7.01 APALUTAMIDE, Tablet 60 mg, Erlyand®, Janssen-Cilag Pty Ltd

1 Purpose of Application

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. The first submission was in November 2018.

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 who are at high risk of developing distant metastases; with high risk defined as PSADT ≤10 months.
Intervention	Apalutamide 240mg/day with background ADT until disease progression.
Comparator	Watchful waiting (placebo) comprised of ongoing ADT, with or without secondary hormonal therapy.
Outcomes	OS, PFS on first subsequent therapy (PFS2).
Clinical claim	On the basis of SPARTAN data and meta-analysis data, apalutamide is associated with a statistically significant and clinically important improvement in survival in patients with m0CRPC at high risk of distant metastases.

ADT=androgen deprivation therapy; CRPC=castrate resistant prostate cancer, m0CRPC=castration-resistant prostate cancer with no distant metastases; OS=overall survival; PFS=progression-free survival; PSADT=prostate specific antigen doubling time
Source: Section 6 to Section 7.4, p27-71 of the resubmission.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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

Category/ Program	GENERAL – General Schedule (GE)
Prescriber type	Medical Practitioners
Condition	Castration resistant carcinoma of the prostate
PBS indication	Castration resistant carcinoma of the prostate
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency

	☐Authority Required - Electronic ☐Streamlined
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 ~~Patient must not develop radiographic disease progression while receiving PBS-subsidised treatment with this drug for this condition~~ *Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug*
Treatment phase:	Continuing
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Treatment must be used in combination with androgen deprivation therapy AND ~~Patient must not develop radiographic disease progression while receiving PBS-subsidised treatment with this drug for this condition~~ *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
Clinical criteria:	Patient must have previously received non PBS-subsidised treatment with this drug for this condition prior to <date> AND Patient does not have distant metastasis on conventional imaging AND Treatment must be used in combination with androgen deprivation therapy AND Patient must have had a PSA doubling time of 10 months or less prior to receiving non-PBS-subsidised treatment with this drug AND ~~Patient must not develop radiographic disease progression while receiving PBS-subsidised treatment with this drug for this condition~~ *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

2.2 The requested ex-manufacturer price was reduced from $[redacted] in the November 2018 submission to $[redacted] ([redacted]% reduction).

2.3 The resubmission requested a grandfather restriction to enable access to apalutamide for patients currently receiving ongoing treatment in the SPARTAN trial, paying for apalutamide on a private prescription or receiving apalutamide through a patient

access program. As they have already begun treatment, these patients would no longer meet the PSA doubling time criteria in the proposed initial restriction and would not meet the criterion of previous PBS-subsidised treatment with apalutamide in the proposed continuing restriction.

2.4 The requested restriction was updated to include the changes proposed by the PBAC for the November 2018 submission (removal of the criterion for a minimum PSA level of 2ng/mL and wording changes; paragraph 2.1, November 2018 PSD) as well the inclusion of a WHO performance score of 0 or 1 in the clinical criteria, which had been accepted by the sponsor in the pre-PBAC response. The ESC noted that "androgen deprivation therapy" was not defined in the restriction, but considered this was appropriate.

2.5 Flow on changes to the abiraterone PBS restriction precluding use after apalutamide were not proposed in the resubmission, despite the PBAC previously stating "there is insufficient data demonstrating the degree of efficacy of abiraterone and enzalutamide after apalutamide, and the most appropriate treatment pathway remains uncertain" (paragraph 7.4, November 2018 PSD). The resubmission presented longer-term PFS2 data from the SPARTAN trial to support the efficacy of a treatment sequence of apalutamide followed by abiraterone. The evaluator considered the PFS2 data did not strongly support the resubmission's claim that abiraterone remains effective in mCRPC despite prior treatment with apalutamide. The ESC noted that there is a difference in the mechanism of action of abiraterone compared with apalutamide and enzalutamide, however the ESC also noted that sequential use of enzalutamide and abiraterone is currently not permitted on the PBS as there is evidence that its effectiveness after enzalutamide is limited (as noted in paragraph 4.7, November 2018 PSD)[1]. Overall the ESC considered that if apalutamide is recommended in m0CRPC, it may be appropriate to maintain abiraterone as a treatment option after apalutamide. However, the PBAC considered that there remains uncertainty regarding the magnitude of any benefit of abiraterone following apalutamide and therefore the cost-effectiveness of sequential use is uncertain (refer to Paragraph 6.15). The PBAC advised that the PBS restrictions should not allow abiraterone to be used after apalutamide, consistent with current listings for abiraterone and enzalutamide in the metastatic setting.

2.6 In regard to sequential use of enzalutamide, the resubmission stated that it may be reasonable to preclude the use of PBS-subsidised enzalutamide after apalutamide, as there is potential for cross-resistance with apalutamide and further considered it is unlikely that clinicians would use enzalutamide after apalutamide, irrespective of whether any changes are made to the enzalutamide mCRPC PBS restriction. Precluding use of enzalutamide following apalutamide was consistent with the

[1] Attard G, Borre M, Gurney H, et al. A phase IV, randomized, double-blind, placebo-controlled study of continued enzalutamide post prostate-specific antigen progression in men with chemotherapy-naïve metastatic castration-resistant prostate cancer (abstract 5004). 2017 American Society of Clinical Oncology meeting.

statement by the ESC in October 2018, which considered that it was unlikely that enzalutamide would demonstrate efficacy following progression on apalutamide given their pharmacological similarity (paragraph 4.7, November 2018 PSD). The PBAC considered that sequential use of apalutamide and enzalutamide would not be appropriate.

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

3 Background

Registration status

3.1 Apalutamide was TGA registered on 5 July 2018 for the treatment of patients with non-metastatic, castration-resistant prostate cancer.

Previous PBAC consideration

3.2 Following is a summary of the key concerns identified in the July 2018 PBAC submission and the response taken by the resubmission.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern (November 2018)	How the resubmission addresses it
Restriction/ treatment pathway	Paragraph 7.4: PBAC considered there were insufficient data demonstrating the degree of efficacy of abiraterone and enzalutamide after apalutamide, and the most appropriate treatment pathway remains uncertain.	On the basis of updated PFS2 evidence the resubmission maintained that abiraterone should be used after apalutamide. The resubmission did not provide evidence that the incremental efficacy of abiraterone would be unchanged by prior use of apalutamide. The resubmission also indicated it may be reasonable to not allow usage of enzalutamide following apalutamide.
Clinical evidence	Paragraph 7.8: PBAC considered that the claim of improvement in OS was not adequately supported by the clinical data. PBAC considered that the claim of improvement in MFS, rPFS and sPFS was reasonable but the magnitude of benefit was highly uncertain given the immaturity of the data.	The resubmission presented meta-analyses of SPARTAN, PROSPER and ARAMIS trials to support a claimed statistically significant advantage for apalutamide in OS. The ESC noted that the PSCR contained updated data on OS from SPARTAN [redacted]
Economic evaluation	Paragraph 7.13: PBAC advised a resubmission would require an economic model that did not assume a direct surrogate relationship between MFS and OS, regardless of the ratio used; PBAC considered that the efficacy parameters of MFS/PFS, time to symptomatic progression and time to chemotherapy would offer a method of assessing clinical benefit and cost-effectiveness of apalutamide. If OS data were included in the economic model it would need to be substantially more conservative and should be based on trial data, this may include extrapolation from the SPARTAN trial or the meta-analysis of the SPARTAN and PROSPER trials.	A revised model which did not assume a direct surrogate relationship between MFS and OS was presented. The revised model applied MFS and OS data from SPARTAN. The revised model remained driven by survival, with life years accounting for [redacted]% of the QALYs gained. The PSCR presented a revised model using the updated OS data from the 2nd interim analysis. The model did not use updated MFS and TTD data as MFS was not reported in the 2nd interim analysis.

Component	Matter of concern (November 2018)	How the resubmission addresses it
Financial estimates	Paragraph 7.11: The PBAC noted the DUSC's advice that the size of the treated population and estimates of the prevalent m0CRPC populations are unknown, the treatment duration was uncertain as it was based on immature MFS data and the dose intensity is uncertain….The PBAC agreed that the dose intensity appeared to be too high given the number of patients with dose reductions and interruptions. The PBAC agreed with the DUSC that overall the financial impact was likely to be underestimated and highly uncertain, based on the alternative approaches to estimating the treated population presented by DUSC.	The resubmission maintained the same methodology used in the November 2018 submission to estimate the treated patient population. Treatment duration remain based on output from the economic model, which applied the same SPARTAN data as used in November 2018. Dose intensity was decreased to [redacted]% from the [redacted]% used in the November 2018 submission. Estimated patient numbers increased slightly (approximately [redacted]%) although estimated net cost to Government reduced (by [redacted]%), largely due to the reduced dose intensity of apalutamide and the reduced effective price. The cost of apalutamide is likely to remain underestimated given the applicability of the assumed dose intensity in clinical practice is unknown.

