS-subsidised treatment with enzalutamide or abiraterone following docetaxel or as a first line treatment for metastatic disease if predicted intolerance to docetaxel.
- 5.5 The PSCR included results from a study by Fendler et al 2019² which retrospectively assessed the extent of disease detected by PSMA-PET in a cohort (N = 200) of high-risk patients with CRPC defined as non-metastatic by conventional imaging. PSMA-PET positive cancer was detected in 98% of all study patients and 55% of the study population had distant metastatic disease despite having no signs of distant metastases on conventional imaging. The PSCR stated that it can therefore be inferred that the SPARTAN trial was also comprised of a significant proportion of patients with PSMA-PET positive distant metastases. The ESC considered that these data supported treatments for mCRPC being relevant in the consideration of the appropriate comparators.
- 5.6 The ESC noted data provided by the DUSC Secretariat (Table 3, provided to the sponsor on 14 September 2020) indicated that a majority of mCRPC patients are being treated with abiraterone and enzalutamide without prior treatment with docetaxel (72% and 70%, respectively, in 2019). The ESC noted that these data indicated enzalutamide and abiraterone have significant first line use for the treatment of mCRPC, but did consider that the data were less informative if the majority of patients received docetaxel in the castrate-sensitive setting.

² Fendler et al. Prostate specific membrane antigen ligand positron emission tomography in men with non-metastatic castration resistant prostate cancer. Clin Cancer Res. 2019;25 (24)

Table 3: DUSC Secretariat analysis of abiraterone, enzalutamide and cabazitaxel use, 2014 to 2019*

		2014	2015	2016	2017	2018	2019
Number of prevalent patients supplied with abiraterone and enzalutamide**							
Abiraterone		2,196	2,053	1,842	2,083	2,236	2,410
Enzalutamide		271	2,272	3,065	3,563	4,081	4,295
Cabazitaxel		495	635	762	771	835	990
Total		2,528	4,169	4,890	5,671	6,360	6,919
Number of patients first initiating on abiraterone or enzalutamide***							
Abiraterone	Without prior docetaxel use, [n(%)]	269 (20)	661 (60)	637 (65)	782 (65)	815 (70)	876 (72)
	With prior docetaxel use, [n(%)]	1,057 (80)	457 (40)	339 (35)	418 (35)	360 (30)	347 (28)
	Total	1,326	1,118	976	1,200	1,175	1,223
Enzalutamide	Without prior docetaxel use, [n(%)]	109 (62)	1,110 (68)	1,115 (68)	1,238 (70)	1,262 (68)	1,237 (69)
	With prior docetaxel use, [n(%)]	68 (38)	515 (32)	521 (32)	534 (30)	580 (32)	547 (31)
	Total	177	1,625	1,636	1,772	1,842	1,784
Cabazitaxel	Without prior docetaxel use, [n(%)]	N.R	16 (3)	16 (2)	20 (4)	18 (3)	19 (3)
	With prior docetaxel use, [n(%)]	N.R	448 (97)	564 (98)	525 (96)	568 (97)	696 (97)
	Total	N.R	464	580	545	586	715

* PBS data was extracted from the Services Australia Prescription database for the period 1 January 2000 to 31 December 2019 based on the date of supply. Patients were classified as having been supplied abiraterone, cabazitaxel or enzalutamide after a prior supply of docetaxel or supplied a mCRPC drug without a prior PBS supply of docetaxel (based on previous 5 years).

** As patient may use more than one drug, sum of prevalent including all drugs is more than the unique count for any drug.

*** Figures are for first ever initiation on either abiraterone, cabazitaxel or enzalutamide. That is, this analysis identifies dispensing of first ever PBS treatment after docetaxel, or first ever drug supplied after no prior record of supply of docetaxel.

Source: DUSC Secretariat

DUSC = Drug Utilisation Sub-Committee; N.R = not reported

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described apalutamide as well-tolerated and with a minimal side-effect profile. The comments also described the demonstrated benefit in delaying progression, improving quality of life and the potential to improve survival by using apalutamide prior to development of metastatic disease.

6.3 The PBAC noted the comments received from the Prostate Cancer Foundation of Australia in support of inclusion of apalutamide on the PBS for mCRPC. The comments described the priorities of patients with prostate cancer to maximise quality of life and overall survival and to minimise treatment side effects.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the apalutamide 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)^[3], based on a comparison with ADT alone.

Clinical trials

- 6.5 The resubmission was based on the SPARTAN randomised controlled trial (RCT) (N=1,207), comparing apalutamide to placebo in patients with m0CRPC receiving concomitant ADT. The resubmission presented new evidence from the updated final analyses (FA) of the SPARTAN trial, with median follow-up of 52 months, and blinded independent central review (BICR)-assessed metastasis-free survival (MFS) data from interim analysis 1 (IA1). The PBAC had previously considered data up to a median follow of 32 months and 41 months (interim analysis 2 (IA2)) in the July 2019 resubmission and its PSCR, respectively.
- 6.6 A new indirect comparison of apalutamide (SPARTAN trial) versus darolutamide (ARAMIS trial) was also presented. The July 2019 resubmission presented a meta-analysis of OS data from SPARTAN, ARAMIS and PROSPER (enzalutamide) trials to estimate the survival benefit associated with this class of drugs to support the still immature OS data from SPARTAN. The PBAC noted the meta-analysis helped to provide confidence that this class of drugs is likely to provide some level of OS benefit (paragraph 7.8, apalutamide PSD, July 2019).
- 6.7 Details of the trials included in the resubmission are provided in the table below.

Table 4: 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 <i>NEJM</i> 2018; 378:1408-1418
ARAMIS	Fizazi K, Shore N, Tammela TL, et al. Darolutamide in non-metastatic castration-resistant prostate cancer.	<i>NEJM</i> 2019; DOI: 10.1056/NEJMoa1815671

Source: Table 7.1, p41 of the July 2019 resubmission

Blue shading represents information previously considered by the PBAC

- 6.8 The key features of SPARTAN and ARAMIS are presented in the table below.

³ 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 5: 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 mths (FA)	m0CRPC with high risk of distant metastases (PSADT ≤10 months)	Primary: MFS Secondary: PFS2, time to symptomatic progression, TTC, OS (new FA data presented in this resubmission)	Used
ARAMIS	Darolutamide: N=954 Placebo: N=554 Total: N=1,508	R, DB, MC, 29.1 mths		Primary: MFS Secondary: time to pain progression, time to first skeletal-related event, OS	Not used

Source: Table 7.2, p43 of the July 2019 resubmission

ADT = androgen deprivation therapy; DB = double blind; FA = final analysis; MC = multi-centre; MFS = metastasis-free survival; mth = months; 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
Blue shading represents information previously considered by the PBAC

- 6.9 Conventional imaging was used in the SPARTAN and ARAMIS trials to screen patients for distant metastasis. While this was consistent with the requested restrictions, it was not consistent with the Australian practice of using PSMA-PET scans to detect metastasis, which is able to detect much smaller volume of disease throughout the body not otherwise seen with other imaging methods. The resubmission did not discuss this applicability issue of the trial results for the Australian population. The PSCR stated that although PSMA-PET may be more sensitive than conventional imaging, patients eligible for treatment in the m0CRPC setting (and in SPARTAN) are identified by a short PSADT (< 10 months) with imaging performed to determine the extent and location of disease.
- 6.10 The resubmission stated that based on SPARTAN FA data, the dose intensity was reduced to 58.9%, but no changes were made in the modelled economic evaluation as PBAC had previously indicated the 66.24%⁴ dose intensity was appropriate. In the Pre-PBAC response in July 2019, the sponsor explained the dose intensity of 66.24%⁴ was calculated from an IPD analysis of pill counts (i.e., the analysis compared the number dispensed and returned 30 mg or 60 mg capsules and divided this by the duration of treatment for each patient). The resubmission did not present any further details on this IPD analysis and did not discuss why the dose intensity had dropped further to 58.9% on longer follow up. This information could not be verified from the CSR as median durations for dose reductions and interruptions were not reported. The ESC considered that the dose intensities observed in the SPARTAN trial were low and would likely not be reflected in clinical practice. The pre-PBAC response acknowledged that there were uncertainties surrounding the dose intensity of apalutamide in the SPARTAN trial.

⁴ Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.11 Of the 46.0% of patients in the apalutamide arm who received subsequent therapy, 84.1% received abiraterone and 39.3% received enzalutamide (see Table 6 for further details). The high proportion of subsequent abiraterone and enzalutamide treatment in the SPARTAN trial limits the applicability of the trial to the Australian setting as the PBAC stated in July 2019 that use of apalutamide in the m0CRPC setting would preclude use of abiraterone or enzalutamide in the mCRPC setting. The PSCR stated that as the PBAC has previously considered that sequential secondary hormonal therapy in this setting provides little additional benefit, the MFS and OS results observed in SPARTAN were driven by the use of apalutamide in the m0CRPC setting.

Table 6: Subsequent therapies post disease progression in the SPARTAN trial (July 2019 resubmission and FA)*

	SPARTAN (July 2019 resubmission) 32 months follow up		SPARTAN FA - 52 months follow up	
	Apalutamide N=806	Placebo N=401	Apalutamide N=806	Placebo N=401
Subsequent therapy	249 (30.9%)	255 (63.6%)	371 (46.0%)	279 (69.6%)
Abiraterone	183 (73.5%) (22.7% of 806)	188 (73.7%) (46.9% of 401)	312 (84.1%) (38.7% of 806)	231 (82.8%) (57.6% of 401)
Enzalutamide	27 (10.8%) (3.3% of 806)	33 (12.9%) (8.2% of 401)	146 (39.3%) (18.1% of 806)	98 (35.1%) (24.4% of 401)
Docetaxel	20 (8.0%) (2.5% of 806)	18 (7.1%) (4.5% of 401)	91 (24.5%) (11.3% of 806)	105 (37.6%) (26.2% of 401)
Cabazitaxel	0 (0%)	1 (0.4%) (0.2% of 401)	35 (9.4%) (4.3% of 806)	30 (10.7%) (7.5% of 401)
Radium Ra 223 Dichloride	1 (0.4%) (0.1% of 806)	0 (0%)	27 (7.3%) (3.3% of 806)	24 (8.6%) (6.0% of 401)
Sipuleucel-T	6 (2.4%) (0.7% of 806)	9 (3.5%) (2.2% of 401)	21 (5.6%) (2.6% of 806)	20 (7.2%) (5.0% of 401)

Source: Table 6.2, p32 of the July 2019 resubmission; Table 2.7, p37 of the resubmission

FA = final analysis

* Patients can receive more than one subsequent therapy

Blue shading represents information previously considered by the PBAC

Comparative effectiveness

- 6.12 The key clinical evidence presented in the resubmission was the BICR-assessed MFS (unchanged from previous submissions as there was only one planned analysis for MFS) and updated OS from the SPARTAN FA, with a median follow-up of 52 months. Other updated secondary outcomes were time to cytotoxic chemotherapy (TTC), time to symptomatic progression, and progression free survival for first subsequent therapy (PFS2).
- 6.13 After reviewing the IA1 results in May 2017, the Independent Data Monitoring Committee (IDMC) recommended unblinding of the SPARTAN trial and allowed placebo patients to be treated with apalutamide. As a result, 76 (19%) of placebo patients who remained metastasis free and were receiving placebo crossed over and received a median of 26.12 months of apalutamide treatment. All patients who started on placebo and did not switch to apalutamide discontinued study treatment in the SPARTAN trial at FA.

