

5.01 APALUTAMIDE, Tablet 60mg, Erlyand[®] Janssen-Cilag Pty Ltd.

1 Purpose of Application

- 1.1 The submission 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. This was the first PBAC submission for apalutamide.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus placebo (watchful waiting). The key components of the clinical issue addressed by the submission 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
Comparator	Watchful waiting (placebo) comprised of ongoing ADT, with or without secondary hormonal therapy.
Outcomes	MFS, OS, rPFS, sPFS, time to initiation of cytotoxic chemotherapy, PFS on first subsequent therapy.
Clinical claim	In patients with m0CRPC at high risk of distant metastases, apalutamide when used in combination with ADT demonstrates superior comparative effectiveness compared with watchful waiting with statistically and clinically significant improvements in MFS, rPFS and sPFS. The submission also claimed that apalutamide showed a strong trend toward a statistically significant but clinically relevant improvement in OS, and an inferior safety profile.

ADT=androgen deprivation therapy; MFS=metastasis-free survival; m0CRPC=castration-resistant prostate cancer with no distant metastases; OS=overall survival; PFS=progression-free survival; PSADT=prostate specific antigen doubling time; rPFS=radiographic progression-free survival; sPFS=symptomatic progression-free survival
Source: Table 1.1, p17 of the submission.

2 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
APALUTAMIDE tablet 60mg	120	5	Effective: \$ [REDACTED] Published: \$ [REDACTED]	ERLYAND® Janssen-Cilag Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	Medical Practitioners
Condition:	Gastrate resistant prostate cancer <i>Castration resistant carcinoma of the prostate</i>
PBS Indication:	Gastrate resistant prostate cancer <i>Castration resistant carcinoma of the prostate</i>
Restriction Level / Method:	Authority Required - Telephone
Clinical criteria (initial):	<p>Patient does<i>must</i> not have distant metastasis on conventional imaging AND Treatment must be used in combination with androgen deprivation therapy AND Patient must have a PSA doubling time of 10 months or less AND Patient must have a PSA level > 2 ng/mL AND Patient must not develop radiographic disease progression while receiving PBS-subsidised treatment with this drug for this condition.</p>
Clinical criteria (continuing):	<p>Patient must have previously been issued with an authority <i>received PBS-subsidised treatment with prescription</i> for 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.</p>
Clinical criteria (initial – grandfather patients):	<p>Patient must have previously received non PBS-subsidised treatment with this drug for this condition prior to <date> AND Patient does not have distant metastasis on conventional imaging AND Treatment must be used in combination with androgen deprivation therapy AND Patient must have had a PSA doubling time of 10 months or less prior to receiving non-PBS-subsidised treatment with this drug AND Patient must have had a PSA level > 2 ng/mL 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.</p>
Note Prescriber instruction	The PSA doubling time must be calculated using at least three PSA values obtained during androgen deprivation therapy.
Administrative advice	<p>Special Pricing Arrangements apply. <i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i></p>

- 2.2 The submission has proposed a special pricing arrangement with a proposed published price of \$ [REDACTED] and an effective price of \$ [REDACTED]. Application of the latest dispensing and administration, handling and infrastructure (AHI) fees from 1 July 2018 would increase the requested published price by \$1.52 to \$ [REDACTED] and the requested effective price by \$0.24 to \$ [REDACTED]. The requested prices used in the economic analysis and financial estimates were not updated during the evaluation.
- 2.3 While the recommended dose is 240mg/day, in SPARTAN just over 20% of patients experienced a dose reduction; 76% experienced a dose interruption and less than half (47.9%) complied with treatment at the recommended level. As such, it is likely that for many patients the specified supply will correspond to more than 6 months treatment.
- 2.4 The requested restriction is narrower than the recommended TGA indication (non-metastatic castration-resistant prostate cancer) as it limits use to patients at high risk of distant metastases (PSADT ≤ 10 months). The submission argued that the specification of PSADT ≤ 10 months is the only required criteria for identifying high risk patients. However, as noted by the TGA evaluator, there are other relevant criteria such as time to biochemical failure and Gleason score. As such, the requested restriction may exclude some patients who are at high risk of distant metastasis. The ESC considered that the requested restriction for high risk patients is in keeping with the SPARTAN trial population and is therefore appropriate. The PROSPER trial of enzalutamide, in the same treatment setting, had a similar definition of high risk to SPARTAN. The ESC noted that whilst there are other patients who may be classified as high risk, there are insufficient data to recommend a broader PBS population for the apalutamide restriction.
- 2.5 The ESC considered that the clinical criteria should specify that patients must have a WHO performance status of 1 or less, consistent with patients included in the SPARTAN trial. The ESC noted that the trial only recruited patients with an ECOG score (or WHO performance status) of 0 or 1 and considered that the submission's reasoning that this is not required, as 95% of the patients would be asymptomatic, was inadequate. The ESC noted that the financial estimates should be updated to reflect this restriction. In the pre-PBAC response the sponsor accepted the inclusion of this criterion in the restrictions and provided updated financial estimates as requested.
- 2.6 The ESC advised that the clinical criterion relating to disease progression should remove the word 'radiographic', consistent with descriptions of disease progression for current PBS listings for metastatic prostate cancer.
- 2.7 The pre-sub-committee response (PSCR) argued that the PBS restriction for apalutamide should not preclude later use of other hormonal therapies in mCRPC, in particular abiraterone. The ESC noted that there is a lack of evidence supporting sequential use of abiraterone or enzalutamide following apalutamide and considered that flow on restrictions to both abiraterone and enzalutamide to prevent sequential therapy should apply. The pre-PBAC response argued that the efficacy of abiraterone

is not reduced by prior treatment with apalutamide and maintained that patients who progress on apalutamide should be eligible for PBS-subsidised sequential therapy with abiraterone or enzalutamide.

- 2.8 The ESC noted that the clinical criteria specify use of conventional imaging to detect metastases, however alternative imaging (prostate-specific membrane antigen (PSMA) scanning) may show that patients otherwise classified as mOCRPC already have occult metastatic disease not detectable on standard imaging.

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. The submission indicated that apalutamide went through a priority review process with the TGA, along with a pilot work sharing initiative with Health Canada.

4 Population and disease

- 4.1 Castration-resistant prostate cancer is defined as progressive disease despite castrate levels of testosterone, as defined by the Cancer Council of Australia. The submission stated that patients with biochemical recurrence may receive ADT to reduce levels of testosterone to castrate levels. Patients on ADT will eventually experience treatment failure, and this stage is known as CRPC.
- 4.2 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 of developing metastatic disease while patients with a PSADT ≤10 months are classified as high risk.
- 4.3 The submission stated that there are no TGA-approved or PBS-listed therapies for patients with mOCRPC at high risk of distant metastases and there is no effective standard of care. Patients are currently managed with ADT with possible use of secondary hormonal therapies.
- 4.4 Apalutamide is an orally administered androgen receptor (AR) inhibitor intended for use in patients with mOCRPC who are at high risk of distant metastases. In addition to apalutamide, there are a number of similar treatments appearing in the same proposed position as apalutamide in the clinical management algorithm (Degener

2017¹). There was the recent publication of the PROSPER trial (Hussain 2018²) which compared enzalutamide plus background ADT with placebo in men with m0CRPC at high risk of distant metastases and trials of darolutamide (data due in September 2018³) and enzalutamide with leuprolide (data due in March 2021⁴) are also forthcoming.

