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

1 Purpose of submission

1.1 The Standard Re-Entry resubmission requested a General Schedule Authority Required (Telephone) listing of apalutamide for metastatic hormone sensitive prostate cancer (mHSPC[1]) in patients with (i) low volume (LV) disease, or (ii) high volume (HV) disease but are unsuitable for docetaxel. This was unchanged from the November 2021 submission. The requested restriction wording was tightened in defining docetaxel unsuitability (see Requested Listing section).

1.2 Apalutamide is to be used in combination with androgen deprivation therapy (ADT). As with the November 2021 submission, the listing was requested on a cost utility basis versus ADT alone. Table 1 summarises the components of the overall clinical claim addressed by the resubmission.

[1] Note metastatic hormone sensitive prostate cancer (mHSPC) is also referred to in the literature as metastatic castration sensitive prostate cancer (mCSPC). To be consistent with the submission, the Public Summary Document (PSD) will use the terminology mHSPC.

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

Component	Description
Population	Patients with mHSPC who have (i) low volume disease or (ii) high-volume disease who are too frail (as assessed by ECOG score ≥ 2) and/or with comorbidities or contraindications that preclude chemotherapy use.
Intervention	Apalutamide is administered orally at a dose of 240 mg daily (as 4 x 60 mg tablets) in addition to ADT.
Comparator	Main comparator: ADT which is comprised of LHRH agonists or an antagonist or surgical ADT (i.e., orchidectomy).
Outcomes	Radiographic progression free survival (rPFS), overall survival (OS), time to initiation of cytotoxic chemotherapy, adverse events (AEs), and quality of life (QoL).
Clinical claim	In patients with mHSPC who have (i) low volume disease or (ii) high-volume disease who are too frail and/or have comorbidities or contraindications that preclude chemotherapy use, apalutamide when used in addition to ADT demonstrates superior comparative effectiveness compared with ADT monotherapy (referred to placebo + ADT in the TITAN trial) as assessed by statistically and clinically significant improvements in rPFS, OS, and time to initiation of cytotoxic chemotherapy. Apalutamide + ADT is associated with additional AEs compared with ADT monotherapy (i.e. placebo + ADT) and therefore is associated with an inferior safety profile. However, these AEs are mild to moderate in severity, manageable (predominantly managed by dose reduction or temporary dose interruption), do not require discontinuation of apalutamide, are unlikely to impact patients HRQoL and are largely consistent with treatment with ADT. As such clinicians are familiar with these AEs and thus are experienced in their management and their prevention.

Blue shading represents information previously considered by the PBAC.
Source: Table 1-1, p12 of the submission.
ADT=androgen deprivation therapy; ECOG=Eastern Cooperative Oncology Group (ECOG) Performance Status score; HRQoL=health-related quality of life; LHRH=luteinising hormone releasing hormone; mHSPC=metastatic hormone sensitive prostate cancer; OS=overall survival; rPFS=radiographical progression free survival

1.3 At the November 2021 meeting, the PBAC considered apalutamide use in the HV population would result in similar OS outcomes and improved tolerability compared to docetaxel (paragraph 7.4, apalutamide mHSPC Public Summary Document (PSD), November 2021). Therefore, the PBAC advised in November 2021 that any future resubmission should (i) revise the PBS restriction to also include HV mHSPC patients who were fit for chemotherapy and, as such, nominate docetaxel plus ADT as a relevant comparator; and (ii) present revised economic model and financial estimates (paragraph 7.18, apalutamide mHSPC PSD, November 2021).

1.4 While acknowledging the PBAC's requests, the resubmission stated that the low and generic price for docetaxel meant that an economic comparison to docetaxel in all fit HV mHSPC patients resulted in a weighted price for apalutamide across all patients in the range of $ to $ per month (see paragraph 6.18). This was stated to be not acceptable to the sponsor.

1.5 The resubmission maintained limiting treatment to HV mHSPC patients who are unable to receive docetaxel was appropriate. The resubmission stated that this group has high clinical need for additional therapy as they can currently only receive ADT, and hence, ADT was the appropriate comparator. The resubmission proposed a revised PBS restriction to better exclude chemotherapy fit patients and target patients who cannot receive docetaxel.

2 Background

Registration status

2.1 Apalutamide was registered by the TGA on 18 January 2021 for the following indication:

"For the treatment of patients with:

- Metastatic castration sensitive prostate cancer or
- Non-metastatic, castration-resistant prostate cancer"

2.2 Apalutamide was recommended by the PBAC for use in non-metastatic castration-resistant prostate cancer (m0CRPC) in November 2021.

Previous PBAC consideration

2.3 Apalutamide was previously considered for treatment of mHSPC by the PBAC in November 2021. Table 2 summarises the key concerns identified in the November 2021 submission and the response taken by the resubmission.

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

Component	Matter of concern raised at the November 2021 PBAC meeting	How the resubmission addresses the concern
Requested restriction	The PBAC considered that a broad restriction allowing use in all fit mHSPC patients was appropriate given the clinical evidence had demonstrated efficacy in both the LV and HV populations (para 7.5, apalutamide mHSPC, PBAC PSD, November 2021).	The requested restriction was revised to better target HV mHSPC chemotherapy unsuitable patients based on the docetaxel PI contraindications, the NICE NHS docetaxel policy statement and NICE guidance of apalutamide for mHSPC (NICE 2021). The resubmission argued that the price of apalutamide for the entire population was not acceptable to the sponsor, so the preference was to tighten the restriction wording to limit use in patients who are unsuitable for docetaxel.
Clinical evidence & clinical claim	The PBAC considered that the claim of superior comparative effectiveness for apalutamide plus ADT over ADT monotherapy based on the TITAN trial was reasonable for patients with LV disease, but not for patients with HV disease. The trial did not provide direct evidence for the requested PBS population of patients with HV disease who are unsuitable for chemotherapy. The PBAC considered that while apalutamide was likely to result in some benefit compared to placebo in patients with HV disease who are unfit for chemotherapy, the degree of benefit was likely reduced compared to that presented in the submission due to their competing comorbidities (para 7.11, apalutamide mHSPC, PBAC PSD, November 2021).	No new clinical data were presented in the resubmission. The final analysis from TITAN was presented in the previous submission. The resubmission stated that uncertainty in the clinical benefits of apalutamide was addressed in the modelled economic evaluation through the use of conservative OS input parameters.

Component	Matter of concern raised at the November 2021 PBAC meeting	How the resubmission addresses the concern
Economic evaluation	To address uncertainty in longer term OS benefits in both the LV and HV models. The PBAC recommended the following changes to the base case economic models (para 7.15-16, apalutamide, PBAC PSD, Nov 2021): • Reduce time horizons to 10 years in LV model and 5 years in HV model. • Apply HV subgroup data in the HV model • Apply Gompertz extrapolations of OS in both models. • Convergence of OS from 5 years in LV model, 44 months in HV model. • ICERs for both models should be in the range of $40-45k per QALY gained. • Include an economic analysis with docetaxel as a comparator for the 75% HV patients, in line with the PBAC recommendation that an expanded listing to include HV patients who are suitable for docetaxel treatment would be appropriate.	The resubmission adopted the PBAC's recommendations in its revised modelled economic evaluation base case except for: • Convergence of OS. The resubmission argued this was too conservative for the base case. Results with convergence were presented in sensitivity analyses. • An economic analysis versus docetaxel as comparator for 75% of HV patients.
Financial estimates & risk share	The PBAC considered the financial impact ($200 million to < $300 million over five years, based on pre-PBAC response estimates) to be high and likely overestimated. There was also a high risk of use in the HV population who were suitable for docetaxel which had not been adequately addressed by the submission. The PBAC considered the proposed [redacted]% rebate above the proposed expenditure caps did not mitigate this risk. The PBAC considered a resubmission should present revised financial estimates consistent with revised restriction to include all fit mHSPC patients and include docetaxel plus ADT as a relevant comparator for chemotherapy suitable HV patients (paras 7.17 and 7.18, apalutamide mHSPC, PBAC PSD, November 2021).	The financial estimates were revised incorporating the following: small reduction in effective price, assuming mHSPC patients initiate docetaxel within 6 months of ADT, proportion with HV disease unsuitable for chemotherapy, proportion treated with docetaxel, uptake rates for LV and HV chemotherapy unsuitable patients. The resubmission proposed a lowering of the annual subsidisation cap and an increased rebate of [redacted]% for the Commonwealth payment above the annual subsidisation cap.

Source: Table 1-8, pp18-20 of the resubmission.
ADT=androgen deprivation therapy; ECOG=Eastern Cooperative Oncology Group (ECOG) Performance Status score HV=high volume; ITT=intention-to-treat; LV=low volume; mHSPC=metastatic hormone sensitive prostate cancer; OS=overall survival; PI=product information, RSA=risk sharing arrangement; PSD=public summary document.

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

3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
APALUTAMIDE Oral tablet, 60 mg	1	120	5	$3,714.52 (published) $[redacted]^ (effective)	ERLYAND® Janssen-Cilag Pty Ltd

Blue shading represents information previously considered by the PBAC.
Source: Table 1-10, p27 of the resubmission.
^ Using the July 2021 Pricing calculator (v38), the effective DPMQ for apalutamide is $[redacted]

Category / Program:	GENERAL – General Schedule (GE)
Prescriber type:	☒Medical Practitioners
Condition:	Castration sensitive metastatic carcinoma of the prostate
PBS Indication:	Castration sensitive metastatic carcinoma of the prostate
Treatment phase:	**Initial and Initial - Grandfathered patients**
Restriction:	☒Authority Required – Telephone
Clinical criteria:	Patient must have low volume metastases defined as no visceral metastases and less than 4 bone lesions OR Patient must be unsuitable for docetaxel *as per clinical assessment* *AND* *Treatment commences ≤ 6 months of treatment initiation with androgen deprivation therapy* AND Treatment must be used in combination with androgen deprivation therapy AND *Patient must only receive treatment with one novel hormonal drug per lifetime* *OR* *Patient must only receive treatment with a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation* AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug
Prescriber Instructions:	*An assessment for docetaxel unsuitability should consider the below and the patient must meet at least one the conditions below:* Contraindications: Hypersensitivity, Severe liver impairment, or Neutrophil count < 1500 uL. *Significant cardiovascular or respiratory disease comorbidity, where prostate cancer is unlikely to be the only life-limiting illness.* Peripheral neuropathy, *Poor bone marrow function,* *Poor cognition which leads to a decreased ability to understand treatment options or make a decision, or* ECOG performance score status of at least 2.
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 *Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide.*
Treatment phase:	**Continuing**

Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Treatment must be used in combination with androgen deprivation therapy AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug

Blue shading represents information previously considered by the PBAC.
Italicised text represents new and revised wordings in the resubmission changed from the November 2021 submission.
Source: Tables 1-11 to 1-12, pp29-31 of the resubmission.

3.1 The resubmission proposed a small reduction in the effective DPMQ of apalutamide to $ (previously $), based on an ex-manufacturer price of $. The effective AEMP was the weighted average price for apalutamide from the two economic models ($ in the LV population and $ in the HV chemotherapy unsuitable population). The resubmission assumed that due to the longer duration of therapy in LV patients, % of prescriptions would be for LV patients and % would be for HV patients over the -year risk sharing arrangement (RSA) period. Revisions to the uptake in the pre-PBAC response (see paragraph 7.10) resulted in % of prescriptions for LV and % for HV.

3.2 The resubmission maintained its request for a grandfathering restriction for an estimated < 500 patients enrolled in a planned early access program (EAP), planned to start before the PBS listing of apalutamide. The EAP will have similar eligibility criteria to the proposed PBS restriction (consistent with the key eligibility criteria for the TITAN trial).

3.3 The requested restriction remained largely unchanged from the November 2021 submission, but was modified in the following aspects:

- Additional clinical criteria ensuring treatment must commence ≤ 6 months of treatment initiation with ADT. The ESC considered that this change was appropriate and aligned with the TITAN trial.
- Clarified the wording around once in a lifetime use of NHAs on PBS to state that switches from alternate NHAs due to severe intolerance would be permitted. Darolutamide recommended for m0CRPC in July 2021 was also added to the list of available NHAs.
- Entirely modified the clinical criteria to assess unsuitability for docetaxel. In the new criteria patient must meet at least one of the following conditions:
  - contraindications (hypersensitivity, severe liver impairment or neutrophil count < 1500 µL) or
  - significant cardiovascular or respiratory disease comorbidity where prostate cancer is unlikely to be the only life-limiting illness, or
  - peripheral neuropathy, or
  - poor bone marrow function, or
  - poor cognition that leads to decrease ability to understand treatment options or make decisions, or
  - ECOG performance status of at least 2. The Pre-Sub Committee Response (PSCR) reiterated that the criterion of an ECOG performance status of 2 or less

specifically related to the assessment of docetaxel unsuitability and should only apply to the HV population.

3.4 In November 2021, the PBAC considered that the restrictions were inadequate to exclude use in patients with HV mHSPC who were suitable for docetaxel as the listed contraindications and comorbidities for docetaxel unsuitability were very broad and did not represent absolute contraindications to docetaxel (paragraph 7.5, apalutamide mHSPC PSD, November 2021).