- 6.14 The resubmission conducted a series of OS analyses adjusted for direct treatment switching from placebo to apalutamide after unblinding and used these results in the base-case modelled economic evaluation, including censoring at treatment switch; the Rank Preserving Structure Failure Time Model (RPSFTM) adjusted for baseline covariates (i.e. age, ECOG performance status, Gleason score (≤ 7 vs ≥ 8)); RPSFTM not adjusted for baseline covariates; and Inverse Probability of Censoring Weights (IPCW).
- 6.15 Table 7 summarises MFS and OS results presented in this and the July 2019 resubmissions.

Table 7: 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 2.27, p73 of the resubmission; pp39-40 of the resubmission; SPARTAN CSR (Table 13, Table 16)

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.

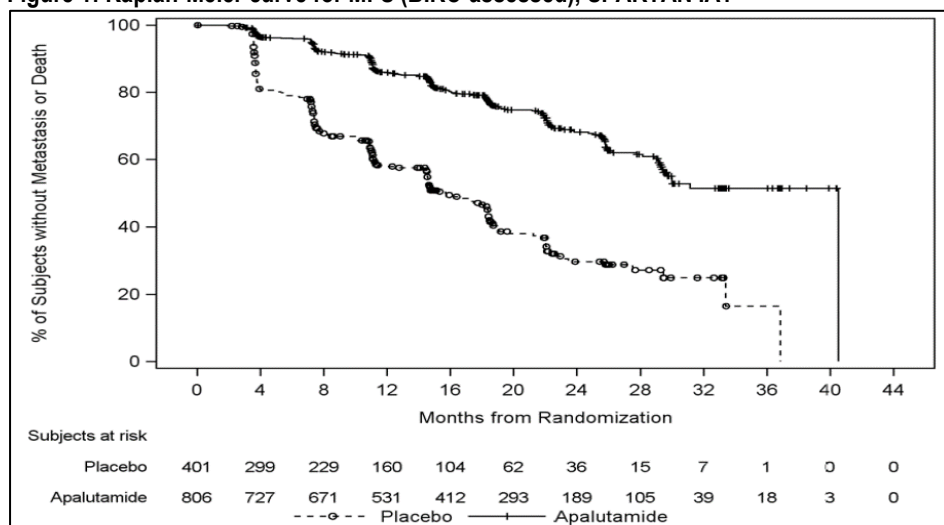
From placebo to apalutamide at treatment unblinding which happened after IA1.

Blue shading represents information previously considered by the PBAC

% Note that the treatment switching results were conducted specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SPARTAN. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

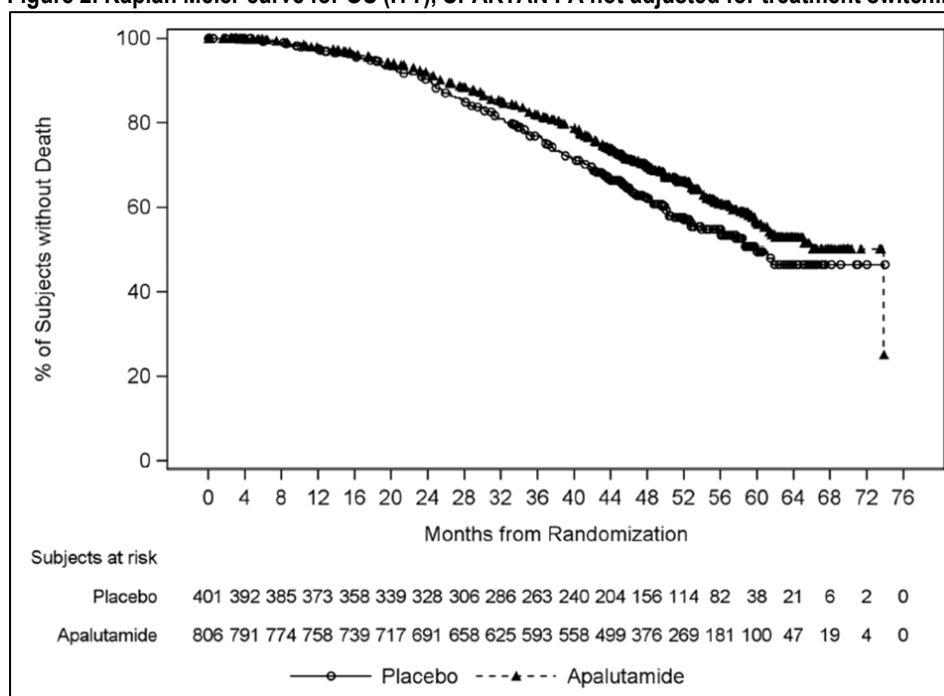
- 6.16 Minor differences in MFS results were noted depending on the censoring method applied; i.e., USA regulatory definition or based on European Medicines Agency (EMA) guidance (i.e., Ex-USA regulatory definition). For the more objective BICR-assessed MFS, the result was more conservative using Ex-USA regulatory censoring.
- 6.17 Updated Kaplan Meier results from SPARTAN are presented in Figures 1 and 2 for MFS and OS, respectively.

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



Source: Figure 2.2, p40 of the resubmission
 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 2.4, p44 of the resubmission
 FA = final analysis; ITT = intention-to-treat; OS = overall survival

- 6.18 Results from Table 7 illustrate that adjustment for treatment switching had the predicted effect of improving the HR comparing apalutamide to placebo for OS.
- 6.19 The methods used for adjusting for treatment switching are well established in the literature, with the complex methods (e.g. RPSFTM, IPCW) preferred over the simple method of censoring patients at switch. The adjusted HR (95% CI) for OS varied

between 0.68 (0.55, 0.84) (IPCW) and 0.74 (0.57, 0.95)⁵ (RPSFTM, adjusted for baseline covariates), compared to 0.78 (0.64, 0.96) for the unadjusted ITT result. The evaluation noted that while bias can arise from large proportions of patients switching from placebo to active treatment, each adjustment method is associated with its own inherent bias, which in some situations may exceed bias in the unadjusted results. Using large simulation studies, Latimer et al (2017)⁶ reported that in scenarios where the treatment effect was relatively low (equivalent to a HR of approximately 0.75 in experimental group patients, i.e., similar to the HR seen in SPARTAN for apalutamide), the ITT analysis often produced the least bias (0-5%), compared to potentially greater than 10% bias with RPSFTM. The authors argued that this is logical, because in these scenarios patients who switch receive very little benefit from the experimental treatment.

- 6.20 The PSCR presented a number of reasons outlining why the conclusions drawn from the Latimer et al (2017) paper did not apply to the SPARTAN trial including that:
- Latimer et al (2017) simulated scenarios where switching took place post-progression, whereas in SPARTAN patients randomised to placebo switched to apalutamide pre-progression; and
 - there is no evidence in the SPARTAN trial to suggest a reduced treatment effect in patients who switched from placebo to apalutamide.
- 6.21 The ESC noted a more recent publication by Latimer et al (2018)⁷ which conducted simulations similar to Latimer et al (2017), but for scenarios where there was moderate (approximately 50%) and low (approximately 20%) proportion switching (Latimer et al (2017) considered high proportions of switching). Latimer et al (2018) concluded that for low to moderate switching proportions, the RPSFTM is likely to produce less biased results than the ITT analysis unadjusted for switching, even when the assumption of common treatment effect is violated, unless the treatment effect is large. If the Acceleration Factor (AF), the amount by which an individual's expected survival time is increased by treatment, is greater than 2 then RPSFTM will be potentially biased. The IPCW tends to produce more volatile results and is likely to be more biased than ITT analysis unadjusted for switching.
- 6.22 The ESC noted that 19% of controls switched to treatment after IA1 in the SPARTAN trial, which is a low proportion, and the estimated AFs were < 2. The ESC noted that the submission reported that the largest AF was calculated to be 1.17, based on the inverse of the estimated shrinkage factor of 0.85. The ESC considered that the

⁵ Note that the treatment switching results were conducted specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SPARTAN. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

⁶ Latimer NR, Abrams KR, Lambert PC, et al. Adjusting for treatment switching in randomised controlled trials – A simulation study and a simplified two-stage method. *Statistical Methods in Medical Research*. 2017;26(2): 724–751

⁷ Latimer NR, Abrams KR, Lambert PC, et al. Assessing methods for dealing with treatment switching in clinical trials: A follow-up simulation study. *Statistical Methods in Medical Research*. 2018;27(3):765-784.

economic analysis should be based on the results from the ITT analysis unadjusted for switching and from the analysis adjusted using the RPSFTM. The ESC considered that the results from the ITT censored at switch and using the IPCW method were not appropriate.