- 4.5 In addition to agents such as apalutamide and enzalutamide, it appears that the clinical management algorithm is rapidly changing for prostate cancer, with a trend towards active treatments earlier in the disease. There are a number of trials that have placed docetaxel earlier in the clinical management algorithm for newly diagnosed hormone sensitive metastatic prostate cancer indicating statistically significant gain in OS of roughly 10 months (CHAARTED⁵, STAMPEDE⁶). One trial in particular had also enrolled patients with locally advanced castration sensitive prostate cancer and found consistently significant survival gains for patients with non-metastatic disease (STAMPEDE).
- 4.6 The submission stated that the positioning of apalutamide for treatment of patients at high risk of distant metastases with m0CRPC will shorten the gap in the current clinical management algorithm where patients currently must experience significant deterioration of their disease for them to be eligible and clinically indicated for docetaxel, in symptomatic or high volume mCRPC. While the gap in the treatment algorithm may be shortened, there will still be a gap for patients between radiographic disease progression to mCRPC and development of symptomatic or high volume mCRPC.
- 4.7 A recent phase IV trial in 251 patients who had previously responded to enzalutamide and then progressed (Attard 2017⁷) indicated abiraterone has only minimal activity in patients who progressed after treatment with enzalutamide. The PBS clinical criteria for abiraterone exclude use in patients who have received prior treatment with enzalutamide, except where patients are intolerant to enzalutamide. Given the similar

¹ Payer acceptability of metastasis-free survival as the primary end point in non-metastatic castration-resistant prostate cancer. Degener F, Holmstrom S, van Engen A, Naidoo S. ISPOR 22nd Annual International Meeting, May 20-24 2017, Boston USA; Poster PCN259. Sourced at:

https://www.ispor.org/research_pdfs/55/pdffiles/PCN259.pdf

² Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *NEJM* 2018; 378:2465-74.

³ first results expected September 2018 as per <https://clinicaltrials.gov/ct2/show/NCT02200614>

⁴ First results expected March 2021 as per <https://clinicaltrials.gov/ct2/show/NCT02319837>

⁵ Sweeney CJ, Chen YH, Carducci M, Liu G et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *NEJM* 2015; 373: 737-746.

⁶ James ND, Sydes MR, Clarke NW, Mason MD et al. Addition of docetaxel, zoledronic acid or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016; 387: 1163-1177.

⁷ 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.

mechanism of action of enzalutamide and apalutamide, similar cross-resistance may also be a relevant consideration for abiraterone or enzalutamide therapy following apalutamide⁸. This was particularly relevant for the economic model, see ‘Economic evaluation’ below. The PSCR acknowledged that there is potential for cross-resistance between apalutamide, abiraterone and enzalutamide but argued that the available evidence for cross-resistance between abiraterone and enzalutamide is of low quality. The PSCR also noted that in SPARTAN, the risk of progression on the first subsequent therapy, which was abiraterone in 72% of patients, was halved with apalutamide vs placebo (HR = 0.49 [95% CI 0.36, 0.66]). The ESC agreed with the evaluation that this issue is of high pertinence to the management algorithm and to determining the correct place and appropriate sequencing of these second generation androgen receptor inhibitors. The ESC noted that clinical guidelines also question whether sequential use is appropriate, given the immaturity of the data. The ESC considered that it is unlikely that enzalutamide would demonstrate efficacy following progression on apalutamide given their pharmacological similarity. The ESC considered that there remains uncertainty regarding the clinical benefit of sequential use of abiraterone. The ESC noted that allowing sequential therapy would have significant impact on the net financial cost and would also potentially impact on the cost-effectiveness of abiraterone and enzalutamide. The ESC recommended that until further data become available confirming the benefit of sequential therapy, flow on restrictions to both abiraterone and enzalutamide to prevent sequential therapy should apply.

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

5 Comparator

- 5.1 The submission nominated ‘watchful waiting’ as the main comparator. ‘Watchful waiting’ was defined as ongoing ADT with or without the addition of secondary hormonal therapies.
- 5.2 The recently published trial of enzalutamide for use in patients with mOCRPC at high risk of distant metastases (PROSPER; Hussain 2018⁹) and forthcoming trials of other agents indicated that treatments are rapidly emerging in this space. Enzalutamide in particular attained similar risk reduction for MFS versus placebo (HR=0.29; 95% CI: 0.24 to 0.35) in the PROSPER trial compared to apalutamide versus placebo in SPARTAN (HR=0.297; 95% CI: 0.244 to 0.362). The ESC agreed with the submission that watchful waiting is the appropriate comparator based on the current management algorithm of mOCRPC patients in Australia. ESC also noted that enzalutamide is likely to enter the same market space as apalutamide, based on the PROSPER study and

⁸ Geynisman DM, Plimack ER, Zibelman M. Second-generation androgen receptor-targeted therapies in nonmetastatic castration-resistant prostate cancer: Effective early intervention or intervening too early? *Eur Urol* 2016; 70: 971-973.

⁹ Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *NEJM* 2018; 378:2465-74.

there appears to be a range of new agents that might become relevant comparators (such as enzalutamide +/- leuprolide, and darolutamide).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, the clinical significance of the transition to metastatic disease, and the preference for treatments such as abiraterone and enzalutamide to be available to patients who progress on apalutamide. The clinician also noted that apalutamide is well-tolerated by patients and effects are manageable, noting that it has a similar mode of action to enzalutamide, where there is extensive experience of use in the metastatic setting. The clinician also addressed other matters in response to the Committee's questions, including agreement that enzalutamide would be expected to have similar benefits as apalutamide, based on the mechanism of action and the PROSPER trial results, and that an OS benefit is expected given the magnitude of the MFS benefit, but there is insufficient data from the SPARTAN trial to support this assumption. The PBAC considered that the hearing was supportive of the clinical benefit for apalutamide in terms of delaying metastasis as presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (9), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the benefits of delaying metastasis and symptomatic progression in terms of maintaining and preserving quality of life and avoiding the pain associated with metastases. The comments also noted that adding apalutamide earlier in the treatment algorithm would help to address the current gap in treatment continuity which causes anxiety in men with prostate cancer. The comments also noted the favourable side effect profile compared with docetaxel.
- 6.3 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. The PBAC noted that the MOGA presented the 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)¹⁰, based on a comparison with placebo.

¹⁰ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Clinical trials

- 6.4 The submission was based on the SPARTAN trial (N=1207), which was a randomised, double-blind, multicentre trial comparing apalutamide and placebo, each in combination with ADT in patients with mOCRPC at high risk of developing distant metastases. Patients at high risk were defined as those with PSADT ≤ 10 months. The mean PSADT in trial patients was 4.75 months. As such, on average patients in SPARTAN had a considerably shorter doubling time than that required under the requested restriction, ≤ 10 months.
- 6.5 The trial was on-going, with an estimated completion date in late August 2019. The clinical study report (CSR) from which the data used in the submission was sourced was dated September 2017, with the data cut being in May 2017. The submission indicated that future data will be confounded by placebo patients switching to apalutamide, however the dataset presented in the submission was not confounded by treatment switching and did not require any adjustment. The PSCR stated that the final analysis may not be available for another 1–2 years.
- 6.6 The submission noted that as a part of randomisation patients were stratified according to PSADT, use of bone-sparing agents and presence of loco-regional disease and it was found that 152 patients (13%) had been mis-stratified. Given this mis-stratification sensitivity analyses of the MFS endpoint were presented in the CSR and the results were consistent with those of the primary analysis. The submission concluded that the risk of selection bias and confounding by these baseline characteristics was negligible. This was reasonable, although the sensitivity analyses correcting for stratification were only conducted for MFS and it remains possible that the mis-stratification could have impacted other outcomes.
- 6.7 The CSR and publication details of SPARTAN are provided in the table below.