3.5 Based on prior PBS experience with enzalutamide and abiraterone use in mCRPC, in November 2021 the PBAC considered that the use of apalutamide in HV mHSPC patients who are fit for docetaxel treatment was likely as:

- the submission did not provide a strong clinical rationale for excluding these patients from accessing apalutamide, particularly as apalutamide is effective in treating HV disease and may be preferred by patients due to better safety compared to docetaxel. The PSCR stated that docetaxel plus ADT remained the most clinically appropriate choice for patients with HV disease who are fit to receive docetaxel as there is no guarantee that these patients will be fit for docetaxel in the metastatic castration resistant prostate cancer (mCRPC) stage. The pre-PBAC maintained that docetaxel is likely to continue to be used in mHSPC for those patients who are suitable even if apalutamide was available given the once-in-a-lifetime novel hormonal agent (NHA) PBS rule and hence preserving of these agents for use at the mCRPC stage. The pre-PBAC response also noted evidence from the retrospective registry-based study by Delanoy et al. (2018)[2] which found that overall survival was shorter when docetaxel was used after NHA versus the reverse sequence; and
- it was noted at the sponsor hearing, that the clinician discussed the difficulty in defining which patients are unsuitable for docetaxel. The clinician stated that age and ECOG status are not sufficient to determine this, and that frailty and comorbidities were highlighted as the most important factors that were taken into consideration by oncologists when treating these patients (paragraph 6.1, apalutamide mHSPC PSD, November 2021).

3.6 The resubmission stated that the revised criteria were based on the contraindications included in the docetaxel Product Information, the NICE NHS docetaxel policy statement, and the NICE UK (2021) guidance for mHSPC. NICE UK (2021) guidance recommended apalutamide plus ADT for mHSPC in patients who cannot have docetaxel and included guiding criteria to identify patients who are unsuitable or contraindicated to docetaxel. However, NICE also noted that defining the patient group for whom docetaxel is unsuitable was complicated and that many factors other

[2] Delanoy N, Hardy-Bessard A, Efstathiou E, et al. Sequencing of taxanes and new androgen-targeted therapies in metastatic castration-resistant prostate cancer: results of the International mulitcentre retrospective CATS database. European Urology Oncology. 2018;1:467-475.

than performance status (e.g. ECOG) may affect whether a patient could have docetaxel. The guidance stated that identifying patients for whom docetaxel was unsuitable or contraindicated should be based on a clinical framework that considered the risk factors of individual patients (pp5-6, NICE UK 2021 Final appraisal document). Given the difficulty in defining the subgroup of mHSPC patients who are chemotherapy unsuitable, the ESC considered that the resubmission's requested restriction would allow use in some fit mHSPC patients, particularly as some criteria (e.g., poor cognition that leads to decreased ability to understand treatment options) were qualitative and thus, the assessment outcome can vary depending on the assessor.

3.7 The PSCR stated that the Secretariat proposed definition for HV disease (visceral metastases or at least 4 bone metastases including at least one outside the vertebral column or pelvis) was reasonable for inclusion in the restriction.

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

4 Population and disease

4.1 mHSPC is a stage of advanced prostate cancer when the cancer has spread past the prostate but the tumour is sensitive/responds to ADT. Metastatic prostate cancer is incurable and patients with mHSPC eventually progress with the tumour becoming castration resistant. The goal of treatment is to delay progression to mCRPC and prolong survival. ADT (lowering the serum testosterone to castrate levels) is an integral part of the initial treatment of men with mHSPC. Recent evidence also supports the use of additional systemic therapies including docetaxel (a chemotherapeutic agent) and NHAs (abiraterone, enzalutamide and apalutamide) in combination with ADT for initial therapy of men with advanced disease. In November 2021, the PBAC noted that NHAs are already PBS-funded for mCRPC and non-metastatic castrate-resistant prostate cancer (m0CRPC). Thus, the PBAC considered that the potential PBS listing of apalutamide in the mHSPC setting would have the effect of shifting NHA treatment to earlier in the treatment pathway, increasing treatment durations compared with NHA current use (paragraph 7.3, apalutamide mHSPC PSD, November 2021).

4.2 The populations identified by the resubmission to be eligible to receive apalutamide therapy were those with:

- LV disease – no visceral metastases and less than 4 bone metastases, or
- HV disease – visceral metastases or at least 4 bone metastases including at least one outside the vertebral column or pelvis and who are too frail and/or contraindicated or have comorbidities that preclude chemotherapy (chemotherapy unsuitable).

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

5 Comparator

5.1 The resubmission maintained that ADT alone (also referred to as placebo plus ADT in the clinical trial) was the appropriate comparator. ADT comprised of luteinizing hormone-releasing hormone (LHRH) agonists or an antagonist or surgical ADT (i.e. orchidectomy).

5.2 In November 2021 the PBAC considered that the nomination of ADT as the main comparator was only reasonable if patients with HV disease accessing treatment were truly docetaxel unsuitable, otherwise docetaxel plus ADT would be an appropriate comparator for patients with HV mHSPC (paragraph 7.6, apalutamide mHSPC PSD, November 2021).

5.3 The main arguments provided in the resubmission in support of the nomination of ADT alone were that:

- the requested restriction was changed to better target patients with mHSPC who are unsuitable for docetaxel. These patients can only receive ADT on the PBS and will not receive docetaxel chemotherapy.
- a cost-minimisation approach of apalutamide to docetaxel with cost-offset scenarios resulted in a potential value range of apalutamide of $ to $ (see paragraph 6.18). The resubmission stated that this price was unacceptably low and hence, the requested restriction was revised to limit use to HV mHSPC chemotherapy unsuitable patients.

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 (21), health care professionals (7), consumer group organisations (8) and medical organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with apalutamide plus ADT including the improved efficacy in terms of overall survival compared to the current standard of care, ADT. The PBAC also noted that a number of comments described the improved quality of life associated with apalutamide +ADT compared to docetaxel or other chemotherapy including improved tolerability and the ease of taking an oral medication compared to injectable chemotherapy. The PBAC noted that input was received from a number of prostate cancer support groups: Prostate Cancer Foundation of Australia, Bathurst District Prostate Cancer Support Group, Prostate Cancer Support Group ACT, South Eastern Prostate Cancer Support Group, Wagga Wagga Prostate Cancer Support Group, Westmead Prostate Cancer Support Group, Nepean Blue Mountains Prostate

Cancer Support Group and Latrobe Valley Prostate Support Group.

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 "highest priority for PBS listing" on the basis of the TITAN trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for apalutamide + ADT, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[3], based on a comparison with ADT plus placebo.

Clinical trials

6.4 The ESC noted that no new clinical data were presented in this resubmission. The November 2021 submission had presented the results of the interim and final analyses from the TITAN trial. The median duration of follow-up at the final data analysis was 43.8 months.

6.5 Details of TITAN were unchanged from the November 2021 submission and are represented in the table below.

Table 3: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
TITAN NCT02489318	A phase 3 randomised, placebo-controlled, double-blind study of apalutamide plus androgen deprivation therapy (ADT) versus ADT in subjects with metastatic hormone sensitive prostate cancer (mHSPC). Final Report of overall survival, efficacy and safety	12 February 2021
	(Agarwal et al. 2019a). 'Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study'	Lancet Oncology, 20(11):1518-1530
	(Chi et al. 2019). 'Apalutamide for metastatic, castration-sensitive prostate cancer'	New England Journal of Medicine, 381(1):13-24

Blue shading represents information previously considered by the PBAC.
Source: Table 2, apalutamide mHSPC, PBAC PSD, November 2021.

6.6 The key features of TITAN (unchanged from November 2021) are presented in the table below. The intention to treat (ITT) population in TITAN consisted of two pre-specified subgroups defined by disease volume at baseline: LV disease defined as no visceral metastases and < 4 bone lesions; and HV disease (the complement population).

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

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	Modelled evaluation
Apalutamide vs placebo (standard of care)							
TITAN	1052	R, MC, PC, DB, 22-44 mths#, OL extension 3 years^	Unclear	Apalutamide 4x60 mg daily plus ADT Placebo daily plus ADT	mHSPC	1°: rPFS, OS 2°: pain progression, SREs, initiation of chemotherapy	rPFS

Blue shading represents information previously considered by the PBAC.

Source: Table 3, apalutamide mHSPC, PBAC PSD, November 2021.

DB=double blind; MC=multi-centre; mHSPC=metastatic hormone sensitive prostate cancer; OL=open label; OS=overall survival; rPFS=radiographic progression-free survival; R=randomised; SRE=skeletal-related event

Median follow-up of interim analysis was 22.7 months and final data analysis was 43.8 months. Following review of data (primary analysis of rPFS and interim analysis of OS) in November 2018, trial investigators decided to unblind the study and patients randomised to placebo could crossover to receive OL apalutamide in the OL extension phase. The final analyses were done in September 2020.

^ The OL extension phase allow patients to receive active drug (apalutamide plus ADT) for approximately 3 years. Patients previously receiving placebo in the Treatment Phase will be allowed to receive apalutamide.

Comparative effectiveness

6.7 Key clinical evidence from TITAN is summarised below.

Table 5: OS and rPFS in TITAN (unadjusted for treatment switching)

	ITT		LV mHSPC		HV mHSPC	
Outcome[a]	**APA**	**PBO**	**APA**	**PBO**	**APA**	**PBO**
	N=525	**N=527**	**N=200**	**N=192**	**N=325**	**N=335**
OS, interim analysis						
Died, n (%)	83 (15.8)	117 (22.2)	14 (7.0)	20 (10.4)	69 (21.2)	97 (29.0)
Median, months (95%CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
HR (95%CI)	**0.671 (0.507, 0.890)[b]**		0.67 (0.34, 1.32)		**0.66 (0.50, 0.92)**	
OS, final analysis#						
Died, n (%)	170 (32.4)	235 (44.6)	36 (18.0)	60 (31.3)	134 (41.2)	175 (52.2)
Median, months (95%CI)	NE (NE, NE)	52.2 (41.9, NE)	NE (NE, NE)	NE (52.2, NE)	NE (NE, NE)	NE (NE, NE)
HR (95%CI)	**0.651 (0.534, 0.793)[b]**		**0.525 (0.347, 0.794)[c]**		**0.699 (0.558, 0.875)[c]**	
rPFS^						
Event, n (%)	134 (25.5)	231 (43.8)	25 (12.5)	58 (30.2)	109 (33.5)	173 (51.6)
Median, months (95%CI)	NE (NE, NE)	22.1(18.5,32.9)	NE (NE, NE)	30.5 (25.8, NE)	NE (NE, NE)	14.9 (NE, NE)
HR (95%CI)	**0.484 (0.391, 0.600)[b]**		**0.358 (0.224, 0.573)[c]**		**0.515 (0.404, 0.657)[c]**	

Blue shading represents information previously considered by the PBAC

Source: Table 4, apalutamide mHSPC, PBAC PSD November 2021.

ADT=androgen deprivation therapy; APA=apalutamide; CI=confidence intervals; HR=hazard ratio; HV=high volume; LV=low volume; mHSPC=metastatic hormone-sensitive prostate cancer; NA=North America; NE=not estimable; OS=overall survival; PBO=placebo; rPFS=radiographic progression-free survival

Bold text indicates statistical significance at p<0.05 level.

^ Analysis only conducted for data cut-off on 23 November 2018

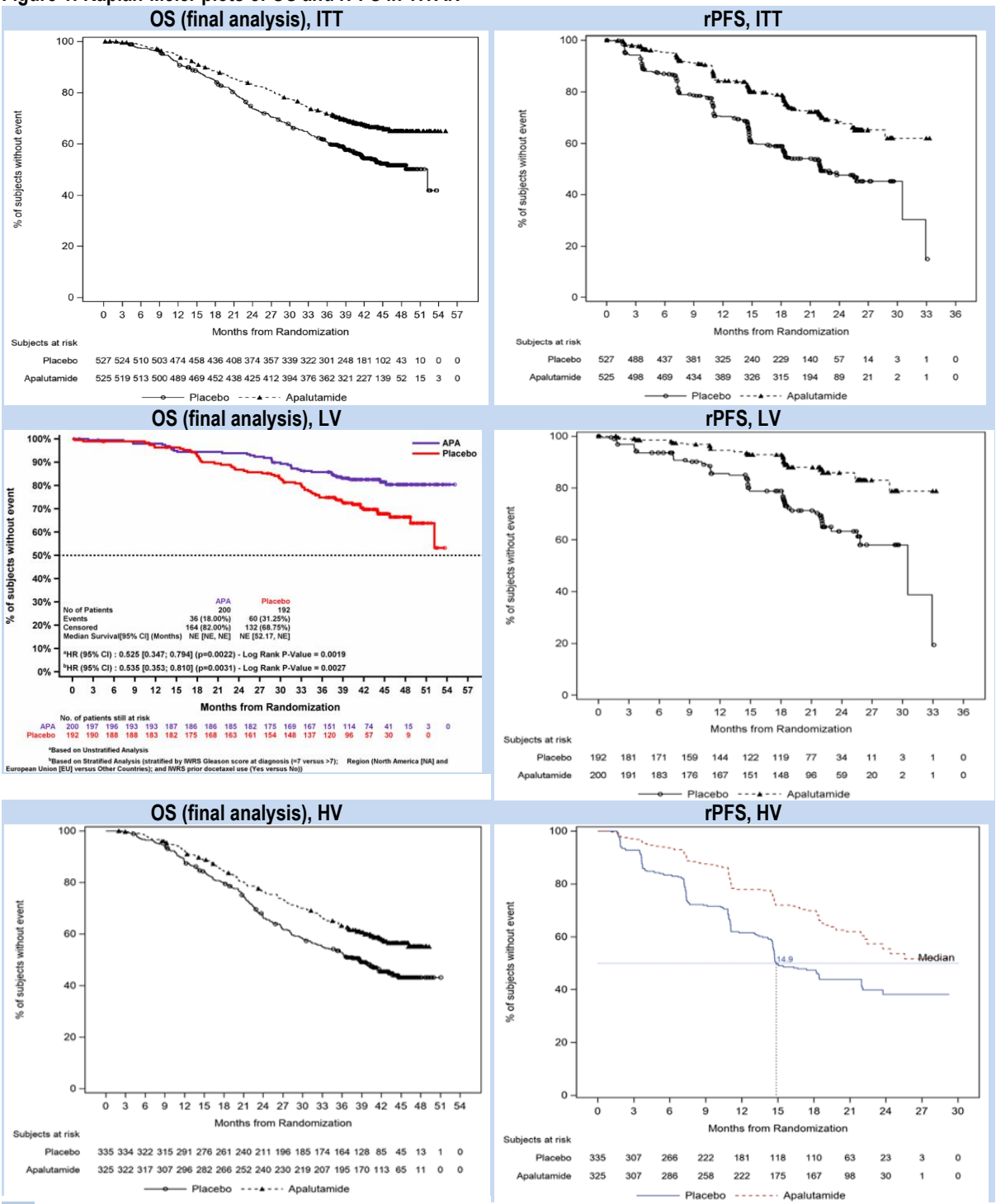
39.5% of placebo patients switching to apalutamide after the first interim analysis, approximately 50% with LV disease and 33% with HV disease.

a HR from stratified proportional hazards model. HR <1 favour active treatment.

b p-value from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries), and Prior docetaxel use (Yes vs. No).

c p-value is from the log-rank test (non-stratified)

Figure 1: Kaplan-Meier plots of OS and rPFS in TITAN



Blue shading represents information previously considered by the PBAC

Source: Figure 1, apalutamide mHSPC, PBAC PSD, November 2021.