- 6.23 An assumption of the RPSTM is that the only difference between treatment groups is the treatment. Although this is a reasonable assumption for a RCT, the ESC noted that there were some differences at baseline, and thus the results using the RPSFTM should be presented as both unadjusted and adjusted for age, ECOG performance status and Gleason score.
- 6.24 A further complication in relation to OS data from SPARTAN was that significant proportions of patients from both arms of the trial had also initiated active treatments after disease progression, including abiraterone and enzalutamide which will not be available for patients post apalutamide on the PBS. Therefore, OS results from SPARTAN may not entirely reflect expected OS for apalutamide on PBS.
- 6.25 Table 8 presents an indirect comparison of apalutamide versus darolutamide using SPARTAN (IA1 for MFS, IA1 and FA for OS) and published results from the ARAMIS trial. 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 8: 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, months	20.3		17.9	
	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, months	52.0		29.1	
	Indirect comparison HR (95% CI) apalutamide vs. darolutamide	1.136 (0.824, 1.568)			

Source: Table 2.24, Table 2.25 and Table 2.26, Appendix 1 of the resubmission

CI = confidence interval; HR = hazard ratio; FA = final analysis; IA1 = interim analysis 1; ITT = intent-to-treat; MFS = metastasis-free survival; OS = overall survival

* Note that the indirect comparison results were conducted specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SPARTAN. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.26 The resubmission claimed that apalutamide was superior to darolutamide in terms of effectiveness based on MFS and non-inferior in terms of effectiveness based on OS. The evaluation considered the superiority claim for MFS was not supported. A CADTH⁸ report of darolutamide reported the ARAMIS trial had misclassified 50 darolutamide-treated patients (5.2%) and 39 placebo patients (7.0%) who had metastasis at baseline after randomisation. A sensitivity analysis excluding these patients from the MFS analysis resulted in a HR for darolutamide vs. placebo closer to that obtained in SPARTAN (HR: 0.356, 95% CI: 0.287 to 0.441). There were also no significant differences between apalutamide and darolutamide in terms of OS, with the point estimates favouring darolutamide despite a shorter duration of follow up and a higher proportion of patients crossing over from placebo to active treatment in ARAMIS compared to SPARTAN. The ESC noted that the resubmission did not specify a non-inferiority margin.

Comparative harms

6.27 The safety data presented in the July 2019 resubmission was based on a median follow-up of 32.0 months in the SPARTAN trial. The resubmission provided updated safety data based on an additional 20 months median follow-up (total 52 months median follow-up). Table 9 presents the updated summary of adverse events (AEs) in the SPARTAN FA safety population.

Table 9: Summary of all AEs (SPARTAN FA: safety population)

	Placebo (N=398)	Placebo to Apalutamide* (N=76)	Apalutamide (N=803)
TEAE ^a	373 (93.7)	68 (89.5)	781 (97.3)
Grade 3-4 TEAE	145 (36.4)	29 (38.2)	449 (55.9)
Treatment-emergent SAE ^b	99 (24.9)	19 (25.0)	290 (36.1)
Grade 3-4 SAE	83 (20.9)	16 (21.1)	232 (28.9)
TEAE leading to treatment discontinuation	29 (7.3)	8 (10.5)	120 (14.9)
TEAE leading to death	2 (0.5)	2 (2.6)	24 (3.0)
All deaths within 28 days of last dose	2 (0.5)	1 (1.3)	22 (2.7)
Due to AE	2 (0.5)	1 (1.3)	18 (2.2)
Death due to prostate cancer	0	0	3 (0.4)
Other	0	0	1 (0.1)

Source: Table 2.19, p60 of the resubmission

AE = adverse event; FA = final analysis; SAE = serious adverse event; TEAE = treatment-emergent adverse event

* This group represents the 19% of placebo patients who crossed over to apalutamide

^a Treatment-emergent adverse events are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days. For each category, patients are counted only once, even if they experienced multiple events in that category.

^b Excludes Grade 5.

6.28 Overall, these data are consistent with the resubmission's claim of inferior safety versus placebo. The resubmission did not comment on treatment emergent adverse

⁸ CADTH Clinical Guidance Report April 2020: Darolutamide (Nubeqa) for non-Metastatic Castration Resistant Prostate Cancer. Available from:

https://www.cadth.ca/sites/default/files/pcodr/Reviews2020/10196DarolutamidenmCRPC_fnCGR_REDACT_EC_22Apr2020_final.pdf, accessed on 19th August 2020.

events (TEAE) leading to dose reductions, which were reported to be higher in the apalutamide arm compared to placebo (10% vs. 1.8%, SPARTAN FA CSR, p.45).

- 6.29 The resubmission presented the most common AEs considered to be of special interest (see Table 10 below), with the addition of ischaemic heart disease (IHD) compared to the previous resubmission. Exposure-adjusted incidence data (events per 100 person-years) for the apalutamide and placebo groups was also included to account for differences in treatment duration (i.e. median treatment duration 32.9 months in those initially randomised to apalutamide, 26 months in placebo patients who crossed-over to apalutamide, and 11.5 months in patients in the placebo group who did not switch treatment).

Table 10: Summary of AEs of special interest (SPARTAN FA: safety population)

	All grades, n (%)			All grades, n (events/100 person-years)		
	PBO N=398	PBO to APA N=76	APA N=803	PBO Patient-years = 446.0	PBO to APA Patient-years = 134.5	APA Patient-years = 2117.9
Patients with ≥1 TEAE* of special interest	87 (21.9)	29 (38.2)	417 (51.9)	145 (32.5)	64 (47.6)	1023 (48.3)
Skin rash	25 (6.3)	19 (25.0)	212 (26.4)	39 (8.7)	28 (20.8)	394 (18.6)
Fall	38 (9.5)	8 (10.5)	177 (22.0)	43 (9.6)	10 (7.4)	262(12.4)
Fracture	30 (7.5)	7 (9.2)	145 (18.1)	37 (8.3)	14 (10.4)	202 (9.5)
Hypothyroidism	8 (2.0)	3 (3.9)	79 (9.8)	10 (2.2)	3 (2.2)	107 (5.1)
IHD	11 (2.8)	4 (5.3)	44 (5.5)	16 (3.6)	9 (6.7)	53 (2.5)
Seizure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	5 (0.2)

Source: Table 2.20 and Table 2.21, pp62-63 of the resubmission; SPARTAN FA CSR, Table 16, pp46-4 and Table TSFAE27AE_2, pp276-277

AE = adverse events; APA = apalutamide; FA = final analysis; IHD = ischaemic heart disease; PBO = placebo; TEAE = treatment-emergent adverse events

* AEs that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days. For each category, patients are counted only once, even if they experienced multiple events in that category.

Bolded text represents events in the apalutamide arm are significantly higher than in the placebo arm.

- 6.30 It is unclear if treatment discontinuations and interruptions were accounted for in the exposure-adjusted safety analysis. The TGA evaluation report (p108) indicated that “the method used to establish adverse drug reactions (ADRs) by standardising events per 100 patient-years does not take the imbalance in treatment interruptions or compliance into consideration, and therefore the effect in the apalutamide arm compared with placebo will be to: (1) overestimate exposure in the apalutamide arm; (2) dilute the event rate particularly in the apalutamide arm where there are higher rates of dose interruptions and lower compliance; based on the Sponsor’s approach to defining ADRs (which requires a difference of > 5% event rate/100 patient-years), and (3) potentially fail to identify and/or underestimate ADRs in the apalutamide arm”.
- 6.31 This issue was also raised in the July 2019 PBAC consideration (paragraph 6.20, apalutamide PSD, July 2019), where it was noted that “the event rate/100 years presented by the resubmission did not accurately reflect the updated (32 month) data. This can be seen with the incidence of rash, where the incidence remained the same

at the updated data cut but the event rate decreased, which will occur with longer follow-up”. The July 2019 resubmission stated that the graphed cumulative incidence of Grade 3 or 4 AEs showed these AEs had plateaued and stabilised with longer time on treatment and were similar between apalutamide and placebo after about 24 months of treatment.

- 6.32 There were no significant differences in AEs between apalutamide and darolutamide, although there was a trend towards higher Grade 3-4 AEs and AEs leading to discontinuation for apalutamide compared to darolutamide.

Benefits/harms

- 6.33 A summary of the comparative benefits and harms associated with apalutamide versus placebo is presented in Table 11 below.

Table 11: Summary of comparative benefits and harms for Apalutamide and Placebo

Benefits						
SPARTAN	Apalutamide N=803	Placebo N=401	Absolute Difference	HR (95% CI)		
Metastasis free survival (median duration of follow up 20.3 months)						
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 (%)	274 (34.0)	154 (38.4)	-	0.784 (0.643, 0.956) p=0.0161		
Median OS, months (95% CI)	73.86 (61.21, NE)	59.89 (52.80, NE)	13.97 months			
5-year survival rate (95% CI)	55.9% (51.1, 60.4)	49.4% (42.6, 55.9)	6.5%			
Harms						
AEs of special interest (median duration of follow up 52.0 months)						
SPARTAN	Apalutamide n/N	Placebo n/N	RR (95% CI)	Events/100 patients		RD (95%CI)
				Apalutamide	placebo	
Skin rash	212/803	25/398	4.20 (2.83, 6.25)	26.4	6.3	0.20 (0.16, 0.24)
Falls	177/803	38/398	2.31 (1.66, 3.21)	22.0	9.5	0.12 (0.08, 0.17)
Fracture	145/803	30/398	2.40 (1.65, 3.48)	18.1	7.5	0.11 (0.07, 0.14)
Hypothyroidism	79/803	8/398	4.89 (2.39, 10.03)	9.8	2.0	0.08 (0.05, 0.10)
IHD	44/803	11/398	1.98 (1.04, 3.80)	5.5	2.8	0.03 (0.00, 0.05)
Seizure	1/803	0/398	1.49 (0.06, 36.46)	0.1	0	0.00 (-0.00, 0.01)

Source: Table 2.8, p39; Table 2.9, p49; Table 2.20 and Table 2.21, pp62-63 of the resubmission

AE = adverse event; CI = confidence interval; HR = hazard ratio; IHD = ischaemic heart disease; MFS = metastasis-free survival; OS = overall survival; RD = risk difference; RR = risk ratio

- 6.34 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 remain alive after 5 years of treatment
 - after a median duration of follow up of 52 months approximately:
 - 20 additional patients would experience skin rash;
 - 12 additional patients would experience a fall;

- 11 additional patients would experience a fracture;
- 8 additional patients would experience hypothyroidism; and
- 3 additional patients would experience IHD.

Clinical claim

- 6.35 The resubmission described apalutamide as superior in terms of effectiveness compared with placebo and inferior in terms of safety compared to placebo.
- 6.36 The PBAC previously considered (paragraph 7.1, apalutamide PSD, July 2019) that apalutamide provided a substantial benefit to some patients in delaying metastases; however, the magnitude of the survival benefit was uncertain. The resubmission stated that the longer-term SPARTAN FA data provided greater certainty in the magnitude of clinical benefit.
- 6.37 The PBAC considered that the claim of superior comparative effectiveness compared with placebo was reasonable, noting that the improvement in OS was modest.
- 6.38 The PBAC previously considered the claim of inferior safety versus placebo was appropriate (paragraph 6.28, apalutamide PSD, July 2019).
- 6.39 The resubmission claimed that apalutamide was superior to darolutamide in terms of effectiveness based on MFS but non-inferior based on OS, time to first cytotoxic chemotherapy, and non-inferior in terms of safety. 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 HR for darolutamide vs. placebo closer to results observed in SPARTAN for apalutamide. No significant difference between apalutamide and darolutamide was found in terms of OS, with the point estimates favouring darolutamide despite a shorter duration of follow up and a higher proportion of patients crossing over from placebo to active treatment in ARAMIS compared to SPARTAN.
- 6.40 The PBAC considered that apalutamide was likely to be non-inferior compared to darolutamide in terms of efficacy and safety.