Table 2: 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. Saad F, Small E, Hadaschik B, Graff J, et al. Patient (pt) reported outcomes (PROs) in SPARTAN, a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo (PBO) plus ADT in men with nonmetastatic castration-resistant prostate cancer (nmCRPC), Small EJ, Lee JY, Lopez-Gitlitz A, Saad F. Prostate-specific antigen (PSA) outcomes in patients (pts) with nonmetastatic castration-resistant prostate cancer (NMCRPC) treated with apalutamide (APA): Results from phase 3 spartan study, Small EJ, Saad F, Hadaschik BA, Graff JN. Patient reported outcomes (PROs) in spartan, a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with nonmetastatic castration-resistant prostate cancer (NMCRPC),	September 2017 <i>NEJM</i> 2018; 378:1408-1418 Annual EAU Congress Copenhagen 2018 (suppl: abstr 17(2);e1070). <i>J Urol</i> 2018; 199, 4S Supplement, PD10-11. <i>J Urol</i> 2018; 199, 4S Supplement, MP52-20

Source: Table 2.4, p85 of the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
SPARTAN	1,207	R, DB, MC On-going	Moderate	m0CRPC with high risk of distant metastases	MFS, OS	Used

DB=double blind; MC=multi-centre; MFS=metastasis-free survival; m0CRPC=non-metastatic castration resistant prostate cancer; OS=overall survival; R=randomised.

Source: Section 2.3 to 2.4, p86-126 of the submission.

6.9 The risk of bias was considered to be moderate due to the potential for unblinding based on the presence of prominent adverse events such as skin rash as discussed in the comparative harms section (paragraph 6.14).

Comparative effectiveness

6.10 The table below provides a summary of results for time-to-event outcomes assessed in SPARTAN, with Kaplan Meier curves for MFS and OS following.

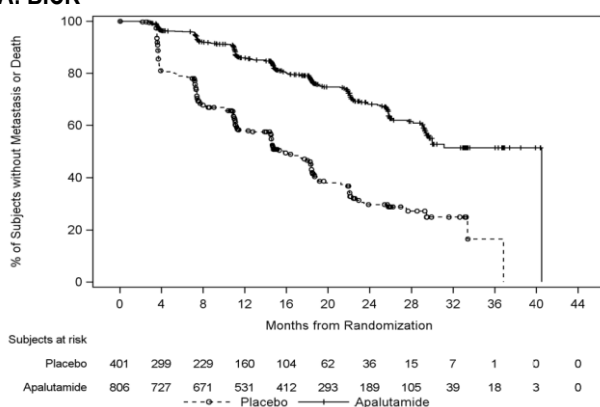
Table 4: Summary of time-to-event outcomes in SPARTAN

Outcome	Apalutamide (N=806)	Placebo (N=401)
Metastasis-free survival (MFS) – BICR assessed		
Event (n %)	209 (25.9%)	210 (52.4%)
Median months to metastasis (95% CI)	40.51 (29.70, 40.51)	15.70 (14.55, 18.40)
HR (95% CI)	0.297 (0.244,0.362)	
Metastasis-free survival (MFS) – investigator assessed		
Event (n %)	212 (26.3%)	231 (57.6%)
Median months to metastasis (95% CI)	41.20 (30.03, 41.20)	14.62 (11.10, 15.24)
HR (95% CI)	0.268 (0.221,0.325)	
Radiographic progression-free survival (rPFS)		
Event (n %)	220 (27.3%)	219 (54.6%)
Median months to progression (95% CI)	40.51 (29.40, 40.51)	14.65 (11.27, 17.97)
HR (95% CI)	0.300 (0.247,0.364)	
Overall survival (OS)		
Died (n %)	62 (7.7%)	42 (10.5%)
Median months to death (95% CI)	NE (NE, NE)	39.03 (39.03, NE)
HR (95% CI)	0.700 (0.472,1.038)	
Time to metastasis (TTM)		
Event (n %)	188 (23.3%)	204 (50.9%)
Median months to metastasis (95% CI)	40.51 (31.15, 40.51)	15.70 (14.55, 18.40)
HR (95% CI)	0.279 (0.227, 0.342)	
Time to symptomatic progression		
Event (n %)	64 (7.9%)	63 (15.7%)
Median months to symptomatic progression (95% CI)	NE (NE, NE)	NE (36.83, NE)
HR (95% CI)	0.447 (0.315, 0.634)	
Time to initiation of cytotoxic chemotherapy		
Event (n %)	46 (5.7%)	44 (11.0%)
Median months to chemotherapy (95% CI)	NE (NE, NE)	NE (NE, NE)
HR (95% CI)	0.435 (0.286, 0.661)	

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; NE=not estimable; **bold**=statistically significant
 Source: Table 2.27, p129; Table 2.28, p134; Table 2.30, p137; Table 2.31, p139; Table 2.32, p14; Table 2.33, p143 of the submission and Table 16, p66 of the SPARTAN CSR.

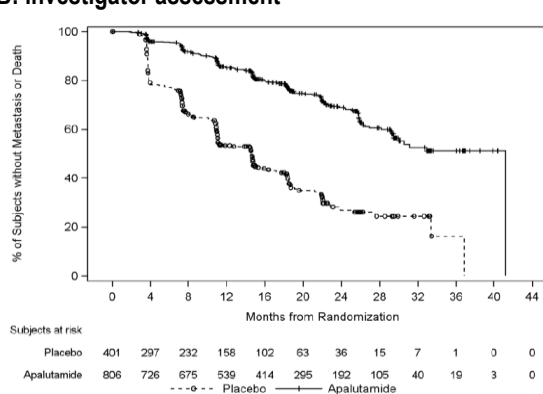
Figure 1: Kaplan-Meier curve for MFS (investigator-assessed and BICR-assessed) from SPARTAN

A: BICR



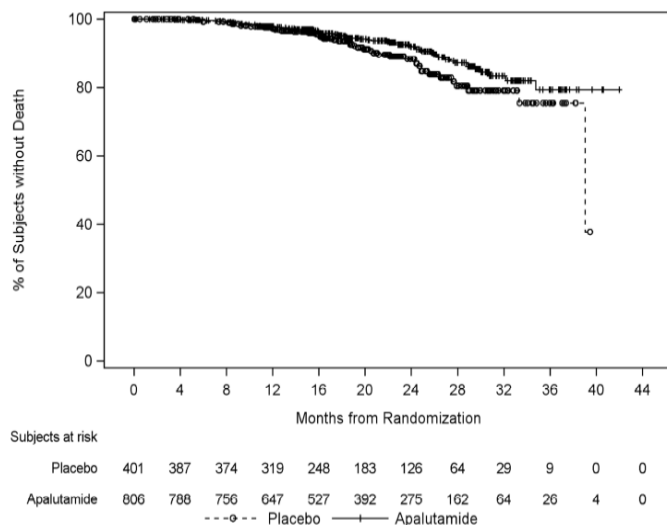
Source: Figure 2.2, p130 of the submission.