MFS=metastasis-free survival; OS=overall survival; PFS2=progression-free survival for first subsequent therapy; PSCR=Pre-Subcommittee Response; rPFS=radiographic progression-free survival; sPFS=symptomatic progression-free survival
Source: November 2018 PSD; Table 4.1, p13-16 of the resubmission.

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

4 Population and disease

4.1 Non-metastatic castrate resistant prostate cancer (m0CRPC) 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 m0CRPC 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 m0CRPC 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 m0CRPC. The PBAC had previously noted that treatment of high risk m0CRPC patients with apalutamide is consistent with a trend in using active treatments earlier in the pathway (paragraph 7.3, November 2018 PSD).

5 Comparator

5.1 The resubmission maintained watchful waiting (also termed placebo) as the main comparator. The PBAC previously considered watchful waiting was the appropriate comparator as patients with m0CRPC are currently managed with observation on standard ADT and are not treated with docetaxel, enzalutamide or abiraterone until there is evidence of metastatic disease (paragraph 7.5, November 2018 PSD).

5.2 The PBAC had also indicated that enzalutamide is likely to enter the same market space as apalutamide, based on the PROSPER trial, and other agents such as darolutamide are also likely to become available for this population (paragraph 7.5, November 2018 PSD), making these agents near market comparators. The resubmission included data from the PROSPER and ARAMIS trials in its meta-analysis

of overall survival (OS) data but did not compare the agents to each other.

5.3 The ESC noted that, although not PBS listed, the first generation anti-androgens (e.g. bicalutamide) are likely being used in the Australian setting for some patients with m0CRPC. Therefore the magnitude of the overall survival benefit seen in the Australian setting may be smaller than that demonstrated in the clinical trial. The pre-PBAC argued that use of first-generation anti-androgens is limited in the m0CRPC setting as demonstrated in data from the ePAD (electronic Castrate Resistant Prostate Cancer Australian Database) clinical registry.

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 (6), health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described apalutamide as well-tolerated and with a manageable, minimal side-effect profile. The consumer comments noted the clinical need in patients with m0CRPC who currently do not qualify for other treatments on the PBS and the psychological and quality of life benefits of having an active treatment available earlier in the treatment pathway. The comments also described the demonstrated benefit in delaying progression and the potential to improve survival by using apalutamide prior to development of metastatic disease.

6.3 The PBAC noted the advice received from Geelong Prostate Support Group in support of inclusion of apalutamide on the PBS for both metastatic and non-metastatic castrate resistant prostate cancer. This advice described the priorities of patients with prostate cancer to maximise quality of life and to minimise physical pain and psychological suffering from the disease and treatment side effects, in addition to extending overall survival. The advice noted the delayed progression shown in patients with metastatic, castration-sensitive prostate cancer (in the TITAN trial) as well as patients with m0CRPC (in the SPARTAN trial).

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 "high priority for PBS listing" on the basis of the SPARTAN trial (publication of the planned first interim analysis). 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 3 (out of a maximum of 5, where 5 and 4 represent the grades

with substantial improvement)[2], based on a comparison with ADT alone. This would increase to 4 if mature data demonstrated an improvement in overall survival.

Clinical trials

6.5 The resubmission was based on SPARTAN (N=1,207) and included meta-analyses of overall survival (OS) using PROSPER (N=1,401; enzalutamide) and ARAMIS (N=1,508; darolutamide). The citation details of the three trials are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SPARTAN	A study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer. Smith MR, Saad F, Chowdhury S et al. Apalutamide treatment and metastasis-free survival in prostate cancer.	September 2017 NEJM 2018; 378:1408-1418
PROSPER	Hussain M, Fizazi K, Saad F et al. Enzalutamide in men with non-metastatic, castration-resistant prostate cancer.	NEJM 2018; 378(26): 2465-2474
ARAMIS	Fizazi K, Shore N, Tammela TL, et al. Darolutamide in non-metastatic castration-resistant prostate cancer.	NEJM 2019; DOI: 10.1056/NEJMoa1815671

Source: Table 7.1, p41 of the resubmission.

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

Table 4: Key features of the included evidence

Trial	Design	N	Patient population	Outcomes	Use in modelled evaluation
SPARTAN	R, DB, MC apalutamide+ADT vs. placebo+ADT	Apalutamide: N=806 Placebo: N=401 Total: N=1,207	m0CRPC with high risk of distant metastases (PSADT ≤10 months)	Primary: MFS Secondary: rPFS, time to symptomatic progression, TTC, OS	Used

ADT=androgen deprivation therapy; DB=double blind; MC=multi-centre; MFS=metastasis-free survival; m0CRPC=non-metastatic castration resistant prostate cancer; OS=overall survival; R=randomised; rPFS=radiographic progression-free survival; TTC=time to initiation of cytotoxic chemotherapy
Source: Table 7.2, p43 of the resubmission.

Comparative effectiveness

6.7 The key clinical evidence presented in the resubmission was the meta-analyses of OS data (see below) as well as updated data for PFS for first subsequent therapy (PFS2). The updated data for PFS2 was based on a median follow-up of 32 months; the data presented in the November 2018 submission was based on a median follow-up of 20.3 months. The updated data for SPARTAN was sourced from a poster presentation (Small 2018). The PSCR provided updated OS and PFS2 data from interim analysis 2 of the SPARTAN trial. The updated data was based on a median follow-up of [redacted]

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

months.

6.8 The table below provides a summary of the effectiveness results presented in the November 2018 submission, along with the updated PFS2 results presented in the resubmission, and the updated OS and PFS2 results provided in the PSCR.

Table 5: Summary of time-to-event outcomes in SPARTAN

Outcome	Apalutamide (N=806)	Placebo (N=401)
Metastasis-free survival (MFS) – BICR assessed		
Event (n %)	[redacted]	[redacted]
Median months to metastasis (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Metastasis-free survival (MFS) – investigator assessed		
Event (n %)	[redacted]	[redacted]
Median months to metastasis (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Radiographic progression-free survival (rPFS)		
Event (n %)	[redacted]	[redacted]
Median months to progression (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Overall survival (OS), 20.3 months median follow-up		
Died (n %)	[redacted]	[redacted]
Median months to death (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Overall survival (OS) updated, 41 months median follow-up (from PSCR)		
Deaths (n %)	[redacted]	[redacted]
Censored (n %)	[redacted]	[redacted]
Median months to death (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
RPSFTM	[redacted]	
RPSFTM (with adjustment for baseline covariates)	[redacted]	
IPCW (corrected)	[redacted]	
Time to metastasis (TTM)		
Event (n %)	[redacted]	[redacted]
Median months to metastasis (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Time to symptomatic progression		
Event (n %)	[redacted]	[redacted]
Median months to symptomatic progression (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Time to initiation of cytotoxic chemotherapy		
Event (n %)	[redacted]	[redacted]
Median months to chemotherapy (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Time to progression during first subsequent therapy (PFS2) – previous submission, median follow-up 20.3 months		
Event (n %)	[redacted]	[redacted]
Median months to progression (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Time to progression during first subsequent therapy (PFS2) – updated data cut from resubmission, median follow-up 32 months		
Event (n %)	NR	NR
Median months to progression (95% CI)	NE (NE, NE)	39.3 (NR)

HR (95% CI)	**0.5 (0.39, 0.63)**
Time to progression during first subsequent therapy (PFS2) – PSCR, median follow-up 41 months	
Event (n %)	[redacted]
Censored (n %)	[redacted]
Median months to metastasis (95% CI)	[redacted]
HR (95% CI)	[redacted]

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; NE=not estimable; NR=not reported; PFS2=progression free survival on first subsequent therapy; **bold**=statistically significant; grey=previously presented to the ESC and the PBAC

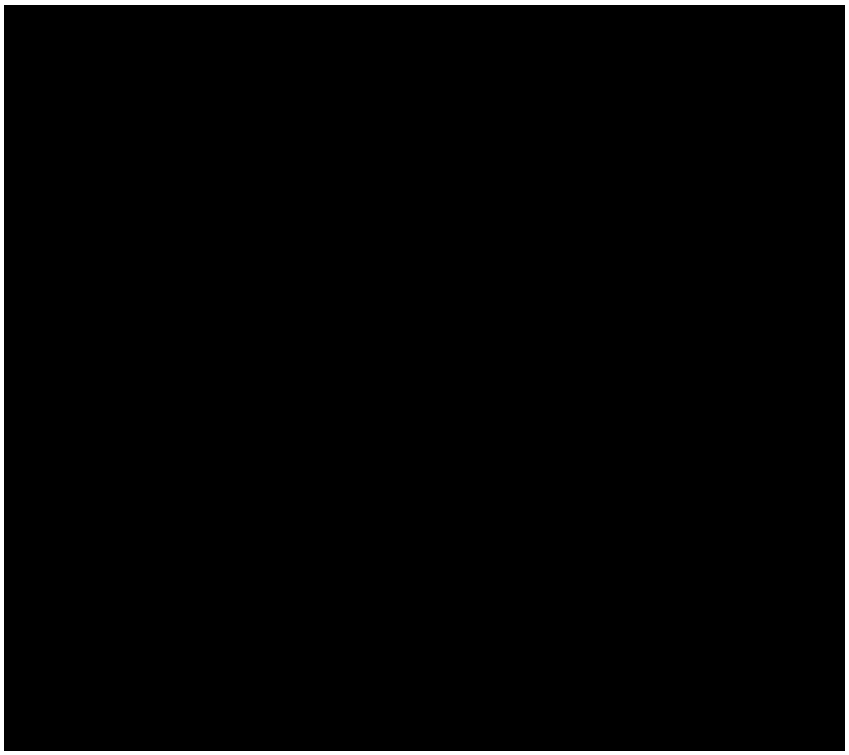
Source: Table 2.5.1, 5.01.COM.57 and Table 2.5.7, 5.01.COM.63, PSCR Table 1 and 2.