Economic analysis

- 6.41 In July 2019 the PBAC advised (paragraph 7.13, apalutamide, PSD, July 2019) that any future economic model should be based on that provided in the July 2019 pre-subcommittee response (PSCR), with the following revisions:
- use of BICR-assessed MFS (rather than the investigator-assessed);
 - a 10 year time horizon;
 - inclusion of updated TTD data if available (the PBAC acknowledged that new MFS data were unlikely to become available, as the resubmission stated that the MFS data-cut provided in the previous submission was the final analysis of MFS); and
 - use of unadjusted OS results (i.e. no adjustments for treatment switching) given the uncertain magnitude of the OS gains.

6.42 The ESC noted that the revised base-case model included all the requested changes except for the use of unadjusted OS results (see discussion in Table 13 key drivers of model). Table 12 below provides a summary of key components of the current revised model and changes from the previous July 2019 model.

Table 12: Key components of the revised economic evaluation

Component	July 2019 model	Current model
Type of analysis	Stepped economic evaluation.	Unchanged
Outcomes	QALYs and Lys gained	Unchanged
Time horizon	15 years	10 years
Methods used to generate results	Partitioned survival model	Unchanged
Health states and transition probabilities	<ul style="list-style-type: none"> • Three health states. Transition probabilities from trial data plus extrapolation from the point where 20% remain at risk in Kaplan Meier curves: <ul style="list-style-type: none"> - High risk mCRPC: transition to mCRPC based on MFS data from SPARTAN IA1 (investigator assessed) extrapolated using Weibull function from: 25.72 months for apalutamide and 18.46 months for placebo. - Alive with distant metastases (mCRPC): transition to death based on OS data from SPARTAN IA1 extrapolated using Weibull function from 28.39 months for apalutamide and 26.71 months for placebo. - Death: Absorbing state • TTD from SPARTAN IA1 was used to determine the cost of apalutamide and the cost of AEs in the model. TTD was extrapolated using the exponential function for apalutamide from 26.35 months and Weibull function for placebo from 18.73 months. 	<p>Health states unchanged.</p> <p>Transition probabilities updated from SPARTAN plus extrapolation from the point where 20% remain at risk in Kaplan Meier curves:</p> <ul style="list-style-type: none"> - BICR-assessed MFS (from IA1) extrapolated using Weibull function from 25.66 months for apalutamide and 18.46 months for placebo. - OS (FA), extrapolated using Weibull function from 57.2 months for apalutamide and 56.1 months for placebo. - TTD (FA), extrapolated using the exponential function for apalutamide from 52.37 months and Weibull function for placebo from 21.98 months.
OS gain	<ul style="list-style-type: none"> • The modelled median survival benefit in the July 2019 model was 9.2 months*. <p>The PBAC had considered the magnitude of this OS uncertain as the data was immature (para 7.7 PSD July 2019).</p>	<p>The modelled median survival benefit was 6.7 months. While the model included more mature OS data from FA its base-case was based on OS adjusted for treatment switching from placebo to apalutamide, which occurred in 76 (19%) patients. Unadjusted OS was presented in step 2. The PSCR stated that the use of FA data, which reported a statistically significant reduction in the risk of death, addressed the PBAC's previous concerns regarding the data immaturity. The PSCR stated that the use of OS data adjusted for treatment switching was appropriate as the OS of placebo patients post switch to apalutamide was similar to the OS of those randomised to apalutamide, supporting the assumption of a common treatment effect.</p>

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Component	July 2019 model	Current model
Utilities	<ul style="list-style-type: none"> • m0CRPC - based on investigator-assessed data from SPARTAN IA1 (apalutamide: 0.826, placebo: 0.829) • mCRPC - based on meta-analysis of the literature (both arms: 0.721), ESC had considered this utility problematic as it reflected a mix of stages within the mCRPC state (para 6.45 ESC advice July 2019) 	<ul style="list-style-type: none"> • m0CRPC – based on BICR-assessed data from SPARTAN IA1 (apalutamide: 0.827, placebo: 0.828) • mCRPC – unchanged.
Subsequent therapy	The sequential therapy used for all apalutamide-treated patients was abiraterone, while placebo-treated patients were treated with enzalutamide or abiraterone.	No changes were made to subsequent therapy received in the base case. Sensitivity analyses applied arbitrary deductions of costs and QALYs for abiraterone in the apalutamide arm, without adjusting for potential increases in use and cost of other subsequent treatments, such as cabazitaxel. This was not appropriate. The PSCR provided sensitivity analyses in which the use of chemotherapy was increased.
Adverse events	% TEAE from SPARTAN IA1	Updated with FA data, using exposure-adjusted incidence of TEAE from SPARTAN FA, which may underestimate TEAEs in the apalutamide arm.
Cost per cycle of apalutamide	\$ [redacted] per month (assuming 66.4% ¹ dose intensity, effective DPMQ \$ [redacted] and 1.01 scripts per month)	No change, slight increase to \$ [redacted] due to change in PBS fees. The resubmission reported that dose intensity had dropped to 58% ¹ .
Cycle length	1 month, half cycle correction applied	Unchanged
Software package	Excel	Unchanged

Source: Table 3.2, p85 of the submission.

AE = adverse event; BICR = blinded independent central review; DPMQ = dispensed price for maximum quantity; ESC = Economic Sub-Committee; FA = final analysis; IA1 = interim analysis 1; LY = life year; m0CRPC = non-metastatic castrate resistant prostate cancer; mCRPC = metastatic castration resistant prostate cancer; MFS = metastasis-free survival; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-Sub-Committee response; PSD = Public Summary Document; QALY = quality adjusted life year; TTD = time to discontinuation; TEAE = treatment emergent adverse event.

* Rounded to 9 months in the July 2019 resubmission.

Blue shading represents information previously considered by the PBAC

¹ Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.43 A summary of the key drivers of the economic model is provided in the table below. In the July 2019 model the key drivers were considered to be MFS (due to immature data), OS (magnitude of benefit uncertain due to immature data) and dose intensity (uncertain applicability to Australian clinical practice). Although more mature data were presented in this resubmission, concerns around the magnitude of the OS benefit and dose intensity remain.

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Table 13: Key drivers of the model

Description	Method/Value	Impact
Magnitude of the OS benefit	<p>The model's base case was based on OS data from SPARTAN FA, adjusted for treatment switching (ICERs between \$ [redacted] 1 to \$ [redacted] 1/QALY), resulting in ICERs that were lower than when unadjusted ITT OS results were used (ICER: \$ [redacted] 1/QALY). The PBAC had previously recommended use of unadjusted OS in the modelled base case economic evaluation given uncertain magnitude of OS gains. Literature suggests unadjusted OS may be associated with the least bias in this case. The ESC noted that the economic model was sensitive to the application of the different hazard ratio point estimates. Although the values were relatively similar numerically, the ICER was sensitive to the value applied with up to a 17% difference in the ICER when the IPCW adjusted value was used compared to the ITT value.</p> <p>While more mature OS data were presented in the resubmission, the predicted OS benefit for apalutamide versus placebo was still dependent on the choice of extrapolation functions. The pre-PBAC response noted that use of the updated trial data resulted in 72% of the life years and 73% of the QALYs gained in the model being based on trial data. If the best fitting curves for MFS (lognormal) and OS (log logistic) were used in the model (see paragraph 6.36), the ICER increased to \$ [redacted] 2/QALY, driven by a smaller predicted difference between the treatment arms. The ESC noted that use of these curves resulted in possibly unrealistic survival at the tail end of the extrapolations.</p> <p>Furthermore, despite correcting for treatment switching from placebo to apalutamide (which occurred in 19% of patients originally randomised to placebo), OS results from SPARTAN remained confounded by (and uncorrected for) use of abiraterone and enzalutamide in 38.7% and 18.1% of the patients post apalutamide, which is not permitted on PBS. The PSCR stated that as the PBAC has previously stated that abiraterone and enzalutamide use post apalutamide has minimal benefit, the resulting incremental QALY gain would be negligible.</p>	High, favours apalutamide
Dose intensity	<p>The dose intensity of apalutamide applied in the economic model remained unchanged from July 2019 (i.e. 66.24%[*]). The resubmission indicated that dose intensity had dropped to 58.9% based on FA data. Assuming a higher intensity of 89.94%[*] (as was estimated in the November 2018 submission), the ICER increased significantly to \$ [redacted] 3/QALY. The PSCR noted that the PBAC previously considered that the dose intensity of 66.24%[*] appeared to reflect use in the SPARTAN trial and was reasonable to apply in the economic and financial estimates (paragraph 7.11, apalutamide PSD, July 2019). The ESC considered that the dose intensities observed in the SPARTAN trial were low and would not be reflected in clinical practice. The pre-PBAC response acknowledged that there remained some uncertainty surrounding the dose intensity and proposed to increase the rebate for use above the subsidisation caps in the RSA from [redacted] % to [redacted] % to address the uncertainties.</p>	High, a lower dose intensity favours apalutamide

Source: Section 3.2 to 3.4, p218-281 of the submission.