B: investigator assessment



Source: Figure 2.3, p131 of the submission.

Figure 2: Kaplan-Meier curve for OS from SPARTAN



Source: Figure 2.5, p134 of the submission.

6.11 Key points regarding the results presented above are as follows:

- There was a statistically significant advantage for apalutamide compared to placebo for all outcomes except OS. The ESC noted the lack of statistical OS benefit results in high uncertainty regarding the magnitude of benefit of apalutamide. The PSCR acknowledged that the current data set is insufficiently powered to detect statistical significance for OS difference and presented an analysis in which data from SPARTAN were pooled with that from the PROSPER enzalutamide trial. The PSCR pooled analysis reported a 26% reduction in the risk of death with a second generation antiandrogen. This pooled analysis has not been independently verified and the ESC noted that it is unknown whether pooling of data from these trials is appropriate. The ESC also noted that although this analysis achieves statistical significance the absolute magnitude of OS gain in the economic model was not supported by the available data.
- There was an increase of 24.8 months in MFS (BICR-assessed) for apalutamide-treated patients (40.51 months) compared to those treated with placebo (15.7 months). The submission noted that the median MFS for apalutamide is likely to change with further follow-up given the median has been determined by just 3 patients who reached the 40 month point. With a median of only 20.3 months of follow-up, as noted by the TGA evaluator, the data were immature and therefore the magnitude of benefit was difficult to determine. Given the switching of treatments, it may not be possible to determine if use of apalutamide improves OS. The submission acknowledged that future analyses of OS will be confounded. In addition, investigator-assessed MFS was almost a month greater for the apalutamide arm (41.2 months) while the placebo arm had approximately a month less, leading to a greater incremental difference. This was the outcome applied in the economic model and favoured apalutamide (see further discussion below). The

ESC considered that the magnitude of benefit of apalutamide is unclear given the immaturity of the data.

- The clinical significance of MFS is unclear because:
 - MFS is a radiographic parameter that does not consider symptomatic progression and its relationship with OS is uncertain.
 - A 2017 review¹¹ assessed the acceptance of MFS in non-metastatic castration resistant prostate cancer (m0CRPC) by national payers to demonstrate clinical benefit to patients. The review found that MFS as an outcome has not been considered in a health technology assessment of an oncology product; the PSCR notes MFS has now been used by the CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC), however the ESC noted the pERC recommendation stated (p4) that an OS benefit for apalutamide could not be readily assumed given that the surrogacy of MFS for OS has not been established and that the OS data observed in SPARTAN were immature.
- While there was a statistically significant advantage for apalutamide for time to symptomatic progression and time to initiation of cytotoxic chemotherapy, with greater proportions of placebo-treated patients experiencing these events, overall occurrence was low and median time to the events had not been reached by either arm in the trial. The ESC noted that in consideration of enzalutamide in patients with asymptomatic mCRPC in November 2015, the PBAC considered that the goal of earlier treatment with novel hormonal therapies was to maintain better quality of life for longer by delaying disease symptoms and delaying the toxicities from chemotherapy, rather than improving survival (Enzalutamide Public Summary Document – November 2015 PBAC Meeting, p16). Subsequently, the use of time to initiation of cytotoxic chemotherapy was considered a reasonable endpoint because, the proposed reversal of the sequence of treatments from a cytotoxic chemotherapy (docetaxel) followed by an oral androgen receptor signalling inhibitor (enzalutamide or apalutamide), was not expected to give patients substantial survival benefit but would provide meaningful improvement in quality of life by avoiding cytotoxic chemotherapy for longer (Enzalutamide Public Summary Document – March 2017 PBAC Meeting, p22). In consideration of this submission for apalutamide, the ESC considered potential improvements in quality of life from delaying time to metastatic disease and therefore symptomatic disease and cytotoxic chemotherapy would be important considerations for patients.

6.12 Quality of life (QoL) outcomes were based on the FACT-P (Functional Assessment Cancer Therapy-Prostate) and EQ-5D-3L scales. The submission concluded:

¹¹ Payer acceptability of metastasis-free survival as the primary end point in non-metastatic castration-resistant prostate cancer. Degener F, Holmstrom S, van Engen A, Naidoo S. ISPOR 22nd Annual International Meeting, May 20-24 2017, Boston USA; Poster PCN259. Sourced at: https://www.ispor.org/research_pdfs/55/pdf/PCN259.pdf

- There were similar mean changes from baseline or median time to clinically significant worsening in the FACT-P total scores and subscale scores for apalutamide and placebo-treated patients.
- There were no differences in mean change from baseline in the EQ-5D VAS between apalutamide and placebo-treated patients at most time points.
- Patients managed by watchful waiting had a gradual worsening in their QoL over time, as demonstrated by numerically more patients with a clinically significant worsening of their FACT-P or FACT-G scores at the 20-30 month time points, and due to a worsening in EQ-5D VAS over time. The submission claimed this was likely due to the progression of patients to the symptoms observed with mCRPC. There was no indication that the greater decrease from baseline for placebo-treated patients was for patients who had symptomatic progression, or what proportion of patients assessed at these points had symptomatic progression. Also, the lack of a statistically significant difference at the later time point (cycle 29) does not support the submission’s claim that the placebo-treated patients would have symptomatic progression.

6.13 Overall, there were very few differences between apalutamide-treated patients and placebo-treated patients on the QoL measures used in SPARTAN and it cannot be directly quantified by how much a move to symptomatic progression led to a worsening of scores for placebo-treated patients. The ESC considered the data were likely too immature to determine the QoL benefits of delaying symptomatic disease and cytotoxic chemotherapy.

Comparative harms

6.14 The submission claimed that apalutamide had inferior safety compared to placebo, which was supported by the evidence.

6.15 The following table provides a summary of the proportion of patients with AEs leading to dose reduction or dose interruption in the SPARTAN trial.

Table 5: Summary of key adverse events in the trials

	Apalutamide N=803	Placebo N=398	RD (95% CI)	RR (95% CI)
Patients with a TEAE leading to dose reduction or dose interruption, n (%)	262 (32.6%)	75 (18.8%)	0.14 (0.09, 0.19)	1.73 (1.38, 2.17)
Patients with a TEAE leading to dose reduction, n (%)	77 (9.6%)	7 (1.8%)	0.08 (0.05, 0.10)	5.45 (2.54, 11.71)
Patients with a TEAE leading to dose interruption, n (%)	237 (29.5%)	71 (17.8%)	0.12 (0.07, 0.17)	1.65 (1.31, 2.10)

RD=risk difference; RR=relative risk; TEAE=treatment emergent adverse event; **bold**=statistically significant

Source: Table 2.53, p182 of the submission.

6.16 There was a statistically significantly greater proportion of apalutamide-treated patients who had a dose reduction or dose interruption due to an AE during the trial. The submission did not provide any information regarding the extent of the dose reductions. Nor did the submission provide any information on the length of dose interruption.

- 6.17 The TGA evaluator noted that the higher rate and higher number of dose interruptions in the apalutamide arm of the trial (due to skin rash, diarrhoea, nausea, haematuria, hypertension) suggested that tolerability is a significant problem but this population is motivated to try and remain on treatment. The TGA evaluator went on to state that the extent to which unmasking of treatment allocation through prominent additional symptoms influenced clinicians and/or motivated patients to try and stay on treatment is unclear, but the imbalance between treatment arms for the number of treatment interruptions suggests this was a factor. As such there is potential there may have been unblinding for a proportion of patients and/or clinicians.
- 6.18 The table below provides a summary of the AEs that were observed to occur significantly more in the apalutamide arm of SPARTAN. These events have been included in the economic model.