[a] Median OS not reached, estimated from Kaplan-Meier curve

6.9 The PSCR claimed that the interim analysis 2 data demonstrated that apalutamide was associated with a [redacted] in the risk of death from any cause compared with placebo (HR = [redacted]; [redacted]%CI: [redacted], [redacted], p=[redacted]). The interim analysis 2 report indicated that the HR for OS was [redacted] The ESC noted that although the difference in OS was [redacted] in the interim analysis 2, it was not [redacted] Thus the ESC considered that the magnitude of the OS benefit remained uncertain. The PBAC considered that it is likely that apalutamide [redacted], however the magnitude of this benefit remained uncertain as the data were immature. The pre-PBAC response noted that the next pre-planned analysis of OS is the final analysis and is not expected until [redacted].

6.10 The PSCR reported that at the time of the second interim analysis [redacted] ([redacted]%) of placebo patients had switched to apalutamide treatment and these patients had received a median of [redacted] months of apalutamide treatment ([redacted]% of the median follow-up period). The PSCR provided results for OS using different statistical methods of adjusting for treatment switching, which are included in the table above. The Kaplan-Meier plot of OS (without adjustment for switching) is shown in the figure below.

Figure 1: Kaplan Meier curves for OS in SPARTAN, interim analysis 2, median follow-up 41 months



Source: Figure 1 PSCR

6.11 The resubmission presented updated data for PFS2 from SPARTAN, which was defined as the time from randomisation to investigator-assessed disease progression with the first subsequent therapy or death. The updated PFS2 data were provided to support the resubmission's claim that since abiraterone was the predominant first subsequent therapy after apalutamide and placebo, abiraterone remains effective in mCRPC despite prior treatment with apalutamide.

6.12 The resubmission reported that the updated data for PFS2 were not adjusted for treatment switching (% of placebo patients had switched to apalutamide). The resubmission indicated that given the superior efficacy of apalutamide over placebo this biases comparisons against apalutamide in terms of underestimating potential clinical endpoint gains. The resubmission stated that an adjustment for treatment switching is appropriate to address this bias, however no adjustments for treatment switching were performed for the longer-term PFS2 data or for the updated PFS2 data provided in the PSCR.

6.13 The PFS2 results are provided in Table 5 above. The updated results presented in the resubmission showed a result similar to that presented in the November 2018 submission, with a hazard ratio of 0.5 (95% CI: 0.39, 0.63) compared to 0.489 (95% CI: 0.361, 0.662). The HR in the updated PFS2 data from the interim analysis 2 provided in the PSCR (; 95% CI: ,). The PSCR stated that the PFS2 data from interim analysis 2 are mature, with median PFS2 having been reached in both arms (months for apalutamide versus months for placebo), however

ESC noted that only [redacted]% in the placebo arm and [redacted]% of patients in the apalutamide arm had an event and therefore considered the PFS2 data are not mature.

6.14 The resubmission claimed that the updated PFS2 data continue to demonstrate that abiraterone remains effective in mCRPC despite prior treatment with apalutamide as abiraterone was the predominant first subsequent therapy after apalutamide and placebo (used by [redacted]% of patients in the apalutamide arm, which comprised over 80% of those patients who received subsequent therapy). The PFS2 data was difficult to interpret as the impact of the first treatment is not separated from that of the second treatment.

6.15 The PFS2 data indicates that a treatment sequence of apalutamide followed by abiraterone is more effective than a treatment sequence of placebo followed by abiraterone. However, the PFS2 data do not provide information as to whether the magnitude of the benefit of abiraterone versus placebo would remain unchanged with prior use of apalutamide. As such, the data do not address the PBAC's previous concerns that there is insufficient data demonstrating the degree of efficacy of abiraterone and enzalutamide after apalutamide (as raised in paragraph 7.4, November 2018 Minutes). Given this, and in the context of data indicating that abiraterone has only minimal activity in patients who progressed after treatment with enzalutamide (refer to Paragraph 2.5 above), the magnitude of efficacy and thus the cost-effectiveness of abiraterone is unclear when used post-apalutamide.

6.16 The results of the meta-analyses of OS are provided in the table below, with the Kaplan Meier curve for the meta-analysis using the three pooled trials following.

Table 6: Results of the meta-analyses of OS across SPARTAN, PROSPER and ARAMIS

Overall survival, median months				**HR (95% CI)**
Trials	**N**	**Active treatment; N**	**Placebo; N**	
SPARTAN (apalutamide)	1,207	not estimable; N=806	not estimable; N=401	0.70 (0.47, 1.04)
PROSPER (enzalutamide)	1,401	not estimable; N=933	not estimable; N=468	0.78 (0.56, 1.07)
ARAMIS (darolutamide)	1,509	not estimable; N=955	not estimable; N=554	**0.68 (0.48, 0.96)**
Meta-analysis (SPARTAN and PROSPER), I^2=NR; p=NR				[redacted]
Meta-analysis (SPARTAN and PROSPER and ARAMIS), I^2=NR; p=NR				[redacted]

CI=confidence interval; HR=hazard ratio; NR=not reported; **bold**=statistically significant
Source: Section 7.1.4.2, p62-64 and p68 of the resubmission.

6.17 The resubmission did not provide any information regarding possible heterogeneity in the meta-analyses nor did the resubmission report weighting of the trials in the meta-analyses. The resubmission did provide results of a published meta-analysis of SPARTAN and PROSPER (Bhindi 2018) which reported an I^2 value of 0% for the OS meta-analysis, with the weighting 61.5% for PROSPER and 38.5% for SPARTAN. The I^2 value of 0% for the OS analysis suggests that any inconsistency across the trials might

not be important. However, a recent publication[3] of a matching adjusted indirect comparison of SPARTAN and PROSPER noted that prior to matching, the SPARTAN and PROSPER patient populations differed with respect to percentage of patients with PSADT <6 months, median PSADT, serum PSA at baseline and PSADT and that the baseline characteristics should be matched.

6.18 The resubmission concluded that the pooled analyses demonstrated that the lack of statistical significance in OS between apalutamide and placebo seen in the SPARTAN trial was due to a lack of power and not insufficient efficacy. While the pooling of the trials has increased patient numbers and resulted in a statistically significant advantage for active treatment, it may not be reasonable to assume that the advantage in OS observed for the three agents combined will be observed for apalutamide alone. The ESC considered that it is not reasonable to assume that an advantage in OS observed for three agents combined in a meta-analysis will be observed for apalutamide alone. However, the ESC considered that [redacted] compared with watchful waiting and therefore the meta-analysis was of less importance.

Comparative harms

6.19 The safety data presented in the November 2018 submission was based on a median follow-up of 20.3 months in the SPARTAN trial. The resubmission has provided updated safety data based on an additional 11.7 months median follow-up (total 32 months median follow-up). The data provided was for the AEs of special interest identified in the November 2018 submission (seizure, skin rash, hypothyroidism, fractures and falls) and was provided for the apalutamide-treated patients in SPARTAN. The resubmission did not indicate why data for placebo-treated patients was not provided but the resubmission sourced the data from a poster presentation (Small 2018) which presented AE data only for the apalutamide arm of the trial. The PSCR did not provide updated AE data from the interim analysis 2, however updated safety data was reported in the interim analysis report and the PSCR indicated that the incidence of specific adverse events (hypothyroidism, fractures and falls) was updated in the economic analysis where data were reported.

[3] Chowdhury S, Oudard S, Hadaschik BA, Uemura H et al. Matching-adjusted indirect comparison of the efficacy of apalutamide and enzalutamide in the treatment of non-metastatic castration-resistant prostate cancer. *Value in Health* 2018; 21(3): S20-S21.