HV=high volume; LV=low volume; mHSPC=metastatic hormone sensitive prostate cancer; OS=overall survival; rPFS=radiographic progression free survival

Comparative harms

6.8 No new comparative safety data were presented in the resubmission. Table 6 summarises the treatment emergent adverse events and adverse events (AEs) of special interest in TITAN, as well as AEs included in the modelled economic evaluation. The safety data for the LV mHSPC subgroup remained unchanged from the previous submission; however, instead of the safety data from the ITT population (applied in the November 2021 submission) the resubmission used the safety data from the HV mHSPC subgroup for the HV modelled economic evaluation.

Table 6: Summary of the overall AEs, AEs of special interest, exposure adjusted AEs and AEs included in the modelled economic evaluation for the ITT, LV mHSPC and HV mHSPC subgroups in TITAN

AEs n(%)	ITT				LV mHSPC		HV mHSPC	
	APA N=524	PBO N=527	PBO-APA N=208	RD (95%CI)[b]	APA N=199	PBO N=192	APA N=325	PBO N=335
Any TEAE[a]	510 (97.3)	510 (96.8)	174 (83.7)	1% (-2%,3%)	197 (99.0)	185 (96.4)	313 (96.3)	325 (97.0)
TEAE (Grade 3-4)	259 (49.4)	220 (41.7)	57 (27.4)	**8% (2%, 14%)**	85 (42.7)	63 (32.8)	174 (53.5)	157 (46.9)
TEAE to discontinuation	62 (11.8)	30 (5.7)	16 (7.7)	**6% (3%, 10%)**	28 (14.1)	13 (6.8)	34 (10.5)	17 (5.1)
TEAE to dose interruption	119 (22.7)	64 (12.1)	36 (17.3)	**11% (6%, 15%)**	43 (21.6)	28 (14.6)	NR	NR
SAE (Grade 3-4)	124 (23.7)	93 (17.6)	27 (13.0)	**6% (1%, 11%)**	46 (23.1)	31 (16.1)	78 (24.0)	62 (18.5)
TEAE leading to death	20 (3.8)	17 (3.2)	7 (3.4)	1% (-2%, 3%)	7 (3.5)	6 (3.1)	13 (4.0)	11 (3.3)
AEs of special interest	222 (42.4)	99 (18.8)	59 (28.4)	**24% (18%, 29%)**				
Any	153 (29.2)	49 (9.3)	45 (22)	**20% (15%, 25%)**	-	-	-	-
Skin rash	24.4	8.3	30.8	-	-	-	-	-
Exposure-adjusted, /100 SY	33 (6.3)	5 (0.9)	-	-	-	-	-	-
Model (grade 3+)	49 (9.4)	37 (7.0)	8 (4)	2% (-1%, 6%)	12 (6.0)	4 (2.1)	21 (6.5)	1 (0.3)
Fall	4.6	6.8	5.7	-	-	-	-	-
Exposure-adjusted, /100 SY	49 (9.4)	37 (7.0)		-	-	-	-	-
Model (all grade)	54 (10.3)	26 (4.9)	5 (2)	**5% (2%, 9%)**	22 (11.1)	19 (9.9)	27 (8.3)	18 (5.4)
Fracture	6.1	4.2	2.1	-	-	-	-	-
Exposure-adjusted, /100 SY	41 (7.8)	21 (4.0)	-	-	-	-	-	-
Model (not SAE)	19 (3.6)	6 (1.1)	-	-	18 (9.0)	7 (3.6)	23 (7.1)	14 (4.2)
Model (SAE)	3 (0.6)	2 (0.4)	0	0 (-1%, 1%)	8 (4.0)	5 (2.6)	11 (3.4)	1 (0.3)
Seizure	0.2	0.3	0	-	-	-	-	-
Exposure-adjusted, /100 SY	1 (0.2)	0	-	-	-	-	-	-
Model (grade 3+)	31 (6)	11 (2)	1 (1)	**4% (2%, 6%)**	1 (0.5)	0	0	0
Ischaemic heart disease	3.3	1.6	0.4	-	-	-	-	-
Exposure-adjusted, /100 SY	21 (4.0)	5 (0.9)	-	-	-	-	-	-
Model (grade 3+/SAE)	13 (2)	8 (2)	5 (2)	1% (-1%, 3%)	9 (4.5)	2 (1.0)	12 (3.7)	2 (0.6)
Ischaemic cerebrovascular disease	1.3	1.3	2.9	-	-	-	-	-
Exposure-adjusted, /100 SY	9 (1.7)	2 (0.4)	-	-	-	-	-	-
Model (grade 3+/SAE)	222 (42.4)	99 (18.8)	59 (28.4)	**24% (18%, 29%)**	3 (1.5)	0	6 (1.8)	2 (0.6)

Blue shading represents information previously considered by the PBAC.

Source: Table 2.39, p114 of the November 2021 submission, Table 5, apalutamide mHSPC, PBAC PSD, November 2021 and Attachment 3-1b. Apalutamide high volume mHSPC economic model.xlsx.

ADT=androgen deprivation therapy; AE=adverse event; APA=apalutamide; CI=confidence intervals; PBO=placebo; RD=risk difference; RR=relative risk; SAE=serious adverse events; SY=subject years (of exposure); TEAE=treatment-emergent adverse event

[a] Excludes Grade 5 events.

[b] RR and RD were calculated for apalutamide + ADT vs placebo + ADT.

Treatment-emergent adverse events are those that occurred between the date of first dose of study drug and date of last dose of study drug+30 days. For each category, patients are counted only once, even if they experienced multiple events in that category.

6.9 The incidence of AEs was comparable between the ITT and the LV and HV mHSPC subgroups. There were more serious AEs (Grade 3-4) and AEs leading to discontinuation experienced in the apalutamide arm compared to placebo. For the modelled economic evaluation, the resubmission included unadjusted rates of AEs of

special interest (rash, falls, fractures, ischaemic heart disease and ischaemic cerebrovascular disorder).

6.10 Overall, the safety outcomes reported in TITAN were consistent with the known safety profile for apalutamide.

Benefits/harms

6.11 A summary of the comparative benefits and harms associated with apalutamide versus placebo is presented below.

Table 7: Summary of comparative benefits and harms between apalutamide and placebo, ITT population

Benefits					
Event	**APA**	**PBO**	**Absolute difference**		**HR (95% CI)**
Progression free survival					
Progressed, n (%)	134/525 (25.5)	231/527 (43.8)	-		
Median PFS, months (95% CI)	NE (NE, NE)	22.1(18.5,32.9)	22.1		**0.48 (0.39, 0.60)**
% not progressed at 12 months (95% CI)	84.3 (80.7, 87.3)	70.3 (66.0, 74.1)	14.0%		
% not progressed at 24 months (95% CI)	68.2 (62.9, 72.9)	47.5 (42.1, 52.8)	20.7%		
Overall survival					
Deaths, n/N (%)	170 (32.4)	235 (44.6)	-		
Median OS, months (95% CI)	NE (NE, NE)	52.2 (41.9, NE)	NE		
% Alive at 12 months (95% CI)	94.6 (92.3,96.2)	90.8 (88.0, 93.0)	3.8%		**0.65 (0.53, 0.79)**
% Alive at 24 months (95% CI)	83.3 (79.8, 86.3)	73.7 (69.7, 77.3)	9.6%		
% Alive at 36 months (95% CI)	71.9 (67.8, 75.6)	61.0 (56.6, 65.0)	10.9%		
% Alive at 48 months (95% CI)	65.1 (60.4, 69.3)	51.8 (46.9, 56.4)	13.3%		
Harms					
TITAN	**APA N=524**	**PBO N=527**	**RR* (95% CI)**	**Event rate/100 SY#**	**RD (95% CI)**
				APA / **PBO**	
AEs of special interest					
Skin rash	153 (29.2)	49 (9.3)	**3.14 (2.33, 4.23)**	24.4 / 8.3	16.1% (NR, NR)
Ischaemic heart disease	31 (5.9)	11 (2.1)	**2.83 (1.44, 5.58)**	3.3 / 1.6	1.7% (NR, NR)

Blue shading represents information previously considered by the PBAC.
Source: Table 6, apalutamide mHSPC, PBAC PSD, November 2021.
APA=apalutamide; HR=hazard ratio; PBO=placebo; RD=risk difference; RR=risk ratio; SY=subject years
* Median follow-up of the final data analysis was 43.8 months (final data cut was in September 2020).
# adjusted for exposure, median of 39 months for apalutamide and 20 months for placebo

6.12 On the basis of direct evidence from TITAN presented by the submission for the ITT population, for every 100 patients treated with apalutamide in comparison with placebo:

- Approximately 21 additional patients will remain progression-free after 24 months.
- Approximately 10 additional patients will remain alive after 24 months and 13 additional patients will remain alive after 48 months.
- Approximately 16 additional patients will experience skin rash, over a 12-month period.
- Approximately 2 additional patients will experience ischaemic heart disease, over a 12-month period.

Clinical claim

6.13 The resubmission maintained the clinical claim that apalutamide plus ADT was superior in terms of effectiveness and inferior (but acceptable) in terms of safety compared with placebo plus ADT.

6.14 The PBAC had previously considered that the claim of superior comparative effectiveness for apalutamide plus ADT over placebo plus ADT was reasonable for patients with LV disease, but not for patients with HV disease who were unsuitable for chemotherapy as the trial did not provide direct evidence for these patients. A post-hoc analysis found only 10% of patients in the HV subgroup in TITAN met the proposed PBS eligibility criteria (i.e. one of the criteria making them unsuitable for docetaxel). The PBAC considered that in patients with HV disease who are unfit for chemotherapy, the degree of benefit was likely reduced compared to that presented in the submission due to their competing comorbidities (paragraph 7.11, apalutamide mHSPC PSD, November 2021). At the July 2022 meeting, the PBAC considered that apalutamide plus ADT was superior to placebo plus ADT in terms of comparative effectiveness in all patients with mHSPC (i.e. LV and HV disease).

6.15 The PBAC reaffirmed its view that the claim of inferior comparative safety was reasonable on the basis that apalutamide plus ADT is associated with additional AEs compared with placebo plus ADT.

Economic analysis

6.16 The resubmission presented an updated stepped economic evaluation (cost-utility analysis using partitioned survival analyses) based on results from TITAN comparing apalutamide versus placebo in mHSPC. Similar to the November 2021 submission, separate models were provided for LV patients and HV patients unsuitable for docetaxel (referred to as LV and HV models herein). The structure of the models was unchanged from the November 2021 submission.

6.17 The PBAC's key concern regarding the November 2021 economic evaluations was that the immaturity of the data resulted in uncertainty in the magnitude of overall survival benefit. The PBAC suggested a number of changes to help mitigate the uncertainty (paragraphs 7.15 and 7.16, apalutamide mHSPC PSD, November 2021) and how the resubmission addressed them is summarised below:

- **HV model should be informed by HV subgroup data from TITAN**. The HV model was amended to be based on TITAN HV subgroup data including time to treatment discontinuation (TTD), PFS, OS, utility estimates, AEs and dose intensity. The ESC noted that although this was more appropriate than the ITT data used in the November 2021 submission, given only 10% of the HV subgroup in TITAN were docetaxel unsuitable, the HV subgroup was also not a good representation of the requested HV population. Data underpinning the utility estimates were also not presented and several adverse events presented in the November 2021 submission were removed without explanation.

- **Reduce the model time horizons**. The resubmission reduced the time horizon of the LV model to 10 years and the HV model to 5 years, in line with the PBAC's recommendations. At the end of the time horizons, 4.6% and 0.3% of patients in the apalutamide and placebo arms respectively of the LV model were still alive and 38.3% and 25.2% of patients in the apalutamide and placebo arms respectively of the HV model were alive.
- **Implement Gompertz extrapolations for OS**. The resubmission implemented Gompertz extrapolations for OS from Kaplan-Meier (KM) data cut-offs as recommended by the PBAC. In the LV model, a Gompertz extrapolation was also used to extrapolate PFS. The Gompertz extrapolation was a poor fit for the HV subgroup OS KM data.
- **ICER should be less than $45,000 per QALY gained**. The resubmission updated the cost of docetaxel in mCRPC to reflect prices in April 2022 and then instituted a small reduction in the effective price of apalutamide (effective prices $ and $ in LV and HV patients respectively, down from $ in the November 2021 submission). The resulting ICERs in both the LV and HV models were $35,000 to < $45,000 per QALY gained. This was in accordance with the PBAC's recommendations; however, any overestimate of subsequent treatment costs or QALY gains would push the ICER beyond $45,000 per QALY gained.