AE = adverse event; ESC = Economic Sub-Committee; FA = final analysis; ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weights; ITT = intention to treat; MFS = metastasis-free survival; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PSCR = pre-Sub-Committee response; PSD = Public Summary Document; QALY = quality adjusted life year
** Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

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[^] Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

The redacted values correspond to the following ranges:

¹\$45,000 to <\$55,000/QALY gained

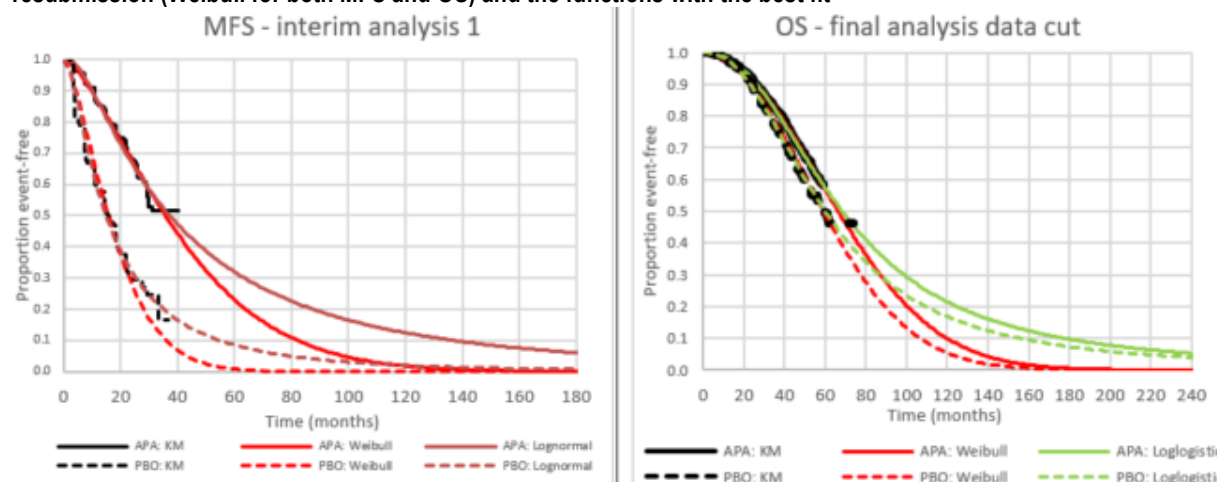
²\$55,000 to <\$75,000/QALY gained

³\$75,000 to <\$95,000/QALY gained

6.44 The structure of the economic model remained unchanged from the July 2019 resubmission and consisted of a partitioned survival model based on extrapolated SPARTAN data.

6.45 Weibull extrapolations were applied to MFS and OS at the time point at which there were less than 20% of the cohort remaining alive in the risk set. The Weibull function, however, was not the best fit for the MFS and OS FA data. Better fit was seen with the lognormal and log logistic functions for MFS and OS, respectively, but these had been discarded due to their non-monotonic hazard functions leading to long heavy tails, which in this context meant prolonged survival for a proportion of patients. Figure 3 illustrates the selected Weibull extrapolations for MFS and OS and the parametric function with the best fit based on lowest AIC/BIC values and goodness of fit on visual inspection.

Figure 3: Parametric extrapolations of MFS and OS data from SPARTAN (FA) illustrating the function selected by the resubmission (Weibull for both MFS and OS) and the functions with the best fit*



Source: Partition survival Apalutamide m0CRPC Economic model.xlsx "OS modelled" sheet.

APA = apalutamide; FA = final analysis; KM = Kaplan-Meier; MFS = metastasis-free survival; OS = overall survival; PBO = placebo

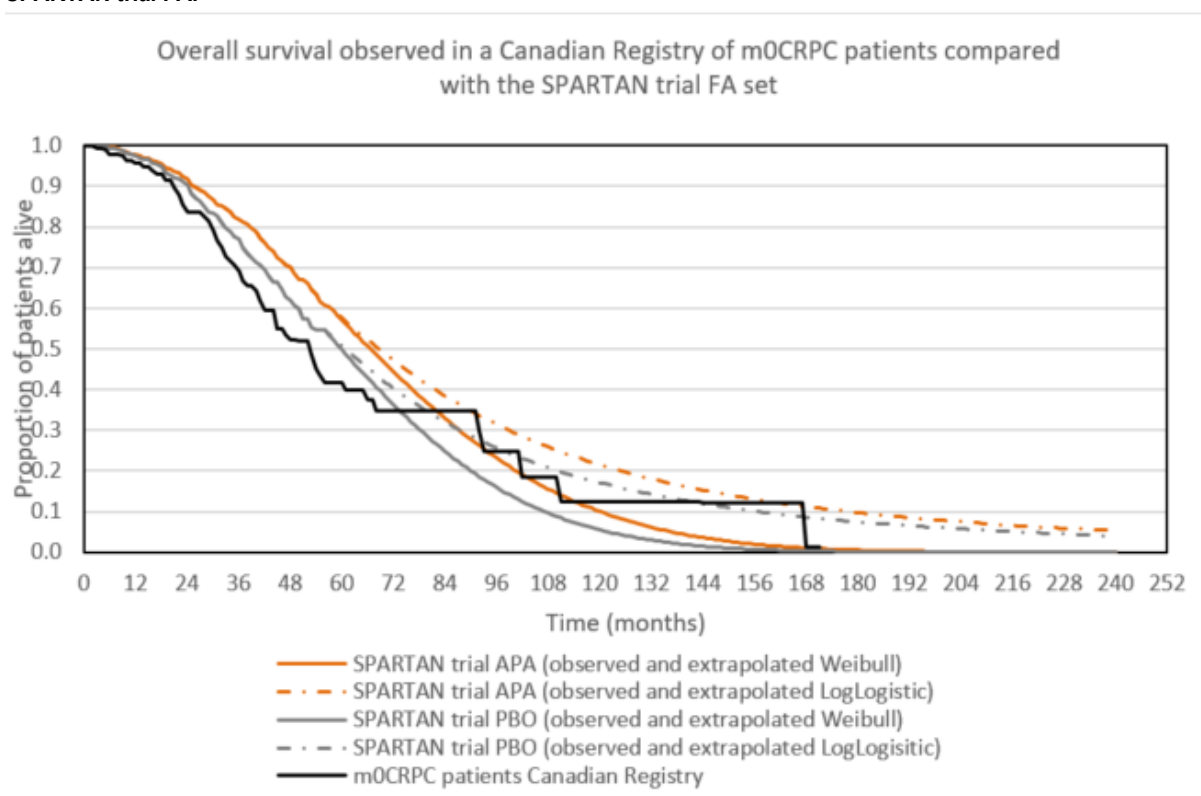
* Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.46 Sensitivity analyses conducted during the evaluation found that while the ICER was not sensitive to the change of MFS extrapolations from Weibull to Log-normal alone, when combined with Log-logistic OS extrapolations the ICER increased to \$55,000 to \$75,000/QALY in Step 2 (OS unadjusted for treatment switching) and to \$45,000 to \$55,000/QALY in Step 3 (OS adjusted for treatment switching with IPCW), thus

illustrating remaining uncertainty of the ICER due to extrapolation of time to event data.

6.47 The resubmission did not present any external validation of extrapolated OS data. In the July 2019 resubmission, extrapolated OS data using the Weibull function was validated using unpublished data from a Canadian prostate cancer registry. This was updated during the evaluation to compare with SPARTAN FA data. Modelled OS results using both the Weibull and Log-logistic parametric functions are illustrated in Figure 4. By the data cut off (month 168) in the Canadian registry, approximately 10% of patients were alive, which matched more closely with the predicted OS using the log-logistic function, compared to almost no patients alive when using the Weibull function. However, it was noted some patients in the Canadian registry may be at a lower risk of progression than those in the SPARTAN trial, so an absolute comparison cannot be made. Overall, the ESC considered that while the model gave a reasonable representation of OS beyond the SPARTAN trial, some uncertainty remained around the magnitude of the extrapolated OS gains.

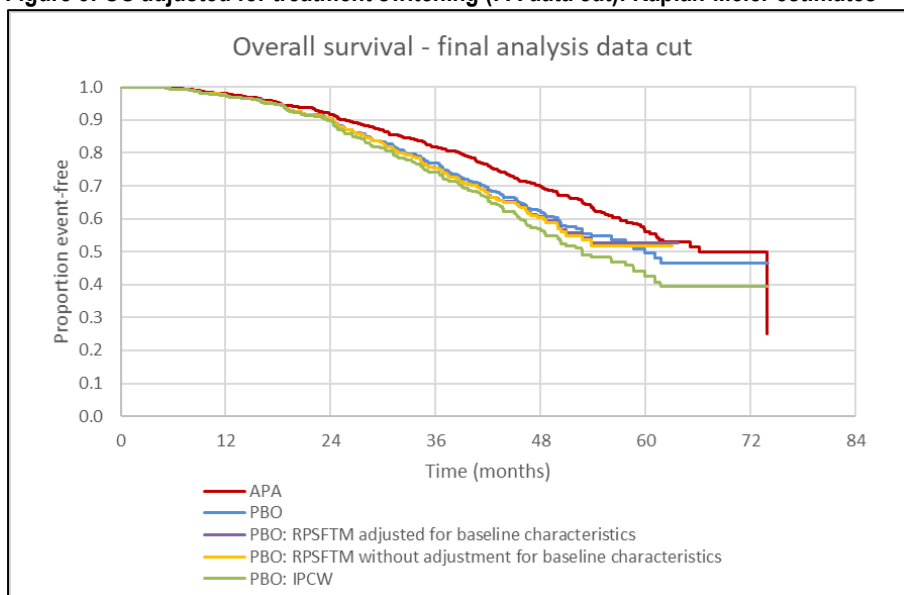
Figure 4: Overall survival of m0CRPC patients in a Canadian registry together with the overall survival in the SPARTAN trial FA.



Source: Canadian RWE (digitized KM curves).xlsx, Appendix 6, July 2019 apalutamide submission, which was updated during the evaluation using OS data from FA (see Partition survival Apalutamide m0CRPC Economic model.xlsx "LY APA" and "Watchful waiting LY" sheets. APA = apalutamide; FA = final analysis; m0CRPC = non-metastatic castration resistant prostate cancer; OS = overall survival; PBO = placebo

6.48 Figure 5 illustrates the impact of adjustments for treatment switching on OS in the model compared to the ITT analysis. Impacts can be seen in the adjusted OS curves for placebo, which predict reduced survival in the placebo arm. All adjusted OS curves were extrapolated using the Weibull function, however extrapolation parameters for these were not reported.

Figure 5: OS adjusted for treatment switching (FA data cut): Kaplan-Meier estimates*



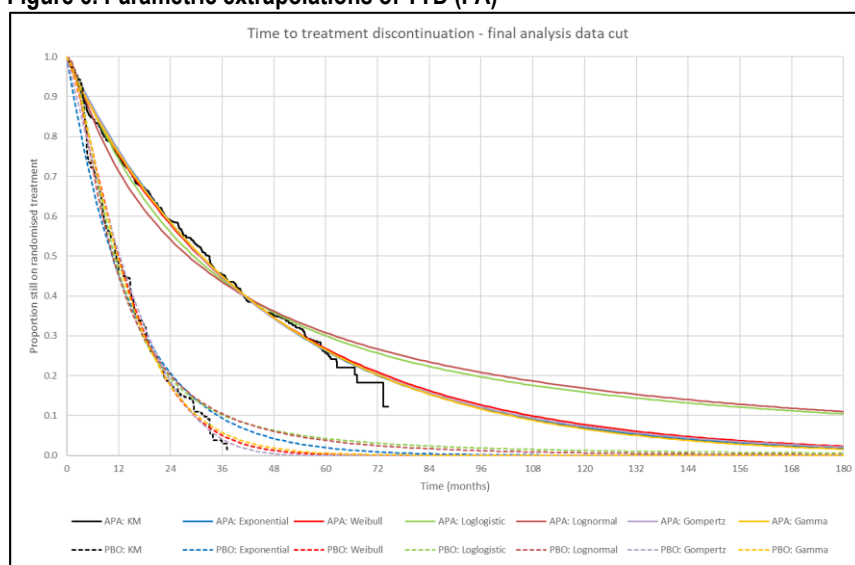
Source: Figure 3-9, p95 of the resubmission.