Table 7: Incidence of AEs of special interest in the apalutamide group in SPARTAN (per resubmission)

Adverse event	Incidence		Event rates/100 years (updated data-cut[a] vs. initial data cut[a])
	'Interim analysis 1' (median follow-up 32 months)	Initial data-cut (median follow-up 20.3 months)	
Grade 4 or 5	0 (0.0%)	[redacted]	NC
Grade 3, n (%)			
Rash	42 (5.2%)	[redacted]	3.1 vs. 4.2
Falls	19 (2.4%)	[redacted]	1.2 vs. 1.2
Fractures	25 (3.1%)	[redacted]	1.7 vs. 2.1
Hypothyroidism	0 (0.0%)	[redacted]	NC
Seizures	0 (0.0%)	[redacted]	NC
Grade 1 or 2, n (%)			
Hypothyroidism	76 (9.5%)	[redacted]	6.3 vs. 7.6
Seizures	2 (0.2%)	[redacted]	0.1 vs. 0.2

[a] Total patient-years of exposure was 1,591 for the updated data cut and 1,160 in the initial data cut.
NC=not calculable; grey=previously considered by the ESC and PBAC.
Source: Table 6.3, p36 of the resubmission.

6.20 The event rate/100 years presented by the resubmission did not accurately reflect the updated 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.

6.21 The resubmission concluded that the safety profile of apalutamide remained unchanged with no significant increase in cumulative toxicity observed in the longer-term SPARTAN data and no substantial change in the incidence of AEs of special interest, Grade 3 or 4 AEs or serious AEs, with the overall event rate for these AEs remaining stable or decreasing over time. Given this, the resubmission stated the clinical claim for safety remained unchanged from the November 2018 submission, that apalutamide has an inferior safety profile compared with watchful waiting. The ESC considered this was reasonable. The PBAC noted that the TGA indicated that additional data was required to assess cardiac risk associated with apalutamide. The PBAC noted that the AE profile of apalutamide is based on immature data and has not been fully characterised.

6.22 Comparative results for AEs of special interest, which were included in the resubmission's economic model, are provided below.

Table 8: Comparative results for AEs of special interest

	Apalutamide N=803	Placebo N=398	RD (95% CI)	RR (95% CI)
Skin rash	191 (23.8%)	22 (5.5%)	**0.18 (0.15, 0.22)**	**4.30 (2.81, 6.58)**
Fall	125 (15.6%)	36 (9.0%)	**0.07 (0.03, 0.10)**	**1.72 (1.21, 2.44)**
Fracture	94 (11.7%)	26 (6.5%)	**0.05 (0.02, 0.08)**	**1.79 (1.18, 2.72)**
Hypothyroidism	65 (8.1%)	8 (2.0%)	**0.06 (0.04, 0.08)**	**4.03 (1.95, 8.31)**
Infection	48 (6.0%)	9 (2.3%)	**0.04 (0.02, 0.06)**	**2.4 (1.31, 5.33)**

RD=risk difference; RR=relative risk; **bold**=statistically significant
Source: Table 2.49, p176 and Table 2.56, p185 of the November 2018 submission.

Benefits/harms

6.23 Tabled presentation of the benefits and harms associated with apalutamide versus placebo are available above.

6.24 On the basis of evidence from the SPARTAN trial (see Table 5 and Table 8 above), for every 100 patients treated with apalutamide in comparison to placebo:

- Approximately 39 more patients would remain metastasis free after 24 months of treatment, given the event-free rate of 68.2% compared to that of 29.6% for placebo; and
- Approximately [redacted] more patients would remain alive after 3 years, given the 3 year survival rate was [redacted]% with apalutamide and [redacted]% with placebo (based on the updated data-cut provided with the PSCR).

Over a median duration of follow-up of 20.3 months:

- Approximately 18 additional patients would experience skin rash;
- Approximately 7 additional patients would experience a fall;
- Approximately 5 additional patients would experience a fracture;
- Approximately 6 additional patients would experience hypothyroidism; and
- Approximately 4 additional patients would experience a serious infection that required hospitalisation.

6.25 While the resubmission presented updated safety data for the apalutamide arm of SPARTAN, since updated comparative results were not provided in the resubmission the statements above regarding safety are based on the comparative evidence presented in the November 2018 submission. Updated adverse event data were supplied in the clinical study report provided with the PSCR.

Clinical claim

6.26 In its assessment of the November 2018 submission, the PBAC had considered that the claim of improvement in MFS, rPFS and sPFS was reasonable, but the magnitude of the clinical benefit was highly uncertain given the immaturity of the data. The PBAC also noted that the OS benefit for apalutamide was not statistically significant as the trial data were immature and the current data set was insufficiently powered, therefore the PBAC considered that the clinical claim of improvement in OS was not adequately supported by the clinical data (paragraph 7.8, November 2018 PSD). On the basis of the updated SPARTAN data provided in the PSCR the sponsor claimed that apalutamide was associated with a [redacted] in patients with m0CRPC at high risk of distant metastases. The PBAC agreed with the ESC that this claim is likely to be reasonable, however the magnitude of OS benefit remains uncertain as the OS data are still

immature and the [redacted].

6.27 While the resubmission did not make a clinical claim based on the updated PFS2 data the resubmission did assume on the basis of these data that it was appropriate to use abiraterone following apalutamide, and such usage was included in the economic model and financial estimates. The ESC considered that the PFS2 data indicated that a treatment sequence of apalutamide followed by abiraterone is more effective than a treatment sequence of placebo followed by abiraterone. However, the PFS2 data do not provide information as to whether prior use of apalutamide would affect the magnitude of the incremental benefit of abiraterone versus placebo.

6.28 For the November 2018 submission the PBAC had considered that the clinical claim of inferior safety was appropriate (paragraph 7.9, November 2018 PSD). The resubmission did not provide a further claim in regard to safety. The ESC considered that the claim of inferior safety remains reasonable.

6.29 The PBAC considered that the claim of superior comparative effectiveness was reasonable, though the magnitude of OS benefit is uncertain.

6.30 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.31 The economic model presented in the resubmission has been substantially revised from that presented in the November 2018 submission. The table below provides a summary of PBAC and ESC consideration of the November 2018 model and the corresponding structure and content of the revised model.

Table 9: PBAC and ESC comments and on the November 2018 model

November 2018 model	PBAC/ESC comments (November 2018 PSD)	Resubmission model
Overall (MFS:OS relationship)	Paragraph 7.10: The PBAC agreed with the evaluation and the ESC that use of MFS as a surrogate for OS in the model was not appropriate and the assumption of a 1:1 relationship between MFS and OS was not supported by the clinical data. Paragraph 7.13: The PBAC advised that a resubmission would require an economic model that does not assume a direct surrogate relationship between MFS and OS, regardless of the ratio used. The PBAC considered that if OS data are included in the economic model it would need to be substantially more conservative and should be based on trial data; this may include extrapolation from the SPARTAN trial or the meta-analysis of SPARTAN and PROSPER trials…The PBAC advised that in the absence of a demonstrated OS benefit, an ICER between $40,000 and $45,000 based on a 10 year time horizon is likely to be considered reasonable.	• The revised model is a partitioned survival model with health state transitions and survival benefit sourced from MFS and OS data from SPARTAN, with extrapolations. This differed from the original model, which was a Markov model applying OS data from the abiraterone 302 trial. The revised model does not assume a direct surrogate relationship between MFS and OS. • Results were provided for both [redacted] year and [redacted] year time horizons, with base case ICERs of $15,000/QALY - $45,000/QALY and 15,000/QALY - $45,000/QALY , respectively. Results for sensitivity analyses were based on the [redacted] year time horizon. The ESC noted that the updated results from the PSCR give an ICER of $45,000/QALY - $75,000/QALY (without cross-over adjustment).
OS gain	Paragraph 7.10: The PBAC considered that the estimated gains in OS in both the submission model and the PSCR model were implausibly high given that the SPARTAN trial did not demonstrate a statistically significant difference in OS.	• The modelled incremental survival benefit in the revised model was [redacted] months ([redacted] months in the updated results from the PSCR). The original model estimated [redacted] months incremental OS gain.
Sequential therapies	Paragraph 7.10: The PBAC considered that the assumption of similar survival for apalutamide and placebo patients after metastasis, without allowance for cross-resistance in sequential therapies, was not appropriate.	• In the revised model the sequential therapy used for apalutamide-treated patients was abiraterone while placebo-treated patients were treated with enzalutamide or abiraterone. While estimated survival is no longer similar for apalutamide and placebo patients in the mCRPC state due to changes in model structure and input, no specific adjustments for possible cross-resistance were made.
Extrapolation	Paragraph 6.27: The ESC noted that six parametric approaches to extrapolation were undertaken and the Weibull method was used, although it was not the best fit according to AIC and BIC. The ESC considered the choice of the Weibull function was not adequately justified.	• The revised model applied the Weibull method for MFS extrapolation on the basis that the parametric extrapolations that have the best fit have non-monotonic hazards leading to a plateau in MFS. Of the monotonic hazards (Weibull and Gompertz) the resubmission indicated Weibull has the best fit. • Extrapolation of OS used the Weibull function on the basis of best fit.