6.18 Key areas of uncertainty in the economic evaluations (paragraphs 7.15 and 7.16, apalutamide mHSPC PSD, November 2021) not addressed in the base cases of the resubmission included:

- **OS convergence from year 5 in the LV model and 44 months in the HV model.** The ESC noted that the models did not include convergence in the base case. Sensitivity analyses with OS convergence from 5 years in the LV model and 44 months in the HV model resulted in ICERs of $55,000 to < $65,000 and $45,000 to < $55,000 per QALY gained respectively, both exceeding the PBAC recommended maximum ICER of $45,000 per QALY gained. Differences in subsequent treatments between TITAN and Australian clinical practice suggest convergence of OS over time is likely. If convergence was implemented as recommended, the effective AEMP of apalutamide would need to be $ (versus $ requested) to result in ICERs below $45,000 per QALY gained (see paragraph 6.23).
- **Separate economic evaluation for HV patients suitable for docetaxel treatment.** The PBAC were concerned that there was the possibility for all HV patients to access apalutamide and considered including these patients in the restriction. The resubmission did not revise the restriction to include docetaxel suitable HV patients and therefore, an economic analysis for these patients with docetaxel as a comparator was not included. A brief cost-minimisation approach (CMA) versus docetaxel was presented in the resubmission. The resubmission presented 2 scenarios. In the first, docetaxel was given by IV infusion for 6 cycles with pegfilgrastim given as a prophylactic prior to each cycle. Apalutamide in the HV patients fit for chemotherapy was assumed to be given for 30.2 months, resulting

in an ex-manufacturer price of apalutamide of $. If weighted across the entire mHSPC population the ex-manufacturer price of apalutamide was calculated to be $. In the second scenario, the cost of 15 months of subsequent NHA therapy was included in the docetaxel arm. This resulted in an ex-manufacturer price of apalutamide of $ and a weighted price across the entire mHSPC population of $. These prices were stated to be not acceptable to the sponsor. The PBAC noted the weighted prices were calculated based on the submissions estimates of LV (47.9%) and HV (52.1%) patients, and the assumption that fit mHSPC patients comprise 75% of HV patients. This resulted in overall weightings of 47.9% LV patients, 13.0% (52.1% x 0.25) unfit HV patients and 39.1% (52.1% x 0.75) fit HV patients. The PBAC noted that if the longer treatment duration for LV patients and the expected substantially reduced uptake in fit HV patients were accounted for, the weighting assigned to LV would be higher (and the weighting applied to fit HV would be less), resulting in an overall higher weighted price.

6.19 A summary of the key components of the economic evaluation and how they compared to the November 2021 submission is presented in the following table.

Table 8: Key components of the revised economic evaluation

Component	November 2021 submission	July 2022 resubmission
Type of analysis	Cost-utility analysis	Unchanged
Outcomes	Quality-adjusted life years, life years	Unchanged
Populations	A separate economic evaluation was presented for two populations: • 'LV model' - patients with LV mHSPC, based on data for the LV subgroup in TITAN. • 'ITT/HV model' - patients with HV mHSPC who are unsuitable for docetaxel, based on the ITT population in TITAN.	LV model unchanged ITT/HV model updated to be the HV model, informed by HV population from TITAN. Reasonable, though still not representative of the requested PBS population. In addition, EQ-5D IPD data was not provided and removal of AEs was not discussed in the resubmission.
Time horizon	• LV model: 20 years. • ITT/HV model: 15 years. Compared to median follow-up of 44 months for OS (final analysis) and 23 months for PFS (interim analysis) in TITAN.	• LV model: 10 years. • ITT/HV model: 5 years. Compared to median follow-up of 44 months for OS (final analysis) and 23 months for PFS (interim analysis) in TITAN.
Methods used to generate results	Partitioned survival model.	Unchanged.
Health states	3 health states: • Progression free survival (PFS) = mHSPC • Progressed disease (PD) = mCRPC • Death.	Unchanged.
Cycle length	Monthly, with half cycle correction.	Unchanged.
Transition probabilities	Transition between health states derived from KM data in TITAN of OS and rPFS. Time on primary treatment derived from post-hoc TTD data. Parametric extrapolation of time to event outcomes when < 20% of patients remain in the risk set of the KM data. The model did not adjust OS for treatment switching in the base case. • LV model: Data for LV subgroup. • ITT/HV model: Data for ITT population.	Unchanged with exception that the HV model was based on data from the HV subgroup of TITAN. Reasonable, though the trial data remains relatively immature compared to the length of the parametric extrapolations in the LV model.

Component	November 2021 submission	July 2022 resubmission
Extrapolation method	The submission fitted parametric proportional hazards and accelerated failure time models with only one covariate for treatment group to the PFS and OS KM data. For TTD data, the submission fitted separate functions to the apalutamide and PBO arms (i.e. assumed no relationship). • PFS: Use of trial-based KM curves: Up to 22-26 months*. Extrapolation: Weibull thereafter. • OS: Use of trial-based KM curves: Up to 45-48 months*. Extrapolation: Weibull thereafter. • TTD: Use of trial-based KM curves: Up to 27-33 months*. Extrapolation: Weibull (ITT/HV model), Gompertz (LV model) thereafter.	The approach was unchanged, but extrapolation choice was altered and HV extrapolations were estimated from HV subgroup of TITAN. • PFS: Use of trial-based KM curves: Up to 19-26 months*. Extrapolation: Weibull (HV model), Gompertz (LV model) thereafter. • OS: Use of trial-based KM curves: Up to 43-48 months*. Extrapolation: Gompertz thereafter. • TTD: Use of trial-based KM curves: Up to 26-33 months*. Extrapolation: Weibull (HV model), Gompertz (LV model) thereafter. The models were unchanged by TTD extrapolation for placebo arm.
Costs	The model included costs for apalutamide, background ADT, management of AEs (one-off costs), monitoring disease progression (PSA tests, specialists, imaging), subsequent treatment post progression (docetaxel, cabazitaxel, abiraterone/enzalutamide, antiandrogens, bone-sparing agents, prednisolone) and end of life costs. The model assumed patients treated with apalutamide for mHSPC did not receive abiraterone/enzalutamide for mCRPC.	Unchanged, except for: • Updated effective prices of apalutamide (differs by model) back calculated so that ICERs were $[redacted][1] per QALY gained. • Updated cost of docetaxel (1 April 2022 DPMQ). • Dose intensity for HV model taken from HV population of TITAN 95.7% (previously ITT population 95.8%). Dose intensity in the LV model remained unchanged at 95.9% based on data from the LV subgroup of TITAN. • AE incidence from HV group of TITAN used to estimate incidence of AEs in the HV model. Appropriate, however it was uncertain why serious infections, haematuria and urinary obstruction were removed from the model. These changes were reasonable, though the proposed PBS listing price was based upon a weighted average of the two effective prices. An effect of reducing the time horizons was the increase in the monthly treatment cost of abiraterone and enzalutamide in the placebo arms in mCRPC health state. Monthly cost was back calculated from a fixed total cost in mCRPC, based on 15 months (i.e., total cost over 15 months/number of months in health state). As time spent in the health state was reduced, the calculated monthly treatment cost increased. Due to differences in OS, there was also less discounting of the mCRPC costs particularly in the placebo arm. Due to differences in the time horizons, the estimated monthly costs were also different across the two models. While this generated some anomalies, on balance, the approach was still reasonable.
Utilities	Health state utilities derived from post-hoc analysis of EQ-5D-5L data in TITAN. • LV model: 0.817 in PFS, 0.707 in PD. • ITT/HV model: 0.789 in PFS, 0.676 in PD.	Unchanged in LV model HV model: 0.773 in PFS, 0.666 in PD Reasonable that HV model now informed by HV population of TITAN, but IPD data was not provided to verify.
Software package	Excel 2016	Unchanged

Blue shading represents information previously considered by the PBAC. Source: Table 3.1 Nov 2021 submission, Table 3-1 resubmission.
FA=final analysis; HV=high volume; IPD=individual patient data; LV=low volume; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone sensitive prostate cancer; OS=overall survival; PD= progressed disease; PFS=progression-free survival; TTD=time to discontinuation

* 20% remaining in the risk set of the KM data.

The redacted values correspond to the following ranges:

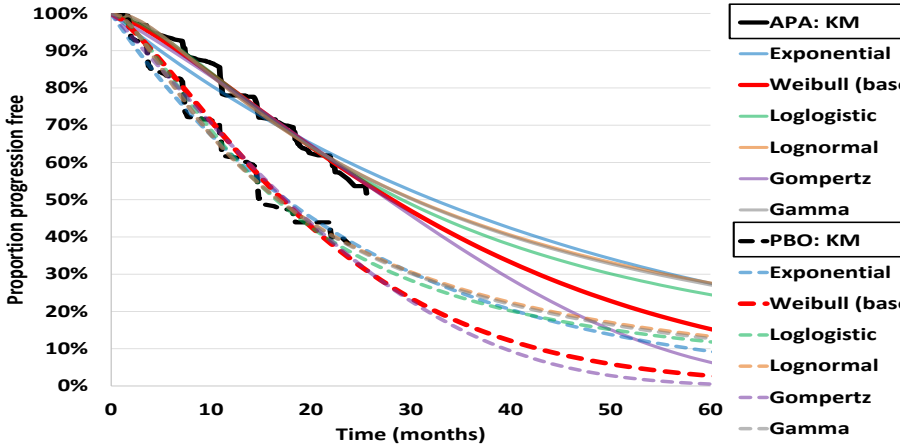
[1] *$35,000 to < $45,000*

6.20 As noted above, HV model inputs in the resubmission were informed by HV subgroup data from TITAN. Updated extrapolations for TTD, PFS and OS were estimated from the HV subgroup data. Updated goodness of fit statistics (i.e., log-likelihood, AIC, BIC) for OS were presented but statistics were not presented for PFS or TTD. No tests for the proportional hazard assumption were presented for the HV subgroup KM data. Extrapolations of the HV model are presented in Figure 2.

- For PFS, based on visual inspection only, all extrapolations (with the exception of the exponential function for the apalutamide arm) appeared to fit the KM data. The chosen Weibull extrapolation presented the second most conservative estimate but may still be reasonable given general good visual fit. The most conservative extrapolation was based on the Gompertz function.
- For OS, while the Gompertz (base case) and the Weibull extrapolations appeared to have the most conservative longer term OS predictions with the shortest tail sections, neither appeared to visually fit the KM data, especially for the placebo arm. In comparison, the log-normal function appeared to have the best visual fit and the lowest AIC and BIC values. If the log-normal function was chosen, the ICER increased to $45,000 to < $55,000 per QALY gained.
- For TTD, the base case Weibull extrapolation did not visually fit the KM data well and crossed PFS in the model. As the model did not allow TTD to exceed PFS, TTD was modelled as equal to PFS for the majority of the extrapolated period. Treatment duration in the placebo arm only affected adverse event costs (time on ADT was estimate using PFS), and as these occurred prior to the end of the KM data cut-off, both the LV and HV models were unaffected by the choice of TTD extrapolation for the placebo arm.

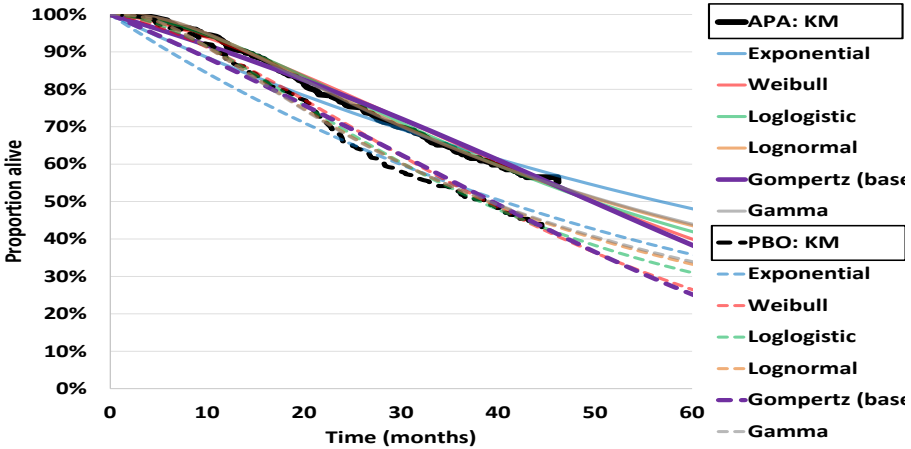
Figure 2 : Extrapolation in the HV model

PFS[a]



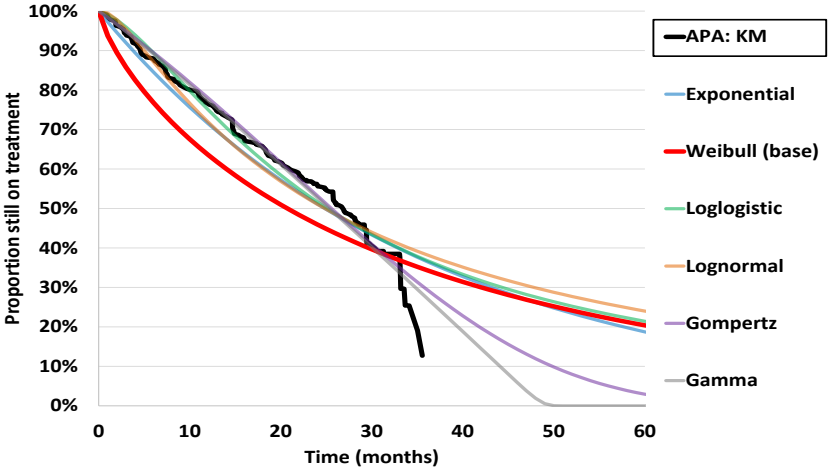
[a] Extrapolations applied from KM data cut-offs (APA 22.10 mths, PBO 18.53 mths)

OS[b]

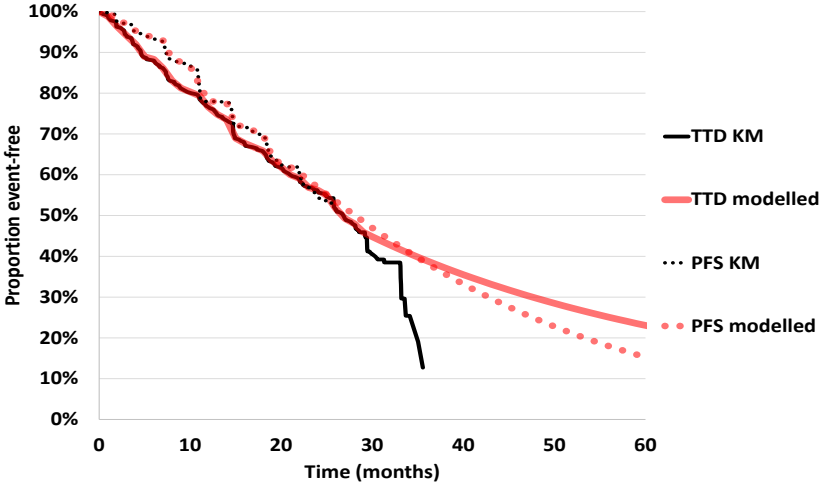


[b] Extrapolations are applied from KM data cut-offs (APA 44.94 mths, PBO 43.20 mths).