APA = apalutamide; FA = final analysis; IPCW = inverse probability censoring weights; PBO = placebo; OS = overall survival; RPSFTM = rank preserving structural failure time model

* Note that the treatment switching results were conducted specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SPARTAN. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.49 The revised model used updated TTD data from the SPARTAN FA, extrapolated using the exponential function for apalutamide from 52.37 months and Weibull function for placebo from 21.98 months. Extrapolated TTD is presented in Figure 6.

Figure 6. Parametric extrapolations of TTD (FA)*



Source: Figure 3.11, p98 of the resubmission

APA = apalutamide; FA = final analysis; KM = Kaplan-Meier; PBO = placebo; TTD = time to treatment discontinuation

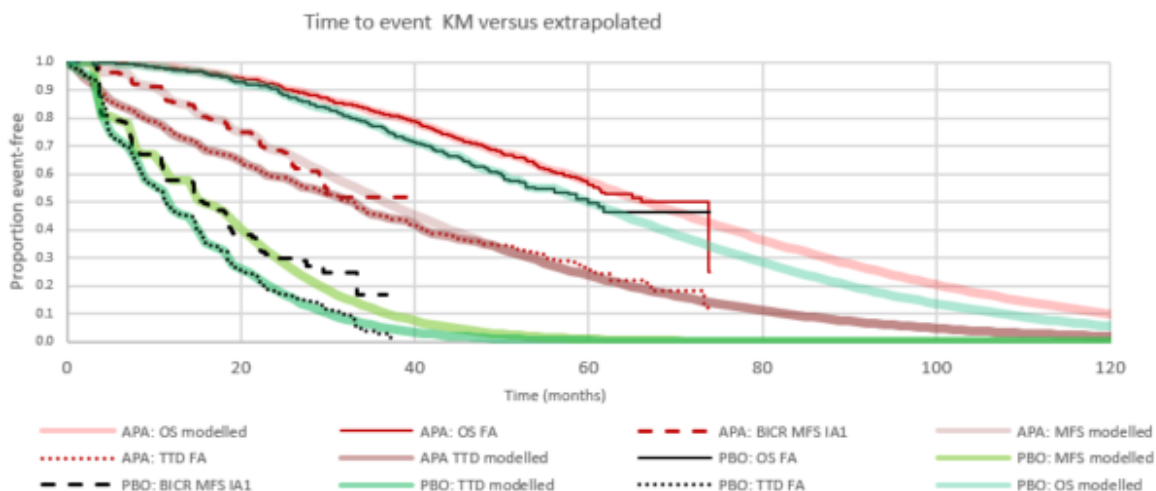
* Note that the results presented in Figure 6 are derived from ad hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.50 The resubmission noted that all six parametric extrapolations of TTD for the apalutamide arm were found to exceed the base case MFS extrapolation in the tail. The model addressed this issue by using MFS inputs instead of TTD at the time at which the TTD extrapolations exceed the MFS extrapolations, thereby reducing the proportion of patients on apalutamide treatment after 48 months. The resubmission argued that the TTD FA data suggested that MFS benefit was underestimated for apalutamide in the base case, which was based on MFS data from the IA1 data cut. The resubmission’s claim may not be supported, the crossing of the TTD and MFS curves was likely due to the MFS and TTD being separately fitted with the respective tail trajectories dependent upon the chosen parametric functions. For example, when the MFS was assumed to follow the Log-normal function rather than Weibull, TTD no longer crosses MFS in the apalutamide arm.

6.51 Overall time to event data in the model is summarised in Figure 7 below. The Figure is plotted using unadjusted OS results. Results show all patients to have progressed, with 12.8% of the apalutamide and 5.5%⁹ of placebo patients still alive at 10 years.

⁹ Note that these results are derived from ad hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Figure 7: Time to event data in the model (MFS, TTD, OS)*



Source: compiled during the evaluation using Partition survival Apalutamide m0CRPC Economic model.xlsx provided with the resubmission. APA = apalutamide; BICR = blinded independent central review; FA = final analysis; IA1 = interim analysis 1; KM = Kaplan-Meier; MFS = metastasis-free survival; OS = overall survival; PBO = placebo; TTD = time to treatment discontinuation

* Note that the results presented in Figure 7 are derived from ad hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.52 While the resubmission’s model had incorporated costs associated with management of AEs, it did not include any disutilities associated with AEs, including serious adverse events such as grade 3-4 fractures. Ischaemic heart disease was also not included as an adverse event in the model, despite being identified as a new AE of special interest in the resubmission. Given men with m0CRPC are largely asymptomatic, albeit for the effects of chronic ADT, adverse events and their impact on QoL is an important consideration for this population.
- 6.53 The resubmission used exposure-adjusted AEs in the apalutamide arm for specific AEs applied to the model. While this was not appropriate and had favoured apalutamide, it had minimal impact on the ICER.
- 6.54 The results of the stepped economic evaluation are provided in Table 14, with results for the July 2019 analysis (10-year time horizon) included for reference.

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Table 14: Results of the stepped economic evaluation

Step and component	Apalutamide	Placebo	Increment
Step 1: trial-based (52 months) time horizon			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
LY	3.57	3.44	0.13
Incremental cost/extra LY gained			\$ [redacted] ¹
Incremental cost/extra LY gained July 2019 (25.7 month time horizon)			\$ [redacted] ²
QALY	2.86	2.64	0.23
Incremental cost/extra QALY gained			\$ [redacted] ³
Incremental cost/extra QALY gained July 2019 (25.7 month time horizon)			\$ [redacted] ⁴
Step 2: 10 year time horizon (OS unadjusted for treatment switching)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
LY	4.96	4.54	0.42
Incremental discounted cost/extra LY gained			\$ [redacted] ⁵
Incremental discounted cost/extra LY gained July 2019 (10 year time horizon results)			\$ [redacted] ⁶
QALY	3.92	3.43	0.49
Incremental discounted cost/extra QALY gained			\$ [redacted] ⁶
Incremental discounted cost/extra QALY gained July 2019 (10 year time horizon results)			\$ [redacted] ⁷
Step 3: Base-case model - 10 year time horizon (OS adjusted) - RPSFTM with baseline adjustment			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
LY	4.96	4.44	0.53
Incremental discounted cost/extra LY gained			\$ [redacted] ⁶
QALY	3.92	3.36	0.56
Incremental discounted cost/extra QALY gained			\$ [redacted] ⁶
Step 3: Base-case model - 10 year time horizon (OS adjusted) - RPSFTM without baseline adjustment			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
LY	4.96	4.40	0.56
Incremental discounted cost/extra LY gained			\$ [redacted] ⁶
QALY	3.92	3.33	0.58
Incremental discounted cost/extra QALY gained			\$ [redacted] ⁶
Step 3: Base-case model - 10 year time horizon (OS adjusted) - IPCW			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
LY	4.96	4.26	0.70
Incremental discounted cost/extra LY gained			\$ [redacted] ⁷
QALY	3.92	3.23	0.69
Incremental discounted cost/extra QALY gained			\$ [redacted] ⁶

Source: Table 3.8, p105; Table 3.9, p106; Table 3.10, p107 of the resubmission; Table 3.8.2, p75, July 2019 COM

IPCW = inverse probability of censoring weights; LY = life year; QALY = quality-adjusted life year; OS = overall survival; RPSFTM = rank preserving structural failure time model

Bold=ICER presented in the current resubmission

Blue shading represents information previously considered by the PBAC

The redacted values correspond to the following ranges:

¹\$135,000 to <\$155,000/QALY gained

²\$455,000 to <\$555,000/QALY gained

³\$75,000 to <\$95,000/QALY gained

⁴\$155,000 to <\$255,000/QALY gained

⁵\$55,000 to <\$75,000/QALY gained

⁶\$45,000 to <\$55,000/QALY gained

⁷\$35,000 to <\$45,000/QALY gained

6.55 ICERs from analyses using OS adjusted for treatment switching (submission base case) ranged from \$45,000 to <\$55,000/QALY to \$45,000 to <\$55,000/QALY, whereas unadjusted OS data resulted in an ICER of \$45,000 to \$55,000/QALY. The ESC noted

that all of the ICERs were above the range of \$40,000 to \$45,000/QALY, which was nominated by the PBAC as an acceptable range in July 2019. The ESC noted that the ICER was sensitive to the OS hazard ratio point estimate applied in the model. The ESC therefore considered that uncertainties remained in the model and that the use of the ITT analysis was the most appropriate and that this, in conjunction with the analysis adjusted using the RPSFTM, should form the basis of the economic analysis.

6.56 The resubmission stated the base case analyses included the cost of treatment with abiraterone/enzalutamide following apalutamide. The resubmission presented further analyses of the base case scenarios in which: (i) the cost of subsequent abiraterone was removed from the apalutamide arm of the economic evaluation (the base case economic model assumed all patients in the apalutamide arm who received subsequent therapy would receive abiraterone), and (ii) a series of threshold analyses were conducted whereby the overall incremental QALY gain was reduced by 5% to 20% to account for any potential effect that abiraterone may confer. The PSCR provided further sensitivity analyses in which the use of docetaxel and cabazitaxel were increased to 15.5% and 6.2% respectively (from 7.9% and 3.2%) to adjust for increased utilisation following the removal of abiraterone (and enzalutamide) in the apalutamide arm. The resubmission stated that the abiraterone sensitivity analyses had the effect of reducing the ICER to within or below the \$40,000 to \$45,000 per QALY range recommended by the PBAC in July 2019.