November 2018 model	PBAC/ESC comments (November 2018 PSD)	Resubmission model
Utility values	Paragraph 6.27: The ESC noted that utilities were based on treatment specific EQ-5D values in the metastasis-free health state and the numerical mean of 20 publications was used for the metastatic health state. The ESC considered that this method of determining utility values lacks face validity but noted that sensitivity analyses indicated that the utility values had little impact on the ICER. This highlights that the model is driven by the difference in OS rather than the difference in QoL.	• The revised model utilised the same sources for utility values. For the mCRPC health state an additional publication was added to the 20 used in the original model. The utility value applied was based on a meta-analysis calculation instead of a numerical average as used in November 2018. The ESC noted that this approach to determining utilities still lacked some face validity.
Dose intensity	Paragraph 6.33: Treatment costs in the model were calculated assuming a dose intensity of 89.94%, which could not be verified. Paragraph 7.13: The PBAC considered that a reduced cost per course would be appropriate given uncertainty in the dose intensity and duration of treatment.	• The revised model applied a dose intensity of [redacted]% (based on a post-hoc assessment of IPD from SPARTAN). • Cost per cycle of apalutamide has been reduced to $[redacted] from $[redacted] in the original model.

AIC=Akaike information criterion; BIC=Bayesian information criterion; IPD=individual patient data; MFS=metastasis-free survival; OS=overall survival; QoL=quality of life; PSCR=Pre-Sub-Committee Response; PSD=public summary document
Source: Table 8.1, p73-74; Section 8.1, p72-77 of the resubmission.

6.32 The key change to the economic model presented in the November 2018 submission was the alteration from a Markov model applying OS data from abiraterone Trial 302 to a partitioned survival model based on extrapolated SPARTAN data, which does not assume a direct surrogate relationship between MFS and OS.

6.33 The table below provides a summary of the key components of the revised economic evaluation, along with corresponding information for the November 2018 model.

Table 10: Key components of the revised economic evaluation

Component	November 2018 model	Current model
Type of analysis	Cost-utility analysis.	As used in the November 2018 model, which was appropriate.
Outcomes	Quality-adjusted life years (QALYs).	As used in the November 2018 model, which was appropriate.
Time horizon	Lifetime (15 years)	Both [redacted] and [redacted] year time horizons were reported. The resubmission considered that a 15 year time horizon was justified. In the resubmission model, there was little difference (<$[redacted]) between the ICERs based on the [redacted] and [redacted] year time horizons. The difference increased with the PSCR's updated model (>$[redacted] difference between the [redacted] and [redacted] year time horizons).
Methods used to generate results	Markov model	Partitioned survival model.
Health states	Three health states: - High risk m0CRPC: Based on MSF data from SPARTAN - Alive with distant metastases (mCRPC): Based on placebo data from abiraterone Trial 302 - Death: Absorbing state	Three health states: - High risk m0CRPC: Based on MSF data from SPARTAN - Alive with distant metastases (mCRPC): Based on OS data from SPARTAN - Death: Absorbing state The use of SPARTAN data instead of abiraterone-sourced data for OS corresponded to the recommendation of the PBAC (paragraph 7.13, November 2018 PSD).
Cycle length	1 month, half cycle correction applied	As per November 2018, which was appropriate.
Transition probabilities	SPARTAN and abiraterone Trial 302 data, including extrapolation.	SPARTAN data, including extrapolation. This was appropriate.
Utility values	Trial-based for the m0CRPC health state and literature based for the mCRPC health state.	As per November 2018. The calculation of the literature-based utility value for mCRPC was based on a meta-analysis instead of the numerical mean used in the November 2018 model.

m0CRPC=non-metastatic castrate resistant prostate cancer; mCRPC=metastatic castration-resistant prostate cancer; MFS=metastasis-free survival; OS=overall survival; PSD=public summary document
Source: Table 3-1, p213-214 of the November 2018 submission; Section 8.1-8.2 of the resubmission.

6.34 A summary of the key drivers of the economic model is provided in the table below. In the November 2018 model the key drivers were considered to be MFS, the assumed 1:1 surrogate relationship of MFS and OS as well as the use of abiraterone Trial 302 data in the mCRPC state.

Table 11: Key drivers of the model

Description	Method/Value	Impact
MFS	The resubmission (and PSCR) have not altered the MFS data applied in the economic model compared with the previous submission. Consequently the applied data remains immature (with only 26% and 58% of patients progressing to metastases in the apalutamide and placebo arms, respectively) and therefore the clinical benefit assumed for apalutamide remains uncertain. While the sensitivity analyses on MFS conducted by the resubmission did not result in large differences to the ICER, the economic evaluation modelled a large gain in MFS based on immature data. The impact of more mature MFS data is unknown.	Uncertain but potentially high, favours apalutamide

Description	Method/Value	Impact
Magnitude of OS gain	The resubmission has applied OS data from SPARTAN. While the updated data-cut provided in the PSCR was [redacted], the ESC considered the magnitude of the OS benefit was uncertain as the data remained immature and the OS benefit was [redacted]. As the model remains driven by survival, the estimated magnitude of the OS advantage for apalutamide was a major source of uncertainty in the model.	High, favours apalutamide
Dose intensity	The reduced dose intensity of apalutamide applied in the economic model ([redacted]% compared to [redacted]% in November 2018) had considerable impact on the resultant ICERs. While the revised dose intensity was stated to reflect dose reductions and interruptions from SPARTAN, the ESC considered that issues remained with the resubmission's methods for calculating dose intensity and it was unlikely that the same dose intensity will be observed in clinical practice. The pre-PBAC response provided additional data about the reasons for dose reductions and interruptions from the CSR for interim analysis 2, and provided further details as to how dose intensity was calculated in the trial. The PBAC considered that this additional information adequately addressed the ESC's concerns.	High, favours apalutamide

<table>
<tr><th>Description</th><th>Method/Value</th><th>Impact</th></tr>
<tr><td>Costs associated with mCRPC (progressed disease)</td><td>The ESC noted that, in the PSCR model, there was a large cost offset associated with less time in mCRPC ('progressed') health state ($[redacted]).
This offset (lower costs in the apalutamide arm compared with the placebo arm) was because patients in the apalutamide arm spend less time in the mCRPC state compared with the placebo arm (mean duration was [redacted] months for apalutamide versus [redacted] months for placebo in the resubmission model, [redacted] versus [redacted] months in the PSCR model).
The ESC noted that costs in the mCRPC health state were applied monthly comprising around $[redacted] for drug costs and $[redacted] for monitoring costs per month. It was unclear whether it was appropriate to apply all of the costs on a monthly basis.

Average health state costs (in PSCR model, unadjusted for treatment switching, 1[redacted] year time horizon):
<table>
<tr><th colspan="3">PSCR model</th><th>Resub-mission</th></tr>
<tr><th></th><th>Apa</th><th>Placebo</th><th>Δ</th><th>Δ</th></tr>
<tr><td colspan="5">High risk m0CRPC health state ('progression free')</td></tr>
<tr><td>Apalutamide</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr>
<tr><td>other</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr>
<tr><td>Total</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td><td>$[redacted]</td></tr>
<tr><td colspan="5">mCRPC health state ('progressed')</td></tr>
<tr><td>Time spent in mCRPC</td><td>[redacted] mths</td><td>[redacted] mths</td><td>[redacted] mths</td><td>[redacted] mths</td></tr>
<tr><td>Subsequent treatment</td><td>$[redacted]</td><td>$[redacted]</td><td>-$[redacted]</td><td>-$[redacted]</td></tr>
<tr><td>Detection of metastasis</td><td>$[redacted]</td><td>$[redacted]</td><td>-$[redacted]</td><td>-$[redacted]</td></tr>
<tr><td>Monitoring</td><td>$[redacted]</td><td>$[redacted]</td><td>-$[redacted]</td><td>-$[redacted]</td></tr>
<tr><td>Total</td><td>$[redacted]</td><td>$[redacted]</td><td>-$[redacted]</td><td>-$[redacted]</td></tr>
</table></td><td>Uncertain, favours apalutamide</td></tr>
<tr><td>Utility value for the mCRPC health state</td><td>Based on a meta-analysis. The ESC noted that this approach to determining utilities still lacked some face validity (e.g. one of the studies included in the meta-analysis had a higher utility value for the mCRPC health state than the utility value that the submission used in the m0CRPC health state (0.85 in Devlin 2017 versus [redacted] in the placebo arm of m0CRPC).</td><td>Uncertain, likely moderate, favours apalutamide</td></tr>
</table>

MFS=metastasis-free survival; OS =overall survival
Source: Section 3.2 to 3.4, p218-281 of the submission.