TTD[c]



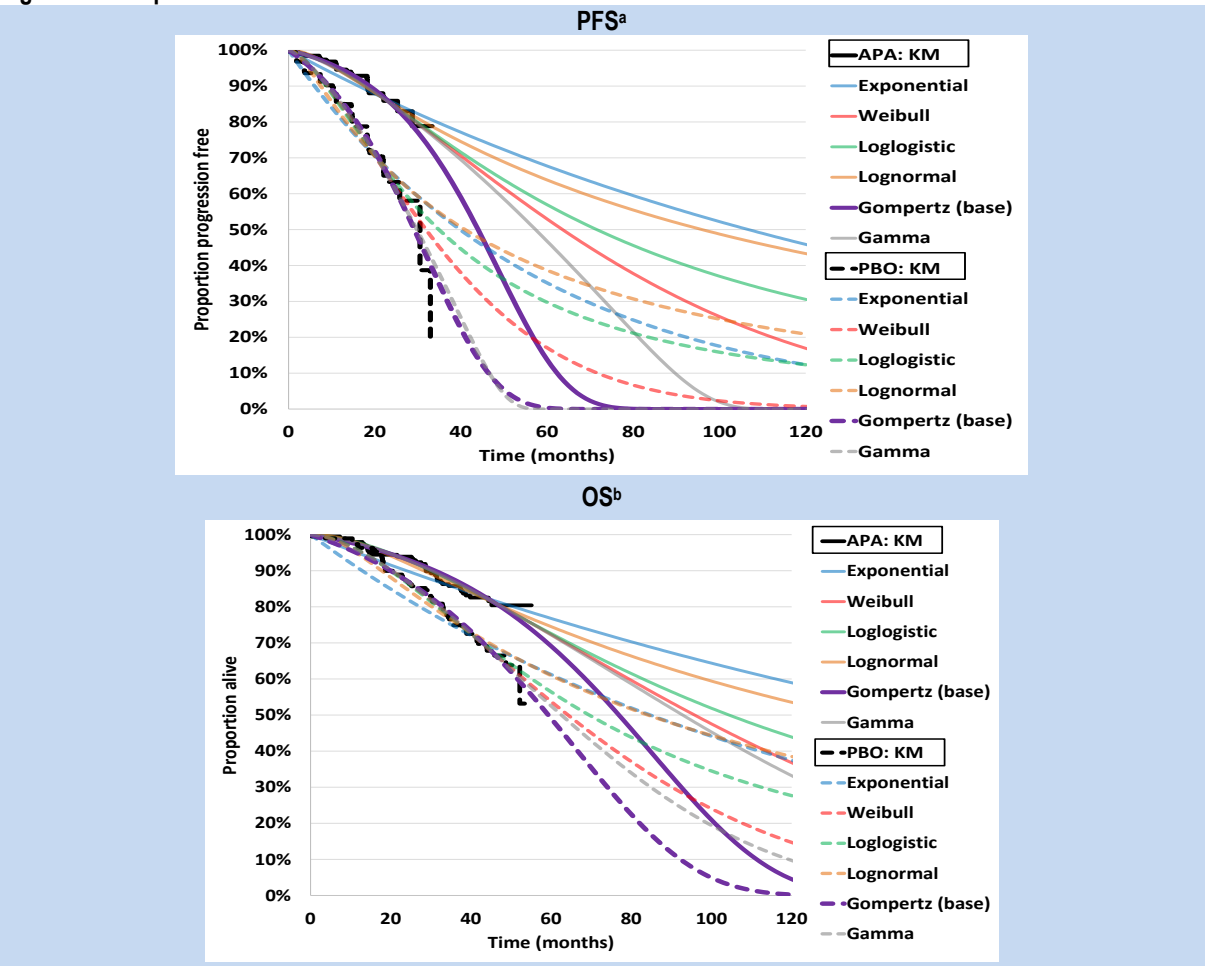
Comparison of TTD and PFS



[c] Extrapolations applied from KM data cut-off (APA 29.67 mths). *TTD extrapolation for placebo arm has no impact on the model (TTD only affects adverse events which occur prior to the KM data cut off) and so are not presented Source: Adapted from Sheet 'rPFS modelled' 'OS modelled' TTD modelled' from Excel workbook '3-1b. Apalutamide High Volume mHSPC Economic Model.xlsx'. APA = apalutamide; HV = high volume; KM = Kaplan-Meier; OS = overall survival, PFS = progression free survival; rPFS = radiographic progression free survival; TTD = time to treatment discontinuation

6.21 For the LV model the Gompertz was the chosen extrapolation for PFS and OS (as compared to Weibull in the November 2021 submission). This aligned with the advice provided by PBAC in November 2021.

Figure 3: Extrapolations in the LV model



Source: Adapted from Sheet 'rPFS modelled' 'OS modelled' TTD modelled' from Excel workbook '3-1a. Apalutamide Low Volume mHSPC Economic Model.xlsx'. APA = apalutamide; HV = high volume; KM = Kaplan-Meier; OS = overall survival, PFS = progression free survival; rPFS = radiographic progression free survival; TTD = time to treatment discontinuation

[a] Extrapolations applied from KM data cut-offs (APA 25.79 mths, PBO 22.93 mths) b Extrapolations are applied from KM data cut-offs (APA 48.10 mths, PBO 46.98 mths)

6.22 The resubmission revised the model time horizons from 20 years in the LV model and 15 years in the HV model to 10 and 5 years respectively, versus median follow up of 44 months for OS (final analysis) and 23 months for PFS (interim analysis) in TITAN. The LV model remained sensitive to assumptions about the sustained survival benefit of apalutamide.

6.23 The PBAC previously considered (paragraph 7.15 and 7.16, apalutamide mHSPC PSD, November 2021) that OS should converge from Year 5 in the LV model and from 44 months in the HV model. The sponsor considered convergence to be clinically implausible as a base case, and instead provided these scenarios as sensitivity analyses

(the ICER increased to $55,000 to < $65,000 per QALY gained in the LV model and $45,000 to < $55,000 per QALY gained in HV model). Trial data from TITAN remained short compared to the extrapolation period, particularly in the LV model (median follow up 44 months versus 10 years in the model base case) and no data were presented to support a sustained survival benefit beyond 5 years. Subsequent treatments received in TITAN are also unlikely to represent use in Australia, as subsequent NHA use was allowed in the trial. In practice, higher subsequent NHA use in the placebo arm (i.e., representing use in mCRPC) and lower subsequent NHAs in the apalutamide arm would be expected (since patients can only receive one NHA on the PBS in a lifetime). These differences suggest that the two OS curves are likely to converge over time. If convergence was implemented as recommended by the PBAC, the effective price of apalutamide would need to be $ in the LV model and $ in the HV model to give ICERs below $45,000 per QALY gained. This would result in a weighted effective price of $ (versus $ requested), applying the resubmission's split of % of prescriptions for LV patients and % of prescriptions for HV patients unsuitable for docetaxel. The weights applied in the resubmission were based on the expected volumes over the -year RSA period and incorporated the expected longer duration of therapy in the LV population. The PSCR and pre-PBAC response reiterated that there was no clinical basis or evidence to support convergence of the OS curves, and that data from the TITAN trial (as well as the SPARTAN trial of apalutamide in m0CRPC) demonstrated a sustained and broadening separation of the OS curves. In addition, the PSCR and pre-PBAC response stated that the uncertainty in the modelled longer-term outcome was sufficiently addressed by conservatively applying the Gompertz function to the OS extrapolations and truncating the time horizons.

6.24 The pre-PBAC response stated that the average QALY gain across the LV and HV models without OS convergence applied of 0.73 (0.83 in the LV model and 0.35 in the HV model; weighted based on the 5-year utilisation estimates) was lower than the QALY gain of 0.76 in the economic model for darolutamide in high-risk m0CRPC accepted by the PBAC (paragraph 4.7, darolutamide PSD, July 2021). The PBAC recalled even though it was considered that the darolutamide model provided moderate certainty in terms of modelled benefits, it was also considered that the estimated gain of 0.76 QALYs was overestimated (paragraph 5.9, darolutamide PSD, July 2021). The PBAC further recalled that the economic model for apalutamide for high-risk m0CRPC estimated a QALY gain of 0.49 (Table 14, apalutamide PSD, November 2020), and noted that the weighted average QALY gain across the LV and HV models with OS convergence applied (0.56) was higher than this. Overall, the PBAC did not accept the claim in the pre-PBAC response that applying OS convergence would unduly undervalue apalutamide.

6.25 The resubmission did not change the utility values in the LV model from the November 2021 model. The same methodology as presented in the November 2021 submission

was used to derive the utilities in the HV model, using the HV subgroup data from TITAN.

Table 9: Utility values used in the economic evaluation

Health state	Utility		Source
	November 2021	July 2022	
PFS (mHSPC)	ITT/HV: 0.789 LV: 0.817	HV: 0.773 LV: 0.817	EQ5D-5L from TITAN
PD (mCRPC)	ITT/HV: 0.676 LV: 0.707	HV: 0.666 LV: 0.707	EQ5D-5L from TITAN

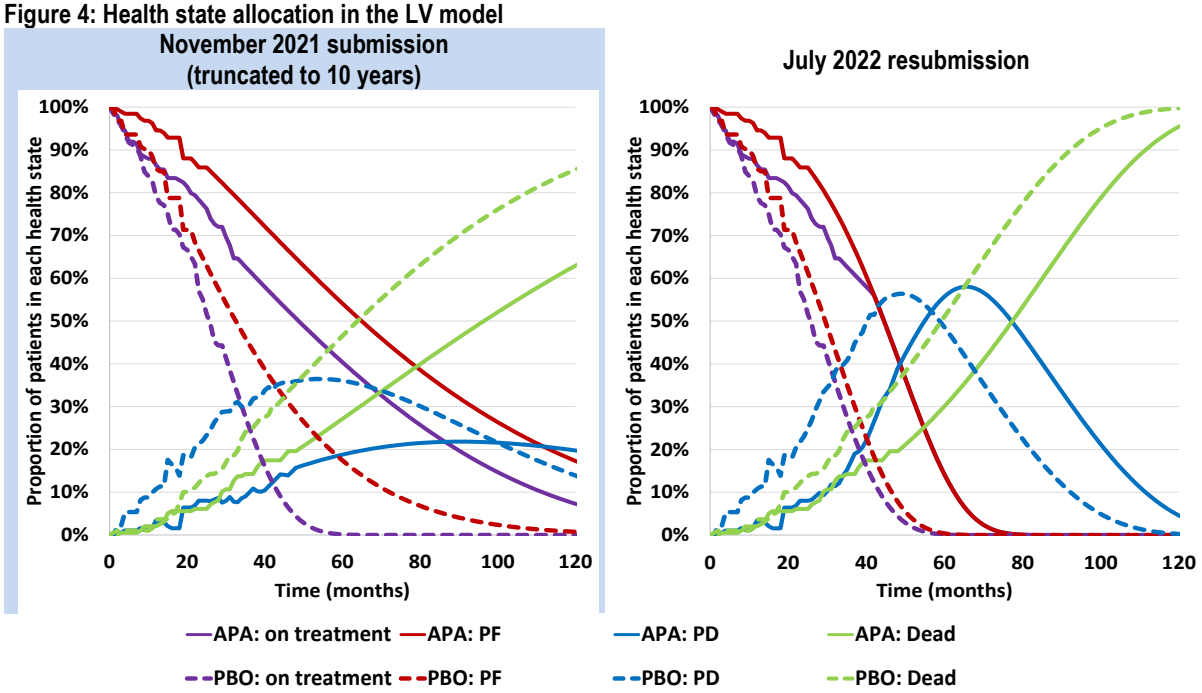
Blue shading represents information previously considered by the PBAC
Source: Tables 3.14, 3.38-3.39, of the November 2021 submission and Section 3.5 of the resubmission
APA = apalutamide; EQ5D-5L = EuroQoL 5 Dimension 5-Level; LV = low volume; PBO = placebo; PD = progressed disease; PFS = progression free survival.