6.57 Results of key sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised in Table 15.

Table 15: Results of sensitivity analyses presented in the resubmission and conducted during the evaluation

Analyses	Incremental cost	Incremental QALY	ICER
Step 2, OS unadjusted for treatment switching, ICER = \$ [redacted] ¹			
Baseline	[redacted]	0.49	[redacted] ¹
MFS extrapolation			
Gompertz	[redacted]	0.44	[redacted] ²
Gamma	[redacted]	0.49	[redacted] ²
Log-normal	[redacted]	0.50	[redacted] ²
OS extrapolation			
Log-logistic	[redacted]	0.46	[redacted] ²
Gamma	[redacted]	0.48	[redacted] ²
MFS + OS extrapolation			
Log-normal + Log-logistic	[redacted]	0.47	[redacted] ²
TTD after 48 months	[redacted]	0.51	[redacted] ²
Dose intensity 89.94%	[redacted]	0.42	[redacted] ³
Dose intensity 89.94% plus MFS + OS extrapolations with Log-normal and Log-logistic respectively	[redacted]	0.47	[redacted] ⁴

Source: Table 3.14, p113 of the resubmission and Excel Workbook Partitioned survival model.

ICER = incremental cost-effectiveness ratio; MFS = metastasis-free survival; OS = overall survival; QALY = quality-adjusted life-years; TTD = time to treatment discontinuation.

The redacted values correspond to the following ranges:

¹\$45,000 to <\$55,000/QALY gained

²\$55,000 to <\$75,000/QALY gained

³\$75,000 to <\$95,000/QALY gained

⁴\$95,000 to <\$115,000

- 6.58 The results of sensitivity analyses found the model was most sensitive to dose intensity and the extrapolation methods used for time to event data.
- 6.59 Assuming a much higher dose intensity (i.e., 89.94% as was used in the November 2018 submission) increased the ICER to \$75,000 to <\$95,000/QALY (using OS unadjusted for treatment switching). The use of Log-normal extrapolations for MFS and Log-logistic for OS, as presented in the French HTA¹⁰ submission also increased the ICER by 12% (using unadjusted OS). Multivariate analysis combining these two analyses resulted in an ICER of \$95,000 to <\$115,000/QALY when using OS unadjusted for treatment switching, which is an increase of 78%.

Drug cost/patient/month

Table 16: Intervention costs 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	219mg/day [^]	240mg/day ^a	240mg/day ^b	228mg/day [^]	240mg/day ^a	240mg/day
Mean duration ^{c#}	31.65 months	52.57 months	44.9 months	13.45 months [^]	21.98 months	18.9 months
Cost/patient/month	-	\$ [REDACTED]	\$ [REDACTED]	-	\$0	\$0
Cost/patient/course	-	[REDACTED]	[REDACTED]	-	\$0	\$0
Cost/patient/month July 2019 model	-	[REDACTED]	[REDACTED]	-	\$0	\$0
Cost/patient/course July 2019 model	-	[REDACTED]	[REDACTED]	-	\$0	\$0

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

^a The economic model applied a dose intensity of 66.24%¹ to apalutamide and 71.1% to placebo.

^b A dose intensity of 66.24%¹ was applied to apalutamide for the 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,

[^] As was reported in the SPARTAN IA1 CSR p 790

* Differences due to different modelled time horizons used in the analyses (10 years for economic and 5 years for financial).

Blue shading represents information previously considered by the PBAC

Note that the mean duration results presented in Table 16 are derived from ad hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

¹ Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.60 The cost per patient per month of apalutamide was slightly increased from \$ [REDACTED] in the July 2019 resubmission to \$ [REDACTED] (calculated as DPMQ \$ [REDACTED] x 1.01 scripts per month x 66.24%¹¹) in the current resubmission, based on a dose intensity for apalutamide of 66.24%¹¹. The assumed dose intensity directly affects the cost of apalutamide and trial estimates may not be observed in clinical practice.

¹⁰ HAS Santé, September 2019, France HTA (in French). Available from: https://www.has-sante.fr/upload/docs/application/pdf/2019-12/erleada_17092019_avis_efficiency.pdf. Accessed on 11th August 2020.

¹¹ Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Estimated PBS usage & financial implications

- 6.61 This submission was not considered by DUSC.
- 6.62 As for the November 2018 and July 2019 submissions, the resubmission applied an epidemiological approach to estimate the number of patients treated with apalutamide. The published and effective ex-manufacturer price of apalutamide also remained unchanged from the July 2019 resubmission, at \$ [REDACTED] and \$ [REDACTED], respectively, for a 30-day supply of the medication.
- 6.63 In July 2019, the PBAC (apalutamide, PSD) raised the following issues associated with the estimated use of apalutamide and financial implications:
- Paragraph 7.15: The PBAC considered that the number of incident and prevalent patients, the likely uptake of apalutamide and the dose intensity in clinical practice remain highly uncertain. The PBAC considered that the use of outcomes from the model, which may not reflect clinical practice, added to the uncertainty in the financial estimates. Thus, the PBAC considered that a risk sharing arrangement with [REDACTED]% rebates for expenditure above the caps would be necessary to address these uncertainties.
 - Paragraph 7.16: The financial estimates assume that patients treated with apalutamide can receive subsequent treatment with abiraterone. The PBAC considered that this required revision in light of its advice that subsequent treatment with abiraterone should not be permitted under the PBS. In addition, the PBAC noted that further detail on the number of grandfathered patients should be provided in any resubmission.
- 6.64 The key changes to the financial estimates were that the resubmission: i) used the updated OS and TTD Kaplan-Meier extrapolations based on the SPARTAN FA to estimate survival and treatment duration over 5 years; ii) removed subsequent treatment with PBS-funded abiraterone or enzalutamide from the financial model (applied as cost offsets instead); and iii) proposed an RSA to address highlighted uncertainties.
- 6.65 Table 17 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 resubmission.

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Table 17: Data sources and parameter values applied in the utilisation and financial estimates

Component	July 2019	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 (PSD, November 2018, Paragraph 6.43). This statement remains applicable as the methodology to estimate the number of m0CRPC patients was unchanged.
Incidence data	Patients treated with ADT sourced from PBS data (10% PBS sample data analysis by Prospecction) 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. The evaluation considered 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 chose not initiate apalutamide.
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.
Number of scripts per month	1.01 scripts/month as one script provides 30 days treatment.	Unchanged.
Dose intensity	66.2%* sourced from the SPARTAN trial. This was a decrease from the 89.94% applied in the November 2018 estimates.	Unchanged.
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.
Cost of medicines		
Apalutamide	\$ [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.
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%)
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 active treatments used in the mCRPC setting after apalutamide. Cost offsets due to reduced use of abiraterone and enzalutamide included. Changes to other therapies also

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Component	July 2019	Current resubmission
		included (e.g. GnRH analogues, anti-androgens, etc.).
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.
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.
MBS items for monitoring	Usage was based on the economic model.	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; DUSC = Drug Utilisation Sub-Committee; GnRH = gonadotrophin-releasing hormone; GP = general practitioner; IHD = ischaemic heart disease; MBS = Medicare Benefits Schedule; mOCRPC = non-metastatic castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme; TEAE = treatment-emergent adverse event; TTD = time to treatment discontinuation

Source: Section 4, pp114-128 of the resubmission; Section 9.3.1 to Section 9.3.6.5, p129-148 of the July 2019 resubmission

Blue shading represents information previously considered by the PBAC

* Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.66 Table 18 summarises the estimated changes in script volume and total cost to the government budget as presented in the resubmission and the July 2019 resubmission.

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Table 18: Financial estimates from July 2019 resubmission (blue shaded) and the current resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 1-6
Estimated extent of use							
APA patient initiations	¹	¹	¹	¹	¹	¹	²
APA scripts	³	⁴	⁴	⁴	⁵	⁵	⁶
Estimated financial implications of apalutamide							
Cost to the PBS/RPBS less copay (effective price)	⁷	⁸	⁸	⁸	⁸	⁸	¹⁰
Change in cost of other medicines to PBS/RPBS*	¹¹	¹²	¹²	¹²	¹²	¹²	¹³
Change in cost for the MBS	¹¹	¹¹	¹¹	¹¹	¹¹	¹¹	⁷
Net cost for the health budget	⁷	¹⁵	¹⁵	¹⁵	¹⁵	¹⁵	¹⁶

APA = apalutamide; GnRH = gonadotrophin-releasing hormone; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-Sub-Committee response; RPBS = Repatriation Pharmaceutical Benefits Scheme

* Abiraterone and enzalutamide at effective prices, docetaxel, cabazitaxel and other therapies (e.g. GnHR analogues and anti-androgens) at published prices

** The PSCR to the July 2019 consideration provided updated utilisation and financial impact estimates

Blue shading represents information previously considered by the PBAC in the July 2019 resubmission

The redacted values correspond to the following ranges:

¹1500 to <5,000

²5,000 to <10,000

³10,000 to <20,000

⁴20,000 to <30,000

⁵30,000 to <40,000

⁶100,000 to <200,000

⁷\$20 million to <\$30 million

⁸\$50 million to <\$60 million

⁹\$60 million to <\$70 million

¹⁰\$200 million to <\$300 million

¹¹\$0 to <\$10 million

¹²\$10 million to <\$20 million

¹³\$70 million to <\$80 million

¹⁴\$80 million to <\$90 million

¹⁵\$30 million to <\$40 million

¹⁶\$100 million to <\$200 million

¹⁷\$300 million to <\$400 million

6.67 The estimated cost of apalutamide to the PBS/RPBS over the first six years of listing was estimated to be \$300 to <\$400 million (not including cost offsets), compared to \$200 to <\$300 million in the July 2019 submission. The estimated net cost to the Government over the first 6 years of listing for apalutamide was \$200 to <\$300 million, compared to \$100 to <\$200 million in the July 2019 resubmission. The increase in the financial impact in the current resubmission was driven by a higher utilisation of apalutamide, with the number of patients treated with apalutamide and number of scripts over the 6-year period increasing from the July 2019 resubmission by 4.2% and 5.0%, respectively.