6.35 The results of the economic evaluation are provided in the table below. In November 2018 the PBAC had advised that in the absence of a demonstrated OS benefit, an ICER between $40,000 and $45,000 based on a 10 year time horizon was likely to be considered reasonable. The resubmission claimed that an OS benefit has been demonstrated and maintained that a [redacted] year time horizon was appropriate, though the resubmission also presented results for a [redacted] year time horizon. The PBAC noted that the OS gain reported in interim analysis 2, though [redacted]. The PBAC considered that, while the additional OS data reported in interim analysis 2 supported the [redacted] in the economic analysis, the magnitude of the OS benefit was uncertain as the data remained immature and the [redacted]. The life years gained in the trial-based analysis (less than [redacted] month

incremental OS gain) were significantly less that the modelled gain in life years ([redacted] months incremental OS gain). In light of these uncertainties, the PBAC reiterated its previous consideration that an ICER between $40,000 and $45,000 would be required.

6.36 The PSCR provided an economic model with the updated (interim analysis 2) OS data. While the results of the PSCR model have been presented below, the updated model was not evaluated given the large amount of new information. However, it was noted that only the OS and adverse event data were updated in the PSCR model; MFS and time to treatment discontinuation (TTD) were not updated and the PSCR stated that the reason for this was that no new MFS data were available (the MFS data-cut provided in the previous submission was the final analysis of MFS). However, the ESC noted that the PSCR stated that the financial estimates had been updated with the new TTD data. The ESC noted that, as the PSCR model did not incorporate the new TTD data, the apalutamide drug costs remained unchanged between the two models. The PBAC noted that using TTD from an earlier data cut (but OS from the later data-cut) is likely to have underestimated treatment costs in the apalutamide arm.

6.37 The PSCR presented the results of the economic evaluation unadjusted for treatment switching and using three different methods of adjustment for treatment switching. The PSCR stated that the base case was "informed by an ICER range bounded by the scenario which adjusts for treatment switching (lower bound, $15,000/QALY - $45,000/QALY) and the scenario which does not adjust for treatment switching (upper bound, $45,000/QALY - $75,000/QALY)". However, adjustments for treatment switching were not included in the resubmission (only the PSCR) and thus the methodology and results were not evaluated.

6.38 The table below presents the results of the updated economic model provided with the PSCR and also the results of the model provided with the resubmission. Given the range of results presented in the PSCR (based on various methods of adjusting for treatment switching), only the unadjusted results and the "lower bound" of the analyses are presented in the table below.

Table 12: Results of the economic evaluation – updated from PSCR

Step and component	Apalutamide	Placebo	Increment
Step 1: trial based (41 months)			
Costs			
LY			
Incremental cost/extra LY gained			
QALY			
Incremental cost/extra QALY gained			
15 year time horizon with updated OS data (no adjustment for treatment switching)			
Costs			
QALY			
Incremental cost/extra QALY gained			$
10 year time horizon with updated OS data (no adjustment for treatment switching)			
Costs			
QALY			
Incremental cost/extra QALY gained			
15 year time horizon with updated OS data (adjustment: IPCW)			
Costs			
QALY			
Incremental cost/extra QALY gained			
Resubmission base case 15 year time horizon (without updated OS data, as presented in the resubmission)			
Costs			
QALY			
Incremental cost/extra QALY gained			
Resubmission base case 10 year time horizon (without updated OS data, as presented in the resubmission)			
Costs			
QALY			
Incremental cost/extra QALY gained			

Source: Table 8.11, p114; Table 8.12, p117 of the resubmission; Table 3.41, p326; Table 3.42, p328 of the November 2018 submission.

The redacted table shows ICERs in the range of $45,000-$75,000/QALY.

6.39 In the model presented in the resubmission, there was little difference ($) in the incremental cost per QALY gained between the year and year time horizons. The ESC noted that with the updated data from the PSCR the longer time horizon had more impact on the ICER (around less than $15,000 per QALY less for the year time horizon).

6.40 The November 2018 model was largely driven by the assumed surrogate relationship between MFS and OS, with a resulting large gain in OS. The resubmission's revised model structure did not assume a MFS:OS surrogate relationship, however the results were driven by survival, with life years accounting for % of the QALYs gained. The ESC considered that the additional data provided in PSCR supported in the economic analysis. However, the magnitude of the OS benefit was uncertain as the data remained immature and the OS benefit was .

6.41 The incremental QALY gain in the November 2018 model was . The gain estimated in the revised model was less than half of that (in the resubmission model, in the PSCR model with no adjustment for treatment switching, year time horizon).

While there has been a considerable decrease in incremental QALYs with the revised model, overall the base case ICER was reduced due to the reduced dose intensity applied [redacted]% in the apalutamide arm), discussed further below.

Table 13: Results of sensitivity analyses (based on 15 year time horizon)

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
Base case (resubmission model)	[redacted]	[redacted]	[redacted]	-
BICR-based assessment of MFS (base case: investigator-based assessment)				
BICR-based	[redacted]	[redacted]	[redacted]	[redacted]
MFS extrapolation (base case: Weibull)				
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
OS extrapolation (base case: Weibull)				
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
MFS and OS extrapolation (base case: Weibull)				
MFS Gompertz; OS gamma	[redacted]	[redacted]	[redacted]	[redacted]
Incremental OS gain (base case: [redacted] months)				
7.5 months	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] months	[redacted]	[redacted]	[redacted]	[redacted]
mCRPC health state utility (base case: [redacted])				
[redacted] (November 2018 submission)	[redacted]	[redacted]	[redacted]	[redacted]
0.823 (Ivanescu 2014)	[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity (base case: [redacted]% apalutamide; [redacted]% placebo)				
[redacted]% apalutamide; [redacted]% placebo (November 2018 submission)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]% apalutamide; [redacted]% placebo	[redacted]	[redacted]	[redacted]	[redacted]
Based on PSCR model (using scenario of: OS results unadjusted for cross-over, [redacted] year time horizon)				
Base case (unadjusted for cross-over, [redacted] year time)	[redacted]	[redacted]	[redacted]	-
BICR-based assessment of MFS	[redacted]	[redacted]	[redacted]	
Dose intensity (base case [redacted]% apalutamide; [redacted]% placebo)				
Dose intensity: [redacted]% apalutamide; [redacted]% placebo (November 2018 submission)	[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity: [redacted]% apalutamide [redacted]% placebo	[redacted]	[redacted]	[redacted]	[redacted]

BICR=blinded independent central review; MFS=metastasis-free survival; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival

Source: Table 8.15, p122 of the resubmission, calculated from PSCR update to the economic model

The redacted table shows ICERs in the range of $15,000/QALY - $75,000/QALY.

6.42 The model provided in the resubmission demonstrated sensitivity to the dose intensity, with some sensitivity shown for the extrapolation method used. The model was sensitive to alternate utilities identified in the literature (up to [redacted]% change in the ICER). The model also showed some sensitivity to MFS assessment (investigator or blinded independent central review; approximately [redacted]%) and cost of treatment for mCRPC (approximately [redacted]%). The submission presented scenarios where the incremental OS gain was varied from [redacted] months to [redacted] and [redacted] months, increasing the ICER up to approximately [redacted]%.

6.43 Use of the dose intensities from the November 2018 submission increased the ICER/QALY to $45,000/QALY-$75,000/QALY ($75,000/QALY - $105,000/QALY , with the PSCR update unadjusted for treatment switching and a [redacted] year time horizon), an

increase of close to 40% from the base case. The resubmission stated that the reduced dose intensities applied in the economic model were to account for the dose reductions and interruptions observed in SPARTAN. While the PSCR provided further information about the dose intensity calculations, the ESC noted the following issues remained, which the sponsor addressed in its pre-PBAC response:

- the clinical rationale for such a low dose intensity in the trial was unclear. For example the low dose intensity may have been due to dose interruptions as the CSR stated [redacted]% of patients in the apalutamide arm had no dose modifications. The pre-PBAC response stated that in the SPARTAN protocol dose modifications (including dose reductions to 180 mg or 120 mg or temporary interruptions) could be performed to manage adverse events, irrespective of the severity of the event. The sponsor noted that in the updated SPARTAN data [redacted]% of apalutamide patients had a dose reduction, including [redacted]% of patients reducing their dose by half and [redacted]% of patients had a dose interruption (39% due to an adverse event and [redacted]% for other reasons). The sponsor concluded that the extent of dosing changes and the dose intensity calculated are reflective of clinical practice and not due to any study-related procedures.
- the clinical study report provided with the resubmission appeared to indicate a dose intensity of [redacted]% (mean dose of [redacted]mg, which represented [redacted]% of a 240 mg dose). The ESC noted it was unclear why there was such a large difference between the proportion indicated by the CSR and that calculated by the resubmission. The pre-PBAC response clarified that this measure did not capture changes in the prescribed dose (such as reductions or interruptions), but only reflects compliance with the prescribed dose; and
- during the trial, the formulation was changed from using 30 mg capsules to 60mg tablets. The sponsor was requested to clarify how this was adjusted for in its dose intensity calculations. The pre-PBAC response stated that the analysis captured all planned and unplanned changes in dosing in SPARTAN, and reflected overall compliance to the prescribed dose, as well as reductions or interruptions to the prescribed dose of 240 mg/day.