6.26 In the models, NHA treatment in the mCRPC health state was a significant cost in the placebo arms. This cost was estimated by assuming a 15 month duration of treatment with subsequent NHA therapies, estimating a total cost of NHA treatment and then dividing the total cost by time in the mCRPC health state to give a monthly NHA therapy cost. The resubmission did not update the duration of subsequent NHA therapy in the placebo arm, arguing that other methodologies underestimated the current utilisation of abiraterone or enzalutamide. No further details were provided as to whether the PBS 10% sample analysis accounted for treatment breaks or imperfect compliance. The models were sensitive to the duration of subsequent NHA therapy applied to the placebo arms. The ESC noted an updated analysis provided by DUSC Secretariat in April 2022 that suggested the average PBS treatment durations for abiraterone and enzalutamide were 9 and 12 months respectively or 11.8 months combined (assuming zero treatment breaks), and that suggested that the submission's estimate may be overestimated. If time on subsequent NHA therapy was reduced to 12 months, in line with results of the updated DUSC analysis (from 15 months in the base case), the ICERs increased to $45,000 to < $55,000 per QALY gained in the LV model and $55,000 to < $65,000 per QALY gained in the HV model. The data informing the analysis were mature, with only 14% of the total 25,745 patients censored. In addition, most of the censored patients had only recently begun treatment and were therefore unlikely to substantively alter the point estimate of 11.8 months. The PSCR noted that the data would not have fully captured the impact of the recent change to the PBS restrictions which removed the requirement for prior chemotherapy, which is expected to increase NHA treatment duration. The pre-PBAC response acknowledged that the DUSC Secretariat data were mature but considered that a mean duration of therapy of 12 months did not reflect current (or future) steady-state Australian practice and that the 15 month mean duration applied in the resubmission remained reasonable.

6.27 The Markov traces for the proportion of patients in each health state in the revised models and from November 2021 are presented in

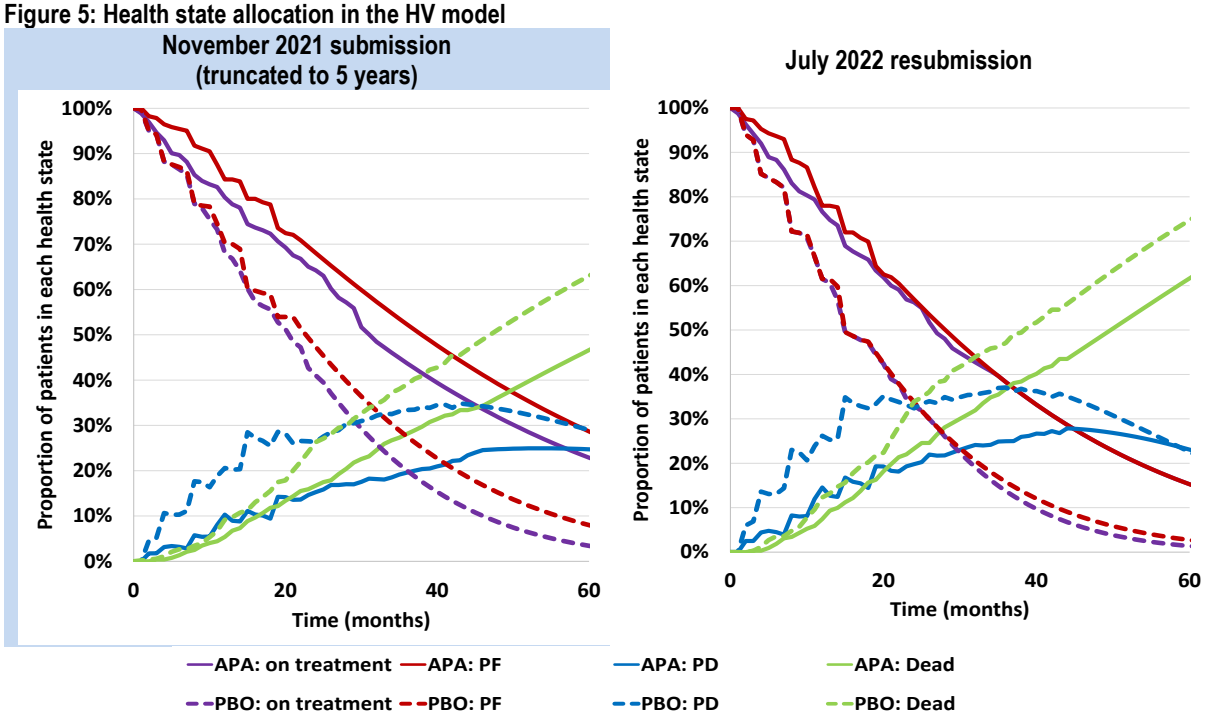
6.28 Figure 4 and Figure 5 below.

Figure 4: Health state allocation in the LV model



Blue shading represents information previously considered by the PBAC. Source: Adapted from Sheets 'Traces' in the Excel workbooks.
APA = apalutamide; HV = high volume; LV=low volume; OS = overall survival; PBO = placebo; PD = progressed disease; PF = progression free.
PBO on treatment only affects adverse event costs

Figure 5: Health state allocation in the HV model



Blue shading represents information previously considered by the PBAC.
Source: Adapted from Sheets 'Traces' in the Excel workbooks
APA = apalutamide; HV = high volume; LV=low volume; OS = overall survival; PBO = placebo; PD = progressed disease; PF = progression free.
PBO on treatment only affects adverse event costs

6.29 The key drivers in the models are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact	
		HV model, BC: $[redacted][1]/QALY	**LV model, BC: $[redacted][1]/QALY**
Treatment duration on APA	Patients discontinue treatment prior to or at disease progression / death, based on TTD curve. However, trial investigators frequently monitor patients for stopping criteria under trial conditions, and hence use of treatment may be longer in practice.	Moderate, favoured APA. The ICER increased to $[redacted][2]/QALY assuming treatment continued until disease progression.	Moderate, favoured APA. The ICER increased to $[redacted][2]/QALY assuming treatment continued until disease progression.
Treatment duration on NHAs for mCRPC	Patients in the placebo arm received an average of 15 months (~15 packs) of NHAs in the mCRPC health state. This estimate was uncertain and considerably longer than other estimates of 9 months or 8.9 packs in the literature.	High, favoured APA. The ICER increased to $[redacted][3]/QALY assuming an average duration on NHAs of 12 months.	High, favoured APA. The ICER increased to $[redacted][2]/QALY assuming an average duration on NHAs of 12 months.
Extrapolation functions	The submission assumed the proportional hazards assumptions holds over the entire modelled time horizon irrespective of the function used. This assumption may not hold in practice. Higher subsequent NHA use in the placebo arm (i.e., representing use in mCRPC) and lower subsequent NHAs in the apalutamide arm are expected (since patients can only receive one NHA on the PBS in a lifetime) in practice compared to TITAN. These differences suggest that the two OS curves are likely to converge over time.	Moderate, favoured APA. The ICER increased to $[redacted][2]/QALY assuming gradual convergence in OS after 44 months.	High, favoured APA. The ICER increased to $[redacted][3]/QALY assuming gradual convergence in OS after 5 years.

Blue shading represents information previously considered by the PBAC.
Source: constructed during the evaluation
APA = apalutamide; PBO = placebo; OS = overall survival; PFS = progression free survival.
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$45,000 to < $55,000*
[3] *$55,000 to < $65,000*

6.30 The results of the stepped economic evaluations are provided in Tables 11 and 12, with results from the November 2021 submission included for reference. The revised ICERs for both models were $35,000 to < $45,000 per QALY gained (increased from $35,000 to < $45,000 per QALY gained in the LV model and $35,000 to < $45,000 per QALY gained in the HV model in the November 2021 submission).

6.31 The results were based on the estimated effective price of enzalutamide as a subsequent therapy.

Table 11: Results of the LV stepped economic evaluation (base case)

Step and component	November 2021 submission			July 2022 resubmission		
	APA	PBO	Increment	APA	PBO	Increment
Step 1: Time horizon, trial based: 44 months						
Costs	$[redacted]	$35,267	$[redacted]	$[redacted]	$38,746	$[redacted]
LYs	3.25	3.08	0.17	3.25	3.08	0.17
QALYs	2.63	2.44	0.19	2.62	2.42	0.20
Incremental cost/extra QALY gained	-	-	**$[redacted][1]**	-	-	**$[redacted][1]**
Step 2: Time horizon, 20 years (Nov 2021), 10 years (July 2022)						
Costs	$[redacted]	$80,335	$[redacted]	$[redacted]	$77,196	$[redacted]
LYs	6.90	5.08	1.83	5.33	4.31	1.01
QALYs	5.45	3.90	1.55	4.13	3.30	0.83
Incremental cost/extra QALY gained	**-**	**-**	**$[redacted]*[2]**	**-**	**-**	**$[redacted][2]**

Blue shading represents information previously considered by the PBAC
Source: Table 3.34 of the November 2021 submission and Tables 3-7 and 3-9 of the resubmission
APA = apalutamide, PBO = placebo; LY = life year; QALY = quality adjusted life year
* The revised ICER presented in the pre PBAC response was $[redacted][2] per QALY gained, for a time horizon of 15 years (p1, pre PBAC response, October 2021)
The redacted values correspond to the following ranges:
[1] *$155,000 to < $255,000*
[2] *$35,000 to < $45,000*

Table 12: Results of the HV model stepped economic evaluation (base case)

Step and component	November 2021 submission			July 2022 resubmission		
	APA	PBO	Increment	APA	PBO	Increment
Step 1: Time horizon, trial based: 44 months						
Costs	$[redacted]	$41,688	$[redacted]	$[redacted]	$50,714	$[redacted]
LYs	2.97	2.75	0.22	2.80	2.56	0.24
QALYs	2.29	2.07	0.22	2.10	1.87	0.23
Incremental cost/extra QALY gained	-	-	**$[redacted][1]**	-	-	**$[redacted][3]**
Step 2: Time horizon, 15-years (Nov 2021), 5 years (July 2022)						
Costs	$[redacted]	$74,919	$[redacted]	$[redacted]	$63,733	$[redacted]
LYs	5.06	3.95	1.10	3.31	2.92	0.39
QALYs	3.81	2.91	0.90	2.47	2.12	0.35
Incremental cost/extra QALY gained	-	-	**$[redacted][2]**	**-**	**-**	**$[redacted][2]**

Blue shading represents information previously considered by the PBAC
Source: Table 3.35 of the November 2021 submission and Tables 3-8 and 3-10 of the resubmission
APA = apalutamide, PBO = placebo; LY = life year; QALY = quality adjusted life year
* The revised ICER presented in the pre PBAC response was $[redacted][2] per QALY gained, for a time horizon of 10 years and input data from the HV subgroup of TITAN (p1, pre PBAC response, October 2021)
The redacted values correspond to the following ranges:
[1] *$115,000 to < $135,000*
[2] *$35,000 to < $45,000*
[3] *$65,000 to < $75,000*

6.32 The incremental costs were driven largely by the cost of apalutamide ($[redacted]) in the HV model, and $[redacted] in the LV model) and cost-offsets associated with no subsequent NHA use (abiraterone/enzalutamide) in mCRPC ($[redacted] in the HV model, and $[redacted] in the LV model).

The incremental benefits resulted from increased survival spent in progression free disease for apalutamide over placebo in both models.

6.33 Key sensitivity analyses are presented in the table below.

Table 13: Results of model sensitivity analyses

Analyses	LV model			HV model		
	Incremental		ICER	Incremental		ICER
	Cost	QALY		Cost	QALY	
Base case	**$**	**0.83**	**$** [1]	**$**	**0.35**	**$** [1]
Discount rate (base 5%)						
3.5%	$	0.89	$ [1]	$	0.36	$ [1]
0%	$	1.06	$ [1]	$	0.39	$ [1]
Convergence of OS extrapolations (from 5 years LV model, 44 months HV model)	$	0.63	$ [2]	$	0.32	$ [3]
Time on apalutamide (base TTD as modelled) Equal to PFS	$	0.83	$ [3]	$	0.35	$ [3]
Time on subsequent therapy (base 15 months)						
9 months	$	0.83	$ [3]	$	0.35	$ [4]
12 months	$	0.83	$ [3]	$	0.35	$ [2]
Revised base case – as specified by ESC Convergence of OS extrapolations with 12 months on subsequent therapy	$	0.63	$ [2]	$	0.32	$ [2]

Source: Table 3-13 of the resubmission and compiled from Excel workbooks '3-1a. Apalutamide Low Volume mHSPC Economic Model.xlsx' and '3-1b. Apalutamide High Volume mHSPC Economic Model.xlsx'

APA = apalutamide; HR = hazard ratio; HV = high volume; ICER = incremental cost-effectiveness ratio; IPCW = inverse probability censoring weighting; LV=low volume; OS = overall survival; QALY = quality adjusted life year; RPSFTM = rank preserving structural failure time model

* All treatment switching scenarios applied the base case monthly cost of subsequent treatments.

The redacted values correspond to the following ranges:

[1] *$35,000 to < $45,000*

[2] *$55,000 to < $65,000*

[3] *$45,000 to < $55,000*

[4] *$65,000 to < $75,000*

6.34 The ESC considered that a suitable revised base case would include convergence as specified by the PBAC in November 2021 (from 5 years in the LV model and 44 months in the HV model) and time on subsequent therapy reduced from 15 to 12 months to align with data provided by the DUSC Secretariat. The ESC noted that this multivariate analysis resulted in ICERs of $55,000 to < $65,000 per QALY for the LV model and $55,000 to < $65,000 per QALY for the HV model. ESC also noted that for the ICERs to remain below $45,000 per QALY, then the weighted effective ex-manufacturer price of apalutamide, assuming % of patients are LV and % are HV (see paragraph 6.23), would need to be $ ($ for the LV patients and $ for the HV patients).