Table 6: Adverse events included in the economic model

	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 submission.

- 6.19 The submission concluded that in general the AEs observed with apalutamide were manageable, most commonly with dose reduction or dose interruption, and few AEs resulted in permanent treatment discontinuation.
- 6.20 The economic evaluation included hospitalisation costs and emergency room visits for AEs which would indicate that at least a proportion of the AEs require substantial intervention for their management. In addition, given the limited duration of treatment with apalutamide (approximately 17 months) as noted by the TGA evaluator, there are insufficient data to enable an assessment of long term safety. In particular, the TGA noted the need for further cardiac data to assess a possible increased risk of ischaemic heart disease and cardiac failure with apalutamide.

Benefits/harms

6.21 A summary of the comparative benefits and harms for apalutamide versus placebo is presented in the table below.

Table 7: Summary of comparative benefits and harms for apalutamide and placebo

Benefits						
Metastasis-free survival^a						
SPARTAN	Apalutamide	Placebo	Absolute difference	HR (95% CI)		
12 month event-free rate	86.1%	57.9%	28.2%	0.297 (0.244,0.362)		
24 month event-free rate	68.2%	29.6%	38.6%			
36 month event-free rate	51.4%	16.5%	34.5%			
Median months MFS	40.51	15.70	24.81			
Overall survival^a						
12 month survival rate	97.9%	97.3%	0.6%	0.700 (0.472,1.038)		
24 month survival rate	92.0%	88.4%	3.6%			
36 month survival rate	79.4%	75.5%	3.9%			
Median months OS	NE	39.03	NE			
Harms						
SPARTAN	Apalutamide N=803	Placebo N=398	RR (95% CI)	Events/100 patients^a		RD (95% CI)
				Apalutamide	Placebo	
Skin rash	191 (23.8%)	22 (5.5%)	4.30 (2.81, 6.58)	24	6	0.18 (0.15, 0.22)
Fall	125 (15.6%)	36 (9.0%)	1.72 (1.21, 2.44)	16	9	0.07 (0.03, 0.10)
Fracture	94 (11.7%)	26 (6.5%)	1.79 (1.18, 2.72)	12	7	0.05 (0.02, 0.08)
Hypothyroidism	65 (8.1%)	8 (2.0%)	4.03 (1.95, 8.31)	8	2	0.06 (0.04, 0.08)
Serious infection	48 (6.0%)	9 (2.3%)	2.4 (1.31, 5.33)	6	2	0.04 (0.02, 0.06)

^a Median duration of follow-up in SPARTAN was 20.3 months.

CI=confidence interval; HR=hazard ratio; NE=not estimable; RD=risk difference; RR=risk ratio; bold=statistically significant

Source: Table 16, p66; Table 2.28, p134; Table 2.49, p176; Table 2.56, p185 of the submission. SPARTAN CSR Table 23 p79, Table 14 p63-64.

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

- Approximately 39 more patients would remain metastasis free after 24 months of treatment, however a difference in overall survival was not demonstrated.

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.

Clinical claim

- 6.23 The submission described apalutamide with background ADT as superior in terms of effectiveness compared with watchful waiting (placebo) and background ADT and inferior in terms of safety compared to watchful waiting (placebo). The ESC noted that the clinical data shows clinical benefit for apalutamide in delaying development of metastases and progression, however there was no statistically significant OS benefit demonstrated. The ESC agreed that the safety profile for apalutamide was inferior to watchful waiting.
- 6.24 The PBAC considered that the claim of superior comparative effectiveness compared with watchful waiting in improvements in MFS, rPFS and sPFS was reasonable.
- 6.25 The PBAC considered that the claim of inferior comparative safety was reasonable.

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

Economic analysis

- 6.26 The submission presented a stepped economic evaluation based on data from the SPARTAN trial and an abiraterone trial (Trial 302). A three health state Markov model was used, and the type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation are summarised in the table below.

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	█ years in the model base case versus a median duration of follow-up of 20.3 months in SPARTAN and 49.2 months in Trial 302 for abiraterone
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Health states	Three health states: high risk m0CRPC; alive with distant metastases (mCRPC) and death
Cycle length	1 month
Transition probabilities	High risk m0CRPC: Kaplan Meier estimates of MFS from SPARTAN extrapolated from █ months for apalutamide and from █ months for placebo using a Weibull function. mCRPC: Kaplan Meier estimates of OS from the placebo arm of the abiraterone 302 trial; extrapolated from █ months using a Weibull function. The same transition probabilities were applied to the apalutamide and placebo arms of the model.

Source: Table 3.1, p213-214 of the submission.

- 6.27 The ESC noted the ICER is not sensitive to the difference between 10 and 15 year time horizons, given the events happen in the early years of the model (see Figure 3 below). The ESC noted that six parametric approaches to extrapolation were undertaken and the Weibull method 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 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.

6.28 A summary of the key drivers of the economic model is provided in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
MFS	Investigator-assessed MFS data from SPARTAN was used in the m0CRPC health state. These data showed a greater benefit (median months MFS of 41.20 months) than BICR-assessed data (40.51 months). The MFS data from SPARTAN were immature.	High, favours apalutamide (However, not possible to quantify in sensitivity analysis due to structural constraints of the model).
MFS as a surrogate for OS	The submission concluded that it is biologically plausible and it is likely that MFS is a valid and reasonable surrogate for OS in patients with m0CRPC at high risk of distant metastases. The demonstration of a correlation between the surrogate (in this case MFS) and the clinical endpoint (OS) is in itself insufficient to validate a surrogate. Given the lack of a demonstrated surrogate relationship between MFS and OS, the implicit assumption of a near perfect relationship between MFS and OS in the economic model was not appropriate, and this impacted on the overall validity of the current economic evaluation.	High, favours apalutamide (However, not possible to quantify in sensitivity analysis due to structural constraints of the model).
Use of abiraterone Trial 302 data	Placebo arm data from abiraterone 302 trial was used for the mCRPC health state as there had been too few deaths in SPARTAN to allow for reliable extrapolations of survival. Although the approach to use more mature survival data was valid, the data used may have been impacted by cross-over and it was uncertain whether the sequential therapies used in Trial 302 will reflect future use. In addition, given the possibility of cross-resistance, the assumption of similar survival after metastasis could favour apalutamide (as these patients may have diminished ability to benefit from subsequent enzalutamide or abiraterone) and bias against placebo (since these patients are unlikely to have cross-resistance issues).	Moderate, favours apalutamide (However, not possible to quantify in sensitivity analysis due to structural constraints of the model).

IPD=individual patient data; MFS=metastasis-free survival; OS =overall survival

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

6.29 The submission provided a detailed discussion of the use of MFS as a surrogate outcome for OS and concluded it is biologically plausible and it is likely that MFS is a valid and reasonable surrogate for patients with m0CRPC at high risk of distant metastases. The evidence provided by the submission did not support this conclusion, for the following reasons:

- While there may be some evidence to support the biological plausibility of a surrogate relationship between MFS and OS, as noted in the Surrogate to Final Outcomes Working Group report (p22), a proposed surrogate measure is more persuasive if it is a necessary step in the development of the target clinical outcome, and is close developmentally to the target outcome. Trial evidence is yet to prove that a significant improvement in MFS is associated with equally significant gains in OS. Even after progression to metastatic disease, death is not immediate, with patients spending considerable time in mCRPC before death (e.g., the submission’s model had estimated around ■ months) thus lacking immediate proximity to death.