6.44 Further, the ESC considered that it is unknown if these dose reductions and interruptions would be observed in clinical practice. While there are AEs of special interest, the resubmission claimed that AEs are manageable, do not require permanent discontinuation of apalutamide, generally do not negatively impact on patient quality of life, and were largely consistent with long-term ADT. The evaluation and the ESC considered that the dose intensity used in the resubmission is lower than would be expected with a generally well tolerated drug, and lower than might be expected in clinical practice. This may reflect conservative use of apalutamide in the clinical trial and it is possible that protocol driven dose interruptions, where patients experienced AEs in the trial, would not occur in clinical practice. However, the PBAC noted the arguments provided in the pre-PBAC response (per the paragraph above)

and considered that a dose intensity of [redacted]% (as used in the resubmission) was appropriate in this particular case.

6.45 The ESC considered that the utilities used for the mCRPC health state remained problematic as they were based on a meta-analysis of studies that reflected a mix of stages within the mCRPC state from first line treatments (with higher utility values) to latter line treatments (with lower utilities).

6.46 The ESC noted that, in the resubmission and PSCR models, there was a large incremental cost in the mCRPC ('progressed') health state (in the PSCR model costs were [redacted] higher in the placebo arm). This was because patients in the apalutamide arm spend less time in the mCRPC state compared with the placebo arm (mean duration in the mCRPC health state was [redacted] months for apalutamide versus [redacted] months for placebo). Costs in the mCRPC health state were applied monthly (i.e. each month that a patient spent in this health state was associated with drug costs of $[redacted] and monitoring costs of $[redacted]). It was unclear whether it was appropriate to apply all of the costs on a monthly basis; costs may be overestimated for patients who are in a relatively stable period of disease and underestimated for patients with more severe disease (with the apalutamide arm potentially having a higher proportion of patients with more severe disease given the shorter duration of time spent in the mCRPC health state).

6.47 The resubmission assumed that apalutamide-treated patients who move to the mCRPC health state could be treated with abiraterone. The clinical study report provided with the PSCR noted that at the time of cut-off [redacted]% of patients in the apalutamide arm received subsequent treatment with abiraterone (it was the most common subsequent therapy; this represented more than [redacted]% of patients who had progressed and received a subsequent therapy). The resubmission's model did not allow for consideration of patients not being treated with abiraterone (post apalutamide), hence it was not possible to determine if the absence of abiraterone therapy following apalutamide would increase or decrease the ICER.

Drug cost/patient/month

6.48 The table below summarises intervention costs per patient, for a duration of one month.

Table 14: Intervention costs per patient across one month

	Apalutamide		
	Trial dose and duration	**Model**	**Financial estimates**
Mean dose	[redacted] mg/day	[redacted] mg/day[a]	[redacted] mg/day[b]
Mean duration	[redacted] months	[redacted] months	[redacted] months
Total mg administered	[redacted] mg	[redacted] mg	[redacted] mg
Cost/patient/month	-	[redacted]	[redacted]
Cost/patient/course		[redacted]	
Cost/patient/month November 2018	-	[redacted]	[redacted]

[a] The economic model applied a dose intensity of [redacted]% to apalutamide and [redacted]% to placebo.
[b] A dose intensity of [redacted]% was applied to apalutamide for the financial estimates.
[c] Cost assumes a dost intensity of [redacted]%.
[d] Cost assumes a dose intensity of [redacted]%.
Source: Excel workbooks 'Apalutamide m0CRPC Economic Model' and 'Apalutamide m0CRPC resubmission financial estimates model'; ARN-509-003_CSR_Final-with Attachments. Italicised values have been calculated.

6.49 The cost per patient per month for apalutamide therapy has decreased ($[redacted]) compared to the November 2018 submission ($[redacted]) due to the reduction in requested effective price for apalutamide and reduction in assumed dose intensity ([redacted]%). The assumed dose intensity may not be observed in clinical practice.

Estimated PBS usage & financial implications

6.50 This resubmission was not considered by DUSC. As for the November 2018 submission the resubmission applied an epidemiological approach to estimate the number of patients treated with apalutamide. The resubmission did not alter the data sources used or the assumptions made which inform the estimates of incidence and prevalence, with the exception of use of ABS-projected population growth for males aged over 50 years rather than the population growth for all ages (0 to 85+ years) as the basis for extrapolating the growth in the prevalent m0CRPC population. The PBAC noted that in November 2018 the DUSC advised there is limited data on the incidence and prevalence of m0CRPC in Australia and the number of prevalent m0CRPC patients and the number of non-metastatic patients on ADT could not be verified. In November 2018, the PBAC considered that the size of the treated population remains unknown. The PBAC also considered that the uptake rates are uncertain and there is a risk of leakage to other high risk patients and also to patients with metastatic, castration sensitive disease, based on evidence from the TITAN trial.

6.51 As in the economic model, the resubmission altered the dose intensity of apalutamide, based on a post-hoc analysis of SPARTAN data, to [redacted]% ([redacted]% was applied in the November 2018 submission). As noted by the resubmission , this revised dose intensity accounted for the dose reductions and dose interruptions observed in SPARTAN.

6.52 The resubmission also altered the calculation of scripts dispensed. For the revised estimates, the TTD Kaplan Meier extrapolation in the economic model was used to model the proportion of patients remaining on treatment over time ([redacted]% at 4 months), upon which the number of scripts dispensed was estimated. As the financial estimates use KM data from the SPARTAN trial and outputs from the economic model,

the financial estimates were updated in the PSCR to incorporate the longer-term OS and TTD data from interim analysis 2 of the SPARTAN trial (PSCR.

6.53 As in the November 2018 submission, cost offsets for changes in the use of other medicines estimated in the resubmission were based on usage of medicines which are used concomitantly with apalutamide, usage of medicines for the management of AEs that occur with apalutamide as well as medicines which the submission proposes would be used subsequent to apalutamide for the treatment of mCRPC, including abiraterone, consistent with the economic model.

6.54 The resubmission provided revised estimates of patient numbers, scripts, cost offsets and net costs. The patient numbers presented by the resubmission are for those commencing treatment each year (as was presented in the November 2018 submission) while script numbers are for initiating and continuing patients. The revised financial estimates provided with the PSCR are also shown in the table below.

Table 15: Estimated use and financial implications (updated per PSCR)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Years 1-6
Estimated extent of use							
Number commencing trt	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR: Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of apalutamide							
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR: Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offsets for change in use of other medicines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR: Cost offsets for change in use of other medicines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications							
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR: Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR: Net Cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS/MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR: Net cost to PBS/PRBS/MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] All estimates for November 2018 were based on the pre-PBAC response estimates.

[b] The TTD Kaplan Meier extrapolation in the economic model was used to model the proportion of the patients remaining on treatment over time ([redacted]% at 4 months), upon which the number of scripts dispensed was estimated (1.01 scripts/month and dose intensity of [redacted]%).

[c] Based on the number of patient-months on apalutamide therapy each year multiplied by the 1.01 scripts per month with a dose intensity of [redacted]% as estimated by the November 2018 submission.

trt=treatment

Source: Table 9.5, p141; Table 9.6, p141; Table 9.7, p142; Table 9.10, p144; Table 9.13, p148 of the resubmission and Excel workbook 'Apalutamide m0CRPC resubmission financial estimates model', PSCR updated financial estimates model, result tables worksheet.

6.55 The November 2018 pre-PBAC response for consideration of the initial submission had altered estimated patient numbers by exclusion of patients who did not have a WHO performance score of 0 or 1, which has been maintained in the resubmission.

6.56 The estimated net cost to the Government for the first 6 years of listing for apalutamide was more than $100 million , which increased to more than $100 million with the updated data in the PSCR. The resubmission stated that this represented a

41.5% reduction from the estimated net cost provided in the November 2018 pre-PBAC response. The resubmission stated that the reduction was attributed to:

- Reduction in the number of apalutamide scripts (accounts for [redacted]% of the reduction);
- Reduced effective price of apalutamide (accounts for [redacted]% of the reduction); and
- Increased cost offsets for the PBS/RPBS and MBS (accounts for [redacted]% of the reduction).