Drug cost/patient/course

Table 14: Drug cost per patient for proposed and comparator drugs

	November 2021				Resubmission		
	Trial dose and duration	**LV model**	**ITT/HV model**	**Financial estimates**	**LV model**	**HV model**	**Financial estimates**
Mean dose (mg/day)	240 mg/day[a]	240 mg/day[a]	240 mg/day[a]	240 mg/day	240 mg/day[a]	240 mg/day[a]	240 mg/day
Mean duration	39.3 months	55.6 months	41.0 months	Dose, dose intensity, cost per script and duration assumptions consistent with the models for HV[b] and LV subgroups.	39.8 months	30.2 months	Dose, dose intensity, cost per script and duration assumptions consistent with the models for HV and LV subgroups.
Cost/patient/month	-	$[redacted][a]	$[redacted][a]		$[redacted]	$[redacted]	
Cost/patient/course	ITT: $[redacted]	$[redacted]	$[redacted]		$[redacted]	$[redacted]	

Blue shading represents information previously considered by the PBAC. Source: Compiled during the evaluation

[a] APA dose intensity of 95.8% in the November 2021 ITT/HV model and 95.9% in the LV model; 95.7% in the revised HV model (LV model unchanged), based on TITAN IPD.

Estimated PBS usage & financial implications

6.35 This submission was not considered by DUSC. The resubmission's approach to estimate the financial implications of the proposed listing of apalutamide was unchanged from the previous submission, which was an epidemiological approach using the same data sources.

6.36 At the November 2021 meeting, the PBAC considered the financial estimates were too high and likely overestimated. There was also risk of use in the population with HV mHSPC who were suitable for docetaxel (intended to be excluded by the submission) and this risk was not adequately addressed in the submission. The PBAC considered the proposed [redacted]% rebate above the expenditure caps did not mitigate this risk (paragraph 7.17, apalutamide mHSPC PSD, November 2021).

6.37 Table 15 summarises the key inputs in the financial estimates. Changes relative to the November 2021 submission are noted in the table. The main changes in the resubmission were:

- Reduction in the incident mHSPC population and the proportion eligible for apalutamide by assuming mHSPC patients would initiate treatment with docetaxel within six months (previously 12 months) of ADT, increased docetaxel uptake rate to 32.7% (previously 27.4%) in mHSPC patients in 2019 and 2020, and decreased proportion of HV mHSPC patients who were unsuitable for chemotherapy to 25% (previously 32.7%);

- Apalutamide uptake rates in the LV and HV mHSPC patients unsuitable for chemotherapy; and
- Small (1.1%) reduction in the effective ex-manufacturer price of apalutamide.

Table 15: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
Incident mHSPC patients treated with docetaxel	2016: 580 2017: 720 2018: 810 2019: 840 2020: 930	PBS 10% sample (re-scaled). The sample included patients treated with docetaxel within 6 months of first ADT. The analysis assumed 6 month duration captures patient who would still be hormone sensitive.	Changed from November 2021 submission and consistent with Azad 2021, which assumed that docetaxel initiated within 6 months of ADT would be for mHSPC, not mCRPC. Additional analysis conducted during the evaluation using updated estimates from the DUSC Secretariat (full PBS sample) reduced the net cost to the PBS/RPBS by 15%. The DUSC data were used in an updated model provided with the pre-PBAC response.
% of incident mHSPC patients treated with docetaxel	2016: 25.2% 2017: 24.3% 2018: 32.7% 2019: 32.7% 2020: 32.7%	Azad 2021. Proportion of 'any docetaxel' within 6 months of diagnosis with mHSPC in the PCOR-Vic registry in 2016, 2017, 2018.	Changed from November 2021 submission. The ESC previously considered that it would have been more appropriate to apply the 2018 rate to 2019 and 2020 (Table 12, apalutamide mHSPC PSD, November 2021).
Growth of total incident mHSPC patients over forecast period	Patients in Yi=(68.95xYi) + 2420.4	Regression model fit to historical estimates	The approach was generally reasonable; however, the predictions were likely overestimated as the historical patients were likely overestimated compared to the DUSC data. The model predicted 2,903 incident patients in Yr 1 and 3,248 in Yr 6. DUSC data were used in an updated model provided with the pre-PBAC response.

Data	Value	Source	Comment
% incident patients with LV and HV disease	LV: 47.7% HV: 52.3%	ENZAMET trial sample.	Uncertain. The ESC considered that the proportion with HV disease may be higher. The ESC previously noted that ENZAMET trial did not initially allow prior docetaxel treatment, resulting in less HV patients enrolled in the initial phase of the trial. Trials included in a network meta-analysis by Wenzel 2021[4] included approximately 50% to 80% of patients with HV disease (Table 12, apalutamide mHSPC PSD, November 2021). Sensitivity analysis assuming 80% of patients with HV disease reduced the cost for the health budget by 34%. The PSCR noted that of the 7 trials included in the Wenzel 2021 meta-analysis, ENZAMET had the highest proportion of Australian patients (57.3%) and was the most representative of the Australian mHSPC population. The PSCR also noted that 6 of the 7 trials had HV populations between 47.5% and 63.0% (median: 54.3%). The PBAC considered the split proposed in the resubmission to be a reasonable estimate. The PBAC noted that the estimates differed slightly from those applied in the submission's cost minimisation approach (LV = 47.9%; HV = 52.1%).
% HV patients ineligible for chemotherapy	13.1%	Assumption based on docetaxel PI.	Changed from 17.1% in the November 2021 submission. In November 2021, the PBAC considered a more plausible estimate was that 25% of the HV patients would be ineligible for chemotherapy (i.e. 13%/52.3%) (Table 12, apalutamide mHSPC PSD, November 2021).
% untreated patients in Yi remaining eligible in Yi+1 (used to derive prevalent patients)	49.12%	11.7 months median time to progression (mCRPC) in ADT-only arm of the CHAARTED trial. 49.12% = 0.5^(1/(11.7/12)).	Uncertain. The method assumed an exponential extrapolation of time to progression that was unrelated to patient characteristics such as HV and LV disease. Applied to incident patients to estimate the prevalent population in Yr 1 of the model (based on the incident historical patients in prior 5 years) as well as the prevalent population remaining eligible for treatment in Yr 2-Yr 6 of the model (untreated patients remaining eligible).
Treatment utilisation			

[4] Wenzel M, Nocera L, Collà Ruvolo C, Würnschimmel C, Tian Z, Shariat SF, Saad F, Tilki D, Graefen M, Kluth LA, Briganti A, Mandel P, Montorsi F, Chun FKH, Karakiewicz PI. Overall survival and adverse events after treatment with darolutamide vs. apalutamide vs. enzalutamide for high-risk non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis. Prostate Cancer Prostatic Dis. 2021 May 30.

Data	Value	Source	Comment
Uptake of APA: LV disease	Yr 1: 40% Yr 2: 50% Yr 3: 55% Yr 4: 57% Yr 5: 59% Yr 6: 60%	Assumption.	Changed slightly from November 2021 submission. The ESC considered that the rates were underestimated, particularly for incident patients - the same uptake rate was applied to incident and prevalent patients, which was not reasonable as incident patients would be more likely to receive treatment. Overall, 59.9% of incident LV patients in Yr 1 are treated with APA over the first six years of the model (given 49.12% of untreated patients in a given year remain eligible in the subsequent year). The pre-PBAC response increased the rate of uptake in the incident population from 40-60% to 50-75%.
Uptake of APA: HV disease	Yr 1: 60% Yr 2: 75% Yr 3: 82% Yr 4-6: 90%	Assumption.	Changed slightly from November 2021 submission. As above, the rates remained uncertain. The same uptake rate was applied to incident and prevalent patients, which may not be reasonable as incident patients may be more likely to get treated. Overall, 76.9% of incident HV patients in Yr 1 are treated with APA over the first six years of the model (given 49.12% of untreated patients in a given year remain eligible in the subsequent year). The pre-PBAC response decreased the rate of uptake in the prevalent population from 60-90% to 50-80%.
% initiations remaining on treatment, by volume of disease	**Yr** / **LV** / **HV** 1 / 92.4 / 88.1 2 / 82.3 / 65.4 3 / 69.1 / 44.8 4 / 53.8 / 31.3 5 / 27.1 / 19.6 6 / 6.3 / 12.0	TITAN trial. Gompertz and Weibull extrapolations of time-to-discontinuation data in the LV and HV subgroups, respectively. The estimates reflect the average annual half-cycle corrected proportions remaining on treatment.	The resubmission used the Weibull extrapolation of the time-to-discontinuation data in the HV disease subgroup (same as November 2021 submission); however, the Gompertz extrapolation was used in the LV disease subgroup (previously Weibull). Using the Gompertz extrapolation data consistent with the resubmission's modelled economic evaluation increased the % initiations remaining on treatment in the HV disease group. The estimates were updated during the evaluation applying Gompertz extrapolation for time-to-discontinuation data in the HV disease subgroup. The ESC considered the time to discontinuation extrapolations were likely to underestimate time on treatment. The ESC considered that patients in the clinical setting were likely to remain on treatment for longer than those in the TITAN trial due to differences in the timing of imaging.
APA scripts/ year	12.18	Based on recommended dose, tablets/script, 365.25 days/year.	-
APA compliance	95.88%	TITAN, dose intensity.	Consistent with the modelled economic evaluation.
Average % of APA treated patients in mCRPC health state over time (treatment with ADT-only for mHSPC)	Yr 1: 11.1% Yr 2: 25.6% Yr 3: 30.7% Yr 4: 34.2% Yr 5: 31.5% Yr 6: 26.1%	Area under the curve for the probability of being in the mCRPC health state, based on the placebo arm in TITAN (ITT).	Unchanged from November 2021

Data	Value	Source	Comment
Average % of time in mCRPC health state spent on ENZ or ABI	55.24%	Assumes 15 months of NHA treatment for mCRPC, corresponding to 55.2% of time spent with mCRPC in placebo arm of the modelled economic evaluation.	Consistent with the modelled economic evaluation, but the average of 15 months treatment with NHAs for mCRPC remained uncertain. The PBAC considered 12 months to be an appropriate estimate for the economic model and should also be revised in the financial estimates.
ENZ/ABI scripts/year (full compliance)	ABI: 12.18 ENZ: 13.04	Based on recommended dose, tablets/script, 365.25 days/year.	-
Market share of ENZ and ABI for mCRPC	ENZ: 66.3% ABI: 33.7%	Based on proportional use of ABI (2698B, 11206T) and ENZ (10174L) on PBS/RPBS (May 2020 to April 2021).	-
Costs			
DPMQ: APA	$[redacted]	Requested effective price.	-
DPMQ: ABI	$[redacted]	Effective price PBS items 2698B and 11206T.	-
DPMQ: ENZ	$[redacted]	Effective price PBS item 10174L.	-
% PBS : RPBS (APA/ENZ/ABI)	PBS: 95.95% RPBS: 4.05%	Based on proportional use of ABI (2698B, 11206T) and ENZ (10174L) on PBS/RPBS (May 2020 to April 2021).	-
Co-payment (APA/ENZ/ABI)	PBS: $11.79 RPBS: $4.86		-

Blue shading represents information previously considered by the PBAC.
Source: Section 4.1 to 4.2, pp90-96 of the submission and Attachment 4-1. Utilisation cost model - apalutamide mHSPC.xlsx.
ABI=abiraterone; APA=apalutamide; ADT=androgen deprivation therapy; ENZ=enzalutamide; HV=high volume; LV=low volume; mCRPC=metastatic castration resistant prostate cancer; mHSPC=metastatic hormone sensitive prostate cancer

6.38 Table 16 summarises the estimated net financial implications to the PBS/RPBS for the proposed listing of apalutamide over the first six years (assumed as 2022 to 2027). The table shows net costs separately for LV and HV disease, derived during the evaluation.