- 6.68 The resubmission stated that the use of the TTD extrapolation to estimate the number of apalutamide scripts would more accurately reflect the use of apalutamide in clinical practice. The evaluation considered this was highly uncertain, as treatment discontinuation in an RCT is not an accurate reflection of clinical practice. Furthermore, patients in the trial had the option of receiving abiraterone or enzalutamide treatment following discontinuation of apalutamide.
- 6.69 The resubmission doubled the proportion of mCRPC patients receiving docetaxel (7.7% to 15.5%) and cabazitaxel (3.1% to 6.2%) in the apalutamide group compared to those not taking apalutamide to account for the removal of subsequent abiraterone and enzalutamide treatment following apalutamide.
- 6.70 The resubmission acknowledged the estimated cost of apalutamide to the PBS/RPBS has increased since the July 2019 resubmission, but explained the more mature TTD trial data (median follow-up of 52 months, over 4 years) provides greater certainty on the financial estimates. The ESC noted that there remain uncertainties regarding the applicability of the trial data to the Australian population, and the impact on the financial estimates. In particular:
- Higher detection of metastasis using more accurate diagnostic methods (PSMA-PET) may decrease the utilisation of apalutamide as more patients could be staged as mCRPC. This could also increase the cost offsets through increased use of abiraterone and enzalutamide.
 - The unavailability of abiraterone and enzalutamide as subsequent treatment options may reduce the uptake of apalutamide, as patients may prefer to reserve active treatments with abiraterone/enzalutamide upon disease progression. The PSCR stated that there is clinical rationale for patients at high risk of developing distant metastases initiating apalutamide in the m0CRPC setting, rather than waiting for to receive treatment once metastases have developed and after chemotherapy.
 - The utilisation of chemotherapies for mCRPC may also be higher than estimated because of restrictions on the use of abiraterone and enzalutamide after apalutamide.

Financial Management – Risk Sharing Arrangements

- 6.71 The resubmission proposed a risk sharing arrangement (RSA) which consisted of a single subsidisation cap at the projected financial impact estimates of apalutamide, beyond which rebates of ■% would be applied (Table 19). The pre-PBAC response offered an increase in the rebate (from ■% to ■%) for any use above the subsidisation caps to address any outstanding economic or financial uncertainties.

Table 19: Proposed subsidisation caps for apalutamide in high risk m0CRPC

	Year 1	Year 2	Year 3	Year 4	Year 5	Years 1-5
Value of subsidisation caps	■	■	■	■	■	■

Source: Table 4.15, p128 of the resubmission.

m0CRPC = non-metastatic castration resistant prostate cancer

- 6.72 In July 2019, the PBAC considered that a RSA with ■■■% rebates for expenditure above the subsidisation caps would be necessary to address uncertainties on patient numbers, likely uptake and dose intensity (paragraph 7.15, apalutamide PSD, July 2019). The November 2020 resubmission argued that a ■■■% rebate was not considered appropriate because the financial estimates did not assume 100% uptake of apalutamide in high risk mOCRPC, and if there were use of apalutamide beyond the caps, it may be due to higher than anticipated uptake in the eligible population for which the resubmission argued that apalutamide was effective and cost effective. . The PBAC had previously identified dose intensity and the number of patients likely to be treated with apalutamide to be uncertain and considered the impact on the financial estimates to be high. Further uncertainty resulted from: i) the selection of patients for apalutamide use on the PBS given more sensitive imaging used in clinical practice to identify distant metastasis, and ii) and modelling uncertainties due to extrapolated data and OS adjustment for treatment switching.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of apalutamide for the treatment of mOCRPC in patients who are at high risk of distant metastases. The PBAC considered that apalutamide provided a substantial benefit to some patients in delaying metastases compared to placebo; however, considered that the magnitude of the survival benefit was modest. The PBAC noted that not all of the requested changes to the economic model were implemented in the resubmission and that the ICER remained high and uncertain. The PBAC considered a price reduction would bring the ICER into an acceptable range. The PBAC also considered that the estimated financial impact of listing apalutamide on the PBS remained high and was uncertain.
- 7.2 The PBAC noted the comments from consumers and from the Medical Oncology Group (MOGA) and the Prostate Cancer Foundation of Australia which were all in support of the requested listing for apalutamide.
- 7.3 The PBAC acknowledged there is a clinical need for effective therapies for patients with mOCRPC who are not adequately controlled with ADT. The PBAC noted that PBS subsidised treatment with enzalutamide and abiraterone following docetaxel or as a first-line treatment in patients with predicted intolerance to docetaxel is currently available in the metastatic setting, and that this includes patients with metastatic disease detected with PSMA-PET scanning.
- 7.4 The PBAC reiterated its previous considerations that watchful waiting was the appropriate comparator and noted that the resubmission appropriately nominated darolutamide as a near market comparator. The PBAC noted that the resubmission did not nominate enzalutamide as a near market comparator, despite the PBAC previously stating that enzalutamide is likely to enter the same market space as apalutamide, based on the PROSPER study (paragraph 7.5, apalutamide PSD,

November 2018).

- 7.5 The PBAC noted PSMA-PET is an increasingly common staging modality for prostate cancer, and is standard of care in many centres in Australia. The PBAC considered the increasing use of PSMA-PET, which is more sensitive than conventional imaging, may result in patients otherwise classified as mOCRPC being classified as having occult metastatic disease. The PBAC noted that the SPARTAN trial utilised conventional imaging to screen for distant metastases and it was therefore likely that a high proportion of patients in SPARTAN would have had occult metastatic disease at study entry (paragraph 5.5). The PBAC considered that the restriction should mirror the SPARTAN trial and that it was appropriate for the restriction for apalutamide to refer to conventional imaging.
- 7.6 The PBAC noted that the resubmission presented new OS data from the updated final analyses of the SPARTAN trial which had a median follow-up of 52 months and which demonstrated an improvement in OS (HR = 0.78; 95% CI: 0.64, 0.96, unadjusted for crossover). The PBAC reiterated its previous consideration that the claim of improved MFS versus placebo was reasonable, noting that the improvement in OS was modest.
- 7.7 The PBAC reiterated its previous consideration that the claim of inferior safety compared to placebo was appropriate.
- 7.8 The PBAC noted that the resubmission presented an indirect comparison of apalutamide (SPARTAN trial) versus darolutamide (ARAMIS trial) using placebo as the common comparator. Noting the potential differences between the trials, the misclassification of 5.2% of patients in the ARAMIS trial and the lack of a nominated non-inferiority margin, the PBAC considered that apalutamide was likely to be non-inferior compared to darolutamide in terms of efficacy. The PBAC noted that there were no significant differences in the AE profiles of apalutamide and darolutamide.
- 7.9 The PBAC noted that the resubmission updated the base case economic evaluation with BICR-assessed MFS, a 10 year time horizon and updated TTD data from the SPARTAN final analysis as requested by the PBAC; however, the PBAC noted that the base case did not use unadjusted OS results (i.e. the OS estimates were adjusted for treatment switching) or present ICERs in the range of \$40,000 to \$45,000 per QALY (paragraph 7.13, apalutamide PSD, July 2019).
- 7.10 The PBAC noted that use of the updated analyses resulted in a modelled survival benefit of 6.7 months, as compared to 9.2 months¹² in the July 2019 submission. The PBAC noted that the base case models presented in the resubmission resulted in ICERs of \$45,000 to <\$55,000 per QALY, when OS was adjusted using the RPSFTM method with baseline adjustment and \$45,000 to <\$55,000 per QALY when OS was adjusted using the RPSFTM without baseline adjustment. The PBAC noted that the ICER was

¹² Note that these results were derived from ad hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

\$45,000 to <\$55,000 per QALY when OS was not adjusted for treatment switching. Although the PBAC noted that more mature OS data was presented in the resubmission, the PBAC considered that the predicted OS benefit for apalutamide was sensitive to the OS hazard ratio point estimate applied in the model, continued to be dependent on the choice of extrapolation function and remained confounded by the use of abiraterone (38.7%) and enzalutamide (18.1%) in patients post apalutamide.

- 7.11 Acknowledging that it had previously considered that the dose intensity appeared to reflect use in the SPARTAN trial and was reasonable to apply in the model (and financial estimates) (paragraph 7.11, apalutamide PSD, July 2019), the PBAC considered that the dose intensity of apalutamide applied in the model (66.24%¹³) was implausibly low and did not reflect expected use in clinical practice. The PBAC also noted that the dose intensity was a key driver of the economic model and adjustments resulted in large changes to the ICER. The PBAC noted that the ICER increased from \$45,000 to <\$55,000 (when OS was not adjusted for treatment switching) to \$75,000 to <\$95,000 per QALY assuming a dose intensity of 89.94% (as per the November 2018 submission). The PBAC recalled the economic model for darolutamide applied a dose intensity of 98.88% (paragraph 6.47, darolutamide PSD, July 2020 PBAC meeting) and considered it was unclear why apalutamide and darolutamide would have such different dose intensities.
- 7.12 The PBAC noted a multivariate sensitivity analysis in which the MFS and OS extrapolations were changed from exponential to log-normal and log-logistic respectively and the dose intensity was increased to 89.94% resulted in an ICER (when OS was not adjusted for treatment switching) of \$95,000 to <\$150,000 per QALY.
- 7.13 The PBAC reiterated that the base case ICER, when OS was not adjusted for treatment switching, should be between \$40,000 and <\$45,000 per QALY. The PBAC considered that the dose intensity applied in the base case economic model should be increased to better reflect that expected in clinical practice.
- 7.14 In terms of the financial impact estimates of listing apalutamide on the PBS, the PBAC noted that the resubmission applied the more mature OS and TTD data to estimate survival and treatment duration and removed subsequent treatment costs associated with abiraterone or enzalutamide (these were instead applied as cost offsets). The PBAC noted that the number of incident and prevalent patients and the uptake rate of apalutamide were not changed in the resubmission. The PBAC considered that these values remained highly uncertain and that uptake was likely overestimated.
- 7.15 The PBAC noted that the estimated cost to the PBS/RPBS over the first six years of listing had increased from \$200 to <\$300 million in the July 2019 submission to \$200 to <\$300 million despite the cost offsets of other medicines on the PBS/RPBS

¹³ Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

increasing from \$70 to <\$80 million to \$80 to <\$90 million. Noting that a dose intensity of 66.24%¹⁴ was applied to the financial estimates, the PBAC considered that the cost of apalutamide had the potential to be much higher.

- 7.16 The PBAC noted that the resubmission proposed a RSA which consisted of a ■% rebate (increased to ■% in the pre-PBAC response) for use above a subsidisation cap at the projected utilisation of apalutamide. The PBAC noted this was less than the ■% rebate for expenditure above the subsidisation cap previously recommended (paragraph 7.15, apalutamide PSD, July 2019).
- 7.17 The PBAC advised that a major resubmission would be required and would need to:
- adjust the dose intensity in the model to reflect that expected in clinical practice and include a price te
 - tion to achieve an ICER in the range of \$40,000 to \$45,000 per QALY, using OS unadjusted for treatment switching;
 - update the financial estimates to reflect the dose intensity applied in the model; and
 - include details of a RSA which appropriately addresses the uncertainty with the financial estimates.
- 7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

¹⁴Note that the dose intensity was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

9 Sponsor's Comment

The sponsor had no comment.