- Literature addressing the validity of surrogate endpoints in oncology¹² notes that the demonstration of a correlation between the surrogate (in this case MFS) and the clinical endpoint (OS) is in itself insufficient to validate a surrogate. Although a correlation has been demonstrated, there is no evidence that indicates a statistically significant dependence between MFS and OS. Furthermore, the submission's analyses suggested that only █% of variability in OS was able to be explained by MFS, therefore inadequately supporting the implicit assumption of an essentially █ relationship between MFS and OS in the model. *See also paragraph 6.11 above.*
- 6.30 The use of data from the placebo arm of the abiraterone Trial 302 to inform both the apalutamide and placebo arms in the mCRPC health state of the model was reasonable given there had been too few deaths in SPARTAN to allow for reliable extrapolations of survival. However, use of these data may have biased results, given the following:
- Approximately █% of placebo-treated patients crossed over and had received abiraterone as first subsequent therapy. Treatment switching was not discussed by the submission and was only mentioned in a table footnote. Use of abiraterone is not likely to reflect Australian clinical practice since abiraterone is only PBS listed for mCRPC after docetaxel therapy or in patients with predicted intolerance to docetaxel. Further, given the trend of using active treatments earlier in the disease pathways and issues of cross-resistance with sequential therapies, it was uncertain whether the sequential therapies in Trial 302 will reflect future use. The ESC agreed that the use of abiraterone as subsequent therapy makes the use of Trial 302 data in the model problematic.
 - The submission's statement that the application of identical transition probabilities based on the placebo arm of Trial 302 for apalutamide and placebo arms had disadvantaged apalutamide was not supported. While removal of discounting and altering the death rates in the mCRPC state had minimal impact on the ICER, potential cross-resistance between apalutamide and subsequent enzalutamide/abiraterone meant the assumption of similar survival after metastasis could favour apalutamide (as these patients may have diminished ability to benefit from subsequent enzalutamide or abiraterone) and bias against placebo (since these patients are unlikely to have cross-resistance issues).
- 6.31 The ESC agreed with the evaluation that the assumption that survival post-metastasis is the same in both treatment arms (i.e. MFS translates to OS) is not supported by the clinical data. The ESC noted that time in the metastatic state is often long, reducing the likelihood of such a relationship existing. The ESC noted that the PSCR presented the link between a range of intermediate outcomes (PFS, radiological PFS, failure free survival) and OS. The ESC noted that the pattern was highly variable with ratios ranging

¹² Institute for Quality and Efficiency in Health Care. Validity of surrogate endpoints in oncology: executive summary of rapid report A10-05, version 1.1 available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0065194/pdf/PubMedHealth_PMH0065194.pdf

between 0.16 and 0.81. The ESC considered that this variability suggests that the relationship may be specific to treatment or disease characteristics and demonstrates the uncertainty in the assumption of a surrogate relationship between MFS and OS.

6.32 The results of the economic evaluation are provided in the table below.

Table 10: Results of the stepped economic evaluation

Step and component	Apalutamide	Placebo	Increment
Step 1: trial-based costs and outcomes			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/LYG			\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Step 2: trial evidence transformed from surrogate to clinical outcome			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained (base case)			\$ [REDACTED]

Source: Table 3.41, p326 and Table 3.42, p328 of the submission.

6.33 The incremental cost/extra QALY gained estimated by the base case of the submission (\$45,000/QALY - \$75,000/QALY) is not likely to accurately represent the cost-effectiveness of apalutamide, for reasons outlined above, in particular the lack of validation of a link between MFS and OS, the use of data from Trial 302 and the failure to consider the impact of potential cross-resistance between apalutamide and subsequent enzalutamide/abiraterone. In addition, treatment costs in the model were calculated assuming a dose intensity of [REDACTED]%, which could not be verified. The PSCR stated that may overestimate the cost of apalutamide and the ICER, however no adjusted figures/revised net costs were provided in the PSCR.

6.34 The table below provides a summary of time spent in each health state in the economic model and the following figure provides Markov traces of the proportion of patients in each health state over the course of the model.

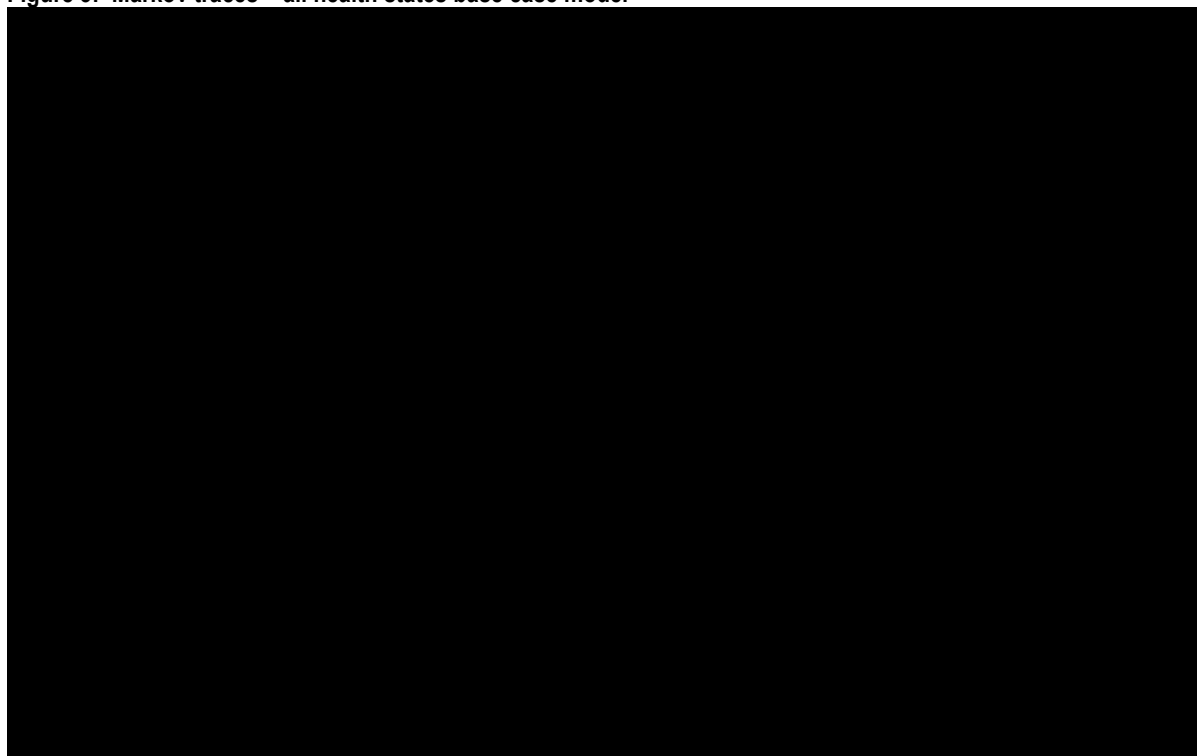
Table 11: Time spent in each health state and survival time in Trial 302

	Apalutamide	Placebo	Difference
High risk m0CRPC health state	[REDACTED] months	[REDACTED] months	[REDACTED] months
mCRPC health state	[REDACTED] months	[REDACTED] months	[REDACTED] months
Total difference between apalutamide and placebo arms in terms of time lived in model			[REDACTED] months
Survival time abiraterone Trial 302	[REDACTED] months		-

m0CRPC=non-metastatic castration resistant prostate cancer; mCRPC=metastatic castration resistant prostate cancer

Source: Section 3.7.2, p321 of the submission.