6.57 The estimated change in usage and cost of PBS/RPBS and MBS items were based on outputs of the economic model, which may not reflect clinical practice. The PSCR argued that the updated financial estimates model is now based on survival data from SPARTAN with a patient follow-up of almost [redacted] years ([redacted]months) before the model reverts to extrapolations to estimate time spent in the mCRPC health state and is therefore no longer based on immature data. The advantages predicted for apalutamide-treated patients in regard to reduced usage and cost of PBS/RPBS (predominantly due to reduced use of subsequent therapies, particularly enzalutamide) and MBS items (predominantly due to a reduction in the number of CT and bone scans due to less time spent in the metastatic health state) are likely to be overestimated, meaning that the estimated cost reductions could be less, leading to increased net cost to Government. In particular, the financial estimates assume that apalutamide patients 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.

Financial Management – Risk Sharing Arrangements

6.58 The resubmission stated that the sponsor may propose a different risk sharing arrangement (to that proposed in the November 2018 pre-PBAC response) for apalutamide in patients with m0CRPC at high risk of distant metastases pending evaluation of the changes made to the financial estimates. No further information was provided in the PSCR or pre-PBAC response. The PBAC considered that a risk sharing arrangement would be required, given the high uncertainty in the patient and script numbers for apalutamide.

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 patients with non-metastatic castration-resistant prostate cancer (m0CRPC) who are at high risk of distant metastases. The PBAC considered that apalutamide provided a substantial benefit to some patients in delaying metastases; however, the magnitude of the survival benefit was uncertain. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was high and uncertain, and that a price reduction would be

required to bring the ICER into an acceptable range. Further, the PBAC considered that the substantial amount of additional information provided in the PSCR would require evaluation.

7.2 The PBAC acknowledged that there is a clinical need for effective treatments in patients with m0CRPC and noted that there is evidence that apalutamide and other drugs in the same class provide clinical benefits in various stages of prostate cancer.

7.3 The resubmission proposed that the PBS restrictions should allow abiraterone to be used after apalutamide, and presented longer-term PFS2 data from the SPARTAN trial. While these data indicate that a treatment sequence of apalutamide followed by abiraterone is more effective than a treatment sequence of placebo followed by abiraterone, the PBAC considered this may be due to earlier treatment with apalutamide rather than being attributable to abiraterone. Overall, the PBAC considered that the PFS2 data do not provide information as to whether the magnitude of the benefit of abiraterone versus placebo would remain unchanged with prior use of apalutamide. Given this, and in the context of data indicating that abiraterone has only minimal activity in patients who progressed after treatment with enzalutamide (refer to Paragraph 2.5), the magnitude of efficacy and thus the cost-effectiveness of abiraterone is unclear when used post-apalutamide. The PBAC advised that the PBS restrictions should not allow abiraterone to be used after apalutamide.

7.4 The resubmission stated that it may be reasonable to preclude the use of PBS-subsidised enzalutamide after apalutamide, as there is potential for cross-resistance and it is unlikely that enzalutamide would demonstrate efficacy following progression on apalutamide given their pharmacological similarity. The PBAC agreed, and advised that that the PBS restrictions should not allow enzalutamide to be used after apalutamide.

7.5 The PBAC reiterated its previous consideration that watchful waiting was the appropriate comparator (paragraph 7.5, November 2018 PSD). The PBAC also noted that enzalutamide is likely to enter the same market space as apalutamide, based on the PROSPER study and other agents, such as darolutamide (ARAMIS study), are also likely to become available for this population (paragraph 7.5, November 2018 PSD), making these agents near market comparators. The resubmission included data from the PROSPER and ARAMIS trials in its meta-analysis of overall survival (OS) data but did not compare the agents to each other.

7.6 The PBAC reiterated its previous consideration that the claim of improved metastasis-free survival (MFS) and progression-free survival was reasonable (Paragraph 7.8, November 2018 PBAC Minutes).

7.7 The PBAC recalled that it had previously considered that the claim of improved OS was not adequately supported by the clinical data; however, the PBAC noted this was based on data from the first interim analysis of the SPARTAN trial which did not report a statistically significant improvement in OS (HR = 0.70 (95% CI: 0.47, 1.04), Paragraph

7.8, November 2018 PSD). The PSCR presented updated OS data from 'interim analysis 2' of the SPARTAN trial (with a median follow-up of [redacted] months), which the sponsor claimed showed an [redacted] in overall survival (HR = [redacted]; 95% CI: [redacted], [redacted], [redacted]). The PBAC considered that, based on these updated data, it is likely that apalutamide provides [redacted], however the magnitude of this benefit remains uncertain as the data were immature (median OS was not yet reached in either arm) and [redacted].

7.8 The PBAC noted that the resubmission had also presented a meta-analysis of pooled data from the SPARTAN, PROSPER and ARAMIS trials. The PBAC considered that alongside the updated data from SPARTAN, the pooled analysis helped to provide confidence that this class of drugs is likely to provide some level of [redacted] in patients with m0CRPC.

7.9 The PBAC considered that the changes to the economic model structure to apply MFS and OS data separately based on outcomes from the SPARTAN trial were appropriate, although the PBAC noted that the model remained driven by OS benefit. The PBAC considered that, while the additional OS data reported in interim analysis 2 supported the [redacted] in the economic analysis, the magnitude of the OS benefit was uncertain as the data remained immature and the [redacted]. The life years gained in the trial based analysis (less than [redacted] month incremental OS gain) were significantly less that the modelled gain in life years ([redacted] months incremental OS gain). In light of these uncertainties, the PBAC reiterated its previous consideration that an ICER between $40,000 and $45,000 would be required.

7.10 The PBAC noted that the economic model used investigator-assessed MFS in the base case, rather than blinded independent central review (BICR)-assessed MFS. The PBAC considered that there was a greater potential for detection bias with investigator-assessed MFS. Further, the PBAC noted the choice of investigator-assessed MFS was not conservative, which the PBAC considered to be an issue in the context of the large gain in MFS that was modelled based on immature data (with only 26% and 58% of patients progressing to metastases in the apalutamide and placebo arms, respectively). Overall, the PBAC considered that, in this case, BICR-assessed MFS was the more appropriate measure for use in the economic model.

7.11 The PBAC noted that the economic evaluation presented in the resubmission applied a dose intensity of [redacted]% (compared with [redacted]% in the November 2018 submission), which the resubmission stated was to account for the dose reductions and interruptions observed in the SPARTAN trial. The PBAC considered that the dose intensity of [redacted]% (as used in the resubmission) appeared to reflect use in the SPARTAN trial and was reasonable to apply in the economic model (and financial estimates).

7.12 The PBAC noted that a revised estimate of the ICER was provided in the PSCR based on updated OS data from interim analysis 2 of the SPARTAN trial, which increased the ICER in the range from $45,000/QALY-$75,000/QALY gained (in the analysis without

adjustment for treatment switching, with a [redacted] year time horizon). The PBAC noted that this ICER increased further (to $45,000/QALY-$75,000/QALY gained) when a [redacted] year time horizon and BICR-assessed MFS were used. The PBAC noted that the PSCR's revised model did not incorporate the updated TTD data, and that using TTD from an earlier data cut but OS from the later data-cut is likely to have underestimated treatment costs in the apalutamide arm. Further, the PBAC noted that the PSCR's revised model was not evaluated given the large amount of new information provided in the PSCR.

7.13 The PBAC advised that the base case should use the economic model provided in the PSCR, with the following revisions:

- use BICR-assessed MFS (rather than the investigator-assessed);
- use a 10 year time horizon;
- include 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 unadjusted OS results (i.e. do not include any adjustments for treatment switching) given the uncertain magnitude of the OS gains.

7.14 The PBAC noted the economic model included subsequent use of abiraterone in the apalutamide arm. The PBAC noted that this was not consistent with its advice that that subsequent treatment with abiraterone should not be permitted under the PBS. However, the PBAC also noted that the PSCR's model did not allow adjustment of both the treatment effect and costs to account for patients not being treated with abiraterone (post apalutamide). Hence the PBAC acknowledged that it was not possible to determine if the absence of abiraterone therapy following apalutamide would increase or decrease the ICER.

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.

7.16 The financial estimates assume that patients treated with apalutamide can receive subsequent treatment with abiraterone. The PBAC considered that this requires 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.

7.17 The PBAC considered that a major resubmission would be required and would need to address the following issues:

- A price reduction would be required to achieve an ICER in the range of $40,000 to $45,000 per QALY, using the base case outlined in Paragraph 7.13;
- the financial estimates should be updated to remove the assumption that abiraterone can be used after apalutamide; and
- a risk sharing arrangement would be required with [redacted]% rebates for expenditure above the caps.

Further, the PBAC considered that the substantial amount of additional information provided in the PSCR and its application in the economic model would require evaluation.

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 in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.