Figure 3: Markov traces – all health states base case model



APA=apalutamide, PBO=placebo

Source: Figure 3.24, p320 of the submission

- 6.35 The model estimated an overall difference in survival of [REDACTED] months (or [REDACTED] years) between apalutamide and placebo. This suggests with respect to OS a level of benefit that is unprecedented for contemporary pharmacological treatments in prostate cancer and far exceeded estimated OS gains from RCTs for enzalutamide, abiraterone and docetaxel in mCRPC (around 4 months additional survival) or docetaxel in hormone sensitive prostate cancer (approximately 10 months additional survival). Given the SPARTAN trial did not demonstrate a statistically significant difference in OS between apalutamide and placebo, it should be considered whether this estimated gain in OS was reasonable. The ESC considered the [REDACTED] year difference in OS is highly implausible, especially in the absence of a demonstrated statistically significant benefit for OS, and given the magnitude of OS benefits derived from other CRPC therapies.
- 6.36 The PSCR acknowledged the uncertainty of the OS benefit and adjusted the death rate in the apalutamide arm by [REDACTED]% such that the ratio of median time spent in MFS to the median time spent in the progressive disease state for apalutamide is reduced from [REDACTED] to [REDACTED], which reduced the modelled gain in MFS relative to OS to [REDACTED]. This resulted in a reduction in OS gain from [REDACTED] months to [REDACTED] months and an increase in ICER from \$45,000/QALY – 75,000/QALY to \$45,000/QALY – 75,000/QALY. The ESC noted the revised model has not been independently evaluated. The ESC considered that the revised assumption is not supported by evidence and appears to be optimistic compared with the trial data where the HR for MFS is 0.30 and the HR for OS is 0.70.

The lack of a demonstrated surrogate relationship between MFS and OS called into question the overall validity of the economic evaluation presented in the submission. The pre-PBAC response argued that the modelled gain in OS presented in the PSCR was consistent with the pooled apalutamide and enzalutamide trial data for OS.

- 6.37 The ESC considered an economic model based on time to symptomatic progression and/or the time to initiation of cytotoxic chemotherapy would provide a more robust basis for assessment of the cost-effectiveness of apalutamide. The pre-PBAC response commented that the economic model currently captures the delay in intermediate outcomes of development of symptoms and initiation of chemotherapy in the delay to metastases and death. The pre-PBAC response also argued that patients who die from prostate cancer, die due to the sequelae of metastases and therefore to assume that the increased MFS would not result in any increase in OS is unreasonable. The pre-PBAC response indicated that the sponsor would not submit an economic model that does not include OS benefit for apalutamide. *See also paragraph 6.11 above.*

Drug cost/patient/month and year

- 6.38 The table below provides apalutamide and ADT costs for one month of treatment and one year of treatment.

Table 12: Drug cost^a per patient for one month and for one year

	Cost of treatment	
	One month	One year
Apalutamide ^b	\$ [REDACTED]	\$ [REDACTED]
Androgen deprivation therapy (ADT)	\$ [REDACTED]	\$ [REDACTED]
Total apalutamide+ADT costs	\$ [REDACTED]	\$ [REDACTED]

^a All costs have been rounded to the nearest dollar.

^b Apalutamide costs assume use of the effective price (\$ [REDACTED]), [REDACTED] scripts per month and a dose intensity of [REDACTED]%. This dose intensity was calculated by the submission based on compliance data from SPARTAN.

Source: Excel workbook 'Apalutamide mOCRPC Economic Model'.

- 6.39 The cost of one month of treatment with apalutamide and background ADT is \$ [REDACTED]. The estimated yearly cost is \$ [REDACTED]. The ESC noted the economic model estimated a mean duration of [REDACTED] months with an associated (undiscounted) cost of \$ [REDACTED]. The apalutamide costs were calculated based on a dose intensity of [REDACTED]%, which the submission stated was based on factors such as dose reductions or temporary interruptions in response to AEs. However the submission did not provide any detail on the calculation of dose intensity and the proportion used could not be verified. As the SPARTAN CSR did not report the duration of dose interruption or dose reduction, it is difficult to estimate what actual usage of apalutamide will be.

Estimated PBS usage & financial implications

6.40 This submission was considered by DUSC. The submission applied an epidemiological approach to estimate the number of patients eligible for treatment with apalutamide. The prevalent population were those who have been diagnosed with mOCRPC and are at high risk of distant metastases up to the end of Year 0, while patients with newly diagnosed mOCRPC at high risk of distant metastases in Years 1 through 6 comprised the incident population.

6.41 Cost offsets for changes in the use of other medicines 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 are used subsequent to apalutamide for the treatment of mCRPC. The table below provides the estimated usage and financial implications for the first 6 years of listing.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
Prevalent patients						
Incident patients						
Total treated						
Number of scripts dispensed ^a						
Estimated financial implications of apalutamide						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Cost offsets for change in use of other medicines	-\$	-\$	-\$	-\$	-\$	-\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$	\$

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

Source: Table 4.5, p353, Table 4.6, p354, Table 4.8, p356, Table 4.21, p378 of the submission and Excel workbook 'Apalutamide mOCRPC financial estimates model Years 1 to 6'.

The redacted table shows that at Year 6 the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$60 - \$100 million per year.

6.42 At year 5, the estimated number of patients was [redacted]. Due to a large number of existing prevalent patients the estimated number of patients in year 1 was [redacted]. In the pre-PBAC response, this was reduced to [redacted] patients in year 5 and [redacted] in year 1 once the 5% of patients not meeting the WHO performance status criterion were excluded. The revised estimated net cost to the PBS/RPBS over the first 5 years of listing was more than \$100 million.

6.43 DUSC considered the estimates presented in the submission to be highly uncertain and likely to be underestimated. The main issues were:

- The assumptions and data informing the estimates of incidence and prevalence of m0CRPC could not be fully verified. The DUSC presented alternative models based on 1) a prevalence approach and 2) forecasting the treated population based on the PBS analysis cohort provided in the submission; both resulted in higher estimates of the financial impact than those presented in the submission. The estimated PBS expenditure on apalutamide increased to more than \$100 million over 5 years (more than \$100 million over 6 years) for approach 1 and to more than \$100 million over 5 years (more than \$100 million over 6 years) for approach 2, compared with the submission's estimate of more than \$100 million over 5 years (more than \$100 million over 6 years).
- Time on therapy with apalutamide was modelled based on metastatic free survival data from the SPARTAN trial. It is uncertain whether this trial-based assumption will reflect use in clinical practice.
- Usage of apalutamide and change in usage of PBS-listed drugs and MBS items were based on outcomes from the economic model. Given that the economic model applied immature data from the SPARTAN trial in conjunction with data from an abiraterone trial for the metastatic CRPC health state, the model outcomes may not reflect the impact of apalutamide in clinical practice. Hence, the change in usage for other agents as estimated in the submission may not represent what will occur in clinical practice.
- Compliance to apalutamide therapy was likely to have been overestimated. The submission applied a dose intensity of [REDACTED]% sourced from the SPARTAN trial. While the SPARTAN trial had a considerable proportion of apalutamide-treated patients with dose interruptions (75%) or dose reduction (20%), the submission did not provide detail on the calculation of this dose intensity and the usage of apalutamide in clinical practice will be difficult to estimate. The dosage requires four tablets; older persons may not be able to readily take this regimen.

6.44 The pre-PBAC response acknowledged the uncertainty in the financial estimates and proposed a risk share arrangement (RSA) with [REDACTED]% subsidisation for expenditure over the proposed caps. The caps for the proposed RSA were based on estimates in the submission after removing [REDACTED]% of patients to account for patients who do not have a WHO performance score of 0 or 1, and then removing an additional [REDACTED]% of apalutamide units. The resulting cap equates to more than \$100 million over 5 years.

Quality Use of Medicines

6.45 The submission provided a description of activities to support the quality use of medicine. The submission listed factors to ensure the quality use of apalutamide and provided discussion of groups of people who play a role in the appropriate use of apalutamide (patients, prescribers and dispensers). The submission stated that each of these groups will be provided appropriate education, resources and support from the sponsor to promote appropriate prescribing and use of apalutamide.

- 6.46 DUSC considered there is a likelihood of cross-resistance if abiraterone or enzalutamide are used sequentially after prior treatment with 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 treatment of non-metastatic castration-resistant prostate cancer. The PBAC considered that apalutamide provided a substantial benefit to some patients in delaying metastases but the overall survival benefit was uncertain. The PBAC advised that the incremental cost-effectiveness ratio was underestimated due to the estimated gain in overall survival being implausibly high in the economic analysis presented.
- 7.2 The PBAC noted that the restriction appropriately reflected the trial population and was consistent with clinical guidelines. The PBAC agreed with ESC that it was appropriate to add a clinical criterion specifying that patients must have a WHO performance status of 1 or less, consistent with patients included in the SPARTAN trial.
- 7.3 The PBAC noted that treatment of high risk mOCRPC patients with apalutamide is consistent with a trend in using active treatments earlier in the pathway. The PBAC noted that the populations in the SPARTAN trial for apalutamide and the PROSPER trial for enzalutamide comprised of patients with rising PSA without detectable metastases on standard imaging and considered that a PSMA scan may show that these patients actually have early occult metastatic disease not detectable on standard imaging.
- 7.4 The PBAC considered the natural history of prostate cancer suggests that over time patients are likely to develop disease progression despite novel hormonal therapies and the impact of resistance to subsequent treatments on OS is uncertain. The PBAC considered that there is insufficient data demonstrating the degree of efficacy of abiraterone and enzalutamide after apalutamide, and the most appropriate treatment pathway remains uncertain.
- 7.5 The PBAC considered that watchful waiting was the appropriate comparator as patients with mOCRPC are currently managed with observation on standard ADT and are not treated with docetaxel, enzalutamide or abiraterone until there is evidence of metastatic disease. 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, are also likely to become available for this population.
- 7.6 The PBAC noted the consumer comments and acknowledged the potential quality of life benefits associated with delaying metastasis and symptomatic progression.
- 7.7 The PBAC noted that efficacy data for apalutamide was based on the SPARTAN trial (N=1207), which was a randomised, double-blind, multicentre trial comparing apalutamide and placebo, each in combination with ADT in patients with mOCRPC at high risk of developing distant metastases. The PBAC noted that the cut off for the data set presented was May 2017 with median follow-up of 20.3 months, and that

future data sets will be confounded by cross-over of patients in the placebo arm to apalutamide treatment.

- 7.8 The PBAC considered that the clinical data shows clinical benefit for apalutamide in delaying development of metastases and progression, however there was no statistically significant OS benefit demonstrated. The PBAC noted that there was a considerable increase in MFS (BICR-assessed) of 24.8 months for apalutamide-treated patients (40.51 months) compared to those treated with placebo (15.7 months) and that the PFS benefit was similar. The PBAC noted that there was a statistically significant advantage for apalutamide for time to symptomatic progression and time to initiation of cytotoxic chemotherapy, however the median time to the events had not been reached by either arm in the trial. The PBAC considered that the time to symptomatic progression is a clinically relevant endpoint. The PBAC noted that the OS benefit for apalutamide was not statistically significant as the trial data are 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. The PBAC considered that the clinical 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.
- 7.9 The PBAC considered that the clinical claim of inferior safety compared with watchful waiting was appropriate. The PBAC noted that significantly more patients treated with apalutamide experienced fatigue, rash, falls, fracture and hypothyroidism, and that the safety data were limited as the trial data are immature. The PBAC noted that there were few differences between apalutamide-treated patients and placebo-treated patients on the QoL measures used in SPARTAN, however longer term data for the impact on HRQoL was limited. The PBAC considered that the safety profile of apalutamide is likely to be similar to that of enzalutamide, with which there is substantially more clinical experience in the mCRPC setting.
- 7.10 The PBAC noted the main areas of uncertainty in the model as identified in the evaluation and considered by ESC. The PBAC agreed with the evaluation and the ESC that the use MFS as a surrogate for OS in the model was not appropriate and the assumption of a [REDACTED] relationship between MFS and OS was not supported by the clinical data. 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. The PBAC noted that the PSCR presented an adjusted model that assumed a difference in OS between the apalutamide and placebo treatment arms, which reduced the modelled gain in MFS relative to OS to [REDACTED], reducing the OS gain for apalutamide from [REDACTED] months to [REDACTED] months. The PBAC considered that the magnitude of OS gain remained highly uncertain and that the estimated gains in OS in the 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.
- 7.11 The PBAC noted the DUSC's advice that the size of the treated population and estimates of the prevalent mOCRPC populations are unknown, the treatment duration

is uncertain as it is based on immature MFS data and the dose intensity is uncertain. The PBAC noted that updated estimates of the financial impact were provided in the pre-PBAC response, with patient numbers reduced by 5% to account for patients who do not meet the WHO performance status criterion. The PBAC considered that, given the average age of this population, the proportion of patients with WHO performance status ≥ 2 may be higher than 5%. The PBAC agreed that the dose intensity appears 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.

- 7.12 The PBAC noted the risk sharing arrangement (RSA) proposed in the pre-PBAC response, with ■■■% subsidisation for expenditure over the proposed caps. The PBAC advised that a RSA is likely to be required to address the uncertainty in patient numbers and treatment duration.
- 7.13 The PBAC advised that any resubmission would be a major submission and 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 the efficacy parameters of MFS/PFS, time to symptomatic progression and time to chemotherapy would offer a method of assessing the clinical benefit and cost-effectiveness of apalutamide. 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 considered that a reduced cost per course would be appropriate given uncertainty in the dose intensity and duration of treatment. The PBAC advised that in the absence of a demonstrated OS benefit, an ICER between \$15,000 – \$45,000/QALY and \$45,000 - \$75,000/QALY based on a 10 year time horizon is likely to be considered reasonable. The PBAC considered that financial estimates should include increased cost offsets for limiting sequential enzalutamide/abiraterone use unless further data demonstrating the efficacy of sequential therapy becomes available. The PBAC also noted that uncertainties in the patient numbers would need to be addressed.
- 7.14 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.

Sponsor's Comment

The sponsor had no comment.