Table 16: Estimated use and financial implications to the PBS/RPBS for the proposed listing of APA

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of patients with mHSPC						
Incident patients	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
LV disease	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
HV disease	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Prevalent patients in Yr1	[redacted]1	-	-	-	-	-
LV disease	[redacted]1	-	-	-	-	-
HV disease	[redacted]1	-	-	-	-	-
Estimated number of patients eligible for the requested restriction						
Total patients eligible (unique)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
LV disease	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
HV disease	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total patients eligible (given yr)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Estimated number of patients likely to take APA						
Total patient initiations	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
LV disease	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
HV disease	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated use of APA						
Patient-years on APA	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
LV disease	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
HV disease^	2	1	1	1	1	1
APA scripts^	3	7	12	12	17	17
LV disease	3	7	13	13	12	12
HV disease	1	8	8	3	3	3
APA net PBS/RPBS cost# ^	$ 4	$ 9	$ 11	$ 15	$ 14	$ 14
LV disease	$ 5	$ 10	$ 9	$ 11	$ 11	$ 15
HV disease	$ 6	$ 5	$ 5	$ 5	$ 5	$ 5
Estimated change in use of ABI / ENZ for mCRPC						
Patients-years eligible ABI/ENZ	- 2	- 1	- 1	- 1	- 1	- 1
LV disease	- 2	- 2	- 1	- 1	- 1	- 1
HV disease	- 2	- 2	- 2	- 2	- 1	- 1
ABI/ENZ scripts	- 1	- 1	- 8	- 3	- 3	- 3
LV disease	- 1	- 1	- 8	- 8	- 3	- 3
HV disease	- 2	- 1	- 1	- 1	- 1	- 1
ABI/ENZ net PBS/RPBS cost #	-$ 6	-$ 6	-$ 6	-$ 5	-$ 5	-$ 4
LV disease	-$ 6	-$ 6	-$ 6	-$ 5	-$ 5	-$ 5
HV disease	-$ 6	-$ 6	-$ 6	-$ 6	-$ 6	-$ 6
Net financial implications to government						
Total net PBS/RPBS cost# ^	$ 4	$ 10	$ 9	$ 11	$ 11	$ 11
LV disease	$ 5	$ 4	$ 10	$ 9	$ 9	$ 9
HV disease	$ 6	$ 6	$ 5	$ 5	$ 5	$ 5
Analysis based on data provided by the DUSC Secretariat, April 2022[a]						
Number of patients who received docetaxel within 6 months of initiating ADT (PBS full sample analysis)	1	1	1	1	1	1
Total net PBS/RPBS cost # ^	$ 5	$ 4	$ 10	$ 9	$ 9	$ 9
LV disease	$ 5	$ 4	$ 4	$ 10	$ 10	$ 10
HV disease	$ 6	$ 6	$ 6	$ 6	$ 6	$ 6
Pre-PBAC response revised financial estimates						
Total patient initiations	1	1	1	1	1	1
LV disease	1	1	1	1	1	1
HV disease	2	2	2	2	2	2
APA net PBS/RPBS cost# ^	$ 4	$ 9	$ 11	$ 15	$ 14	$ 14
Total net PBS/RPBS cost# ^	$ 4	$ 10	$ 9	$ 11	$ 11	$ 11
Net financial implications to government (November 2021 submission)						
Total patient initiations	1	1	1	1	1	1
APA PBS/RPBS cost #	$ 4	$ 11	$ 14	$ 16	$ 18	$ 18
Total net PBS/RPBS cost #	$ 4	$ 9	$ 11	$ 15	$ 14	$ 16
LV disease	$ 5	$ 10	$ 9	$ 11	$ 15	$ 15
HV disease	$ 6	$ 5	$ 5	$ 5	$ 5	$ 5
Net financial implications to government (revised in November 2021 pre-PBAC response)*						
Total patient initiations	1	1	1	1	1	1
APA PBS/RPBS cost #	$ 4	$ 9	$ 11	$ 15	$ 16	$ 19
Total net PBS/RPBS cost #	$ 4	$ 10	$ 9	$ 11	$ 15	$ 15

Blue shading represents information previously considered by the PBAC.

Italics indicate results estimated during the evaluation (see footnotes for changes applied).

Source: Tables 4.2 to 4.15, pp92-101 of the resubmission, Attachment 4-1 Utilisation cost model - apalutamide mHSPC.xlsx, Table 13, apalutamide mHSPC, PBAC PSD, November 2021.

ABI=abiraterone; APA=apalutamide; ADT=androgen deprivation therapy; ENZ=enzalutamide; HV=high volume; LV=low volume; mHSPC=metastatic hormone sensitive prostate cancer.

Net costs presented in the table reflect estimates without rounding of RPBS patient numbers. The resubmission rounded the number of patients treated on the RPBS, which impacts on the proportion of PBS: RPBS patients and corresponding co-payment amounts.

^ Estimates used Gompertz extrapolation of the time-to-discontinuation data in the HV disease subgroup consistent with the resubmission modelled economic evaluation, which increased the % initiations remaining on treatment in the HV disease group (tab 'Persistence compliance', cells $D:$D updated with data from Attachment 3-1b Apalutamide high volume mHSPC economic model.xlsx -> tab 'APA LY', cells $N:$N) . The resubmission used the Weibull extrapolation of the time-to-discontinuation data in the HV disease subgroup (unchanged from November 2021 submission) and the Gompertz extrapolation data in the LV disease subgroup.

* Sourced from Utilisation cost model - apalutamide mHSPC Pre-PBAC sensitivity analysis.xlsx, '5. Impact - net', cells C43:H43.

a Net financial implication to the government based on DUSC Secretariat analysis using full PBS sample from 1 January 2013 to 31 December 2021. Only PBS supplies to males over 18 years were included in the analyses. All supplies of PBS listings of ADT (triptorelin, degarelix, leuprorelin, goserelin, flutamide, bicalutamide, nilutamide and darolutamide) were extracted over the full data extraction period. First initiators on ADT were identified if they had no prior supply of an ADT listing with a look back period of at least 3 years. That is, patient counts were derived from 1 January 2016 onwards with a lookback to 1 January 2013. Supplies of docetaxel and ADT were linked by the de-identified unique patient identifier. The time between initiation on ADT to the first supply of docetaxel was calculated for all patients in the linked data set. Calculations were done separately for the supply of docetaxel within 6 months of first initiation on ADT.

The redacted values correspond to the following ranges:

[1] 500 to < 5,000
[2] < 500
[3] 10,000 to < 20,000
[4] $20 million to < $30 million
[5] $10 million to < $20 million
[6] $0 to < $10 million
[7] 20,000 to < 30,000
[8] 5,000 to < 10,000
[9] $40 million to < $50 million
[10] $30 million to < $40 million
[11] $50 million to < $60 million
[12] 40,000 to < 50,000
[13] 30,000 to < 40,000
[14] $70 million to < $80 million
[15] $60 million to < $70 million
[16] $80 million to < $90 million
[17] 50,000 to < 60,000
[18] $100 million to < $200 million
[19] $90 million to < $100 million

6.39 The net cost to the PBS/RPBS for the proposed listing of apalutamide in mHSPC in the resubmission was estimated to be $200 million to < $300 million over the first six years of listing compared to $300 million to < $400 million in the November 2021 submission and $200 million to < $300 million in the November 2021 pre-PBAC response (based on reduced uptake of docetaxel in 2019-2020). The total cost of apalutamide (without cost offsets) to the PBS/RPBS was estimated to be $300 million to < $400 million in the resubmission over the first 6 years of listing. This was a reduction of 25.7% compared to the November 2021 submission and of 7.0% compared to the November 2021 pre-PBAC response. The estimated net cost over the first 6 years of listing in the pre-PBAC response was $200 million to < $300 million, with an estimated cost of apalutamide (without cost offsets) of $300 million to < $400 million .

6.40 The resubmission's financial estimates remained uncertain as:

- there was a lack of Australian data to inform the eligible population with mHSPC who have LV or HV disease who are chemotherapy unsuitable;
- although the resubmission updated its assumptions, which included reducing the number of patients taking docetaxel and the proportion of HV mHSPC patients

unsuitable for chemotherapy, the method to estimate the incident patients was unchanged from the previous submission and could potentially overestimate the target population;

- the uptake of apalutamide in the LV and HV populations could be underestimated, particularly in the LV population listing, given that there is currently no other NHA listed on the PBS for mHSPC. In addition, the ESC noted that the same uptake rates were applied to the incident and prevalent populations. The ESC considered that incident patients would be more likely to receive treatment. The pre-PBAC response increased the uptake in the incident LV patients from 40-60% to 50-75% and reduced uptake in the prevalent HV population from 60-90% to 50-80% to reflect the difference in uptake in the incident and prevalent populations; and
- an additional analysis conducted during the evaluation using estimates provided by the DUSC Secretariat which were based on the full PBS sample of the number of patients who received docetaxel within 6 months of initiating ADT, showed a 15% reduction in the net cost to the PBS/RPBS. The PSCR stated that the DUSC analysis incorrectly used the historical data (2016 to 2021) to estimate the incidence of mHSPC for the forecast period (2022 to 2027) without accounting for growth, thus significantly underestimating the number of patients and utilisation of apalutamide in the forecast period. The PSCR also stated that the DUSC data (2016-2021), the Prospection PBS 10% sample analysis and Azad 2021 all suggested that the incidence of mHSPC is growing. The DUSC Secretariat stated that the DUSC data applied to the utilisation cost model provided with the resubmission included growth to estimate the projected incident mHSPC patient population. However, the rate of growth based on the DUSC data (m = 59.2) was lower than the 10% PBS sample (m = 82). The ESC noted that this resulted in an average 8% lower projected number of incident mHSPC patients (at initiation of ADT) and the 15% reduction in the net cost to the PBS/RPBS. This also has implications in reducing the total value of the subsidisation cap on the proposed Risk Sharing Arrangement (RSA). The pre-PBAC response acknowledged that the DUSC data did apply growth to the projected incidence of mHSPC and that use of this data resulted in the projected number of incident patients being approximately 8% lower than that estimated in the resubmission.

As discussed above, there remained a risk of leakage of use into the fit HV mHSPC population given the difficulty in defining the subgroup of HV patients who are chemotherapy unsuitable and as many of the restriction criteria are subject to interpretation by the assessor.

6.41 The resubmission stated that sensitivity analyses for the utilisation and financial impact estimates were not presented because the sources of uncertainty identified during the PBAC consideration of the November 2021 submission were addressed in

the revised financial estimates. The sources of uncertainty identified from the previous submission included:

- Historical and projected incidence of mHSPC in Australia - varying the number of incident patients from 2017 to 2021 also varied the number of prevalent mHSPC patients in Year 1. The PBAC considered the DUSC Secretariat analysis provided a reliable basis to estimate the incidence of mHSPC.
- Proportion of mHSPC patients having LV versus HV metastases, for example, if assuming a higher proportion with HV disease as reported by Wenzel 2021 of 80% reduced the cost for the health budget by 34%. The PBAC considered the estimate in the resubmission based on the TITAN trial to be reasonable.
- Proportion of mHSPC patients having HV metastases and being unsuitable for chemotherapy. The PBAC noted its advice from November 21 regarding this input was applied in the resubmission.
- The PBAC noted the percent of untreated patients remaining eligible for treatment in the subsequent year (49.12%) which was used to derive the number of prevalent patients remained uncertain.

6.42 The limit of only one NHA per lifetime per patient on the PBS may mitigate the risk of inappropriate use; however, given that there are few options post NHA, patients are likely to stay on treatment longer than observed in the clinical trials (median duration of treatment was 39 months in TITAN). The ESC noted the clinical benefit of a longer treatment was unknown, but such use is unlikely to be cost-effective.

Quality Use of Medicines

6.43 The resubmission stated that the sponsor has planned quality use of medicines activities for the treatment of mHSPC. The November 2021 submission provided detailed description of the activities.

Financial Management – Risk Sharing Arrangements

6.44 To mitigate the financial risk of any apalutamide use beyond the proposed PBS population or that patients will remain on apalutamide for longer than estimated based on the TITAN trial, the sponsor proposed a RSA with annual subsidisation cap based on estimated PBS/RPBS expenditure of apalutamide (for both LV mHSPC and HV chemotherapy unsuitable mHSPC subgroups), and an [redacted]% (previously [redacted]%) rebate for the Commonwealth payment above the annual subsidisation cap. The total value of the subsidisation cap was estimated in the resubmission as $200 million to < $300 million over the five-year RSA period. Based on the revised estimates in the pre-PBAC response the total value of the subsidisation caps increased to $200 million to < $300 million over 5 years.

Table 17: Risk-sharing arrangement for apalutamide in LV mHSPC and HV chemotherapy unsuitable mHSPC^ #

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Resubmission						
Apalutamide scripts for mHSPC	[redacted][1]	[redacted][4]	[redacted][7]	[redacted][7]	[redacted][10]	[redacted][12]
Commonwealth Payment (value of the subsidisation cap)	$[redacted][2]	$[redacted][5]	$[redacted][8]	$[redacted][9]	$[redacted][11]	$[redacted][13]
Pre-PBAC response						
Apalutamide scripts for mHSPC	[redacted][1]	[redacted][4]	[redacted][7]	[redacted][7]	[redacted][10]	[redacted][12]
Commonwealth Payment (value of the subsidisation cap)	$[redacted][2]	$[redacted][5]	$[redacted][8]	$[redacted][9]	$[redacted][11]	$[redacted][13]
Apalutamide AEMP = $[redacted] (as per paragraph 7.13)						
Commonwealth Payment (value of the subsidisation cap)	$[redacted][3]	$[redacted][6]	$[redacted][5]	$[redacted][8]	$[redacted][9]	$[redacted][13]

Source: Table 4-17, p103 of the resubmission. Italics indicate results estimated during the evaluation (see footnotes for changes applied).
HV=high volume; LV=low volume; mHSPC=metastatic hormone sensitive prostate cancer

Note the script numbers and value of subsidisation caps matched the estimated APA scripts and net/PBS/RPBS costs (Table 16). They were however slightly higher than the numbers presented in Table 4-17, p103 of the submission due to a number of corrections applied during the evaluation, as detailed by the footnotes below.

^ Estimates used Gompertz extrapolation of the time-to-discontinuation data in the HV disease subgroup consistent with the resubmission modelled economic evaluation, which increased the % initiations remaining on treatment in the HV disease group (tab 'Persistence compliance', cells $D:$D updated with data from Attachment 3-1b Apalutamide high volume mHSPC economic model.xlsx -> tab 'APA LY', cells $N:$N) . The resubmission used the Weibull extrapolation of the time-to-discontinuation data in the HV disease subgroup (unchanged from November 2021 submission) and the Gompertz extrapolation data in the LV disease subgroup.

Net costs presented in the table reflect estimates without rounding of RPBS patient numbers. The resubmission rounded the number of patients treated on the RPBS, which impacts on the proportion of PBS:RPBS patients and corresponding co-payment amounts.

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000
[2] $20 million to < $30 million
[3] $10 million to < $20 million
[4] 20,000 to < 30,000
[5] $40 million to < $50 million
[6] $30 million to < $40 million
[7] 40,000 to < 50,000
[8] $50 million to < $60 million
[9] $60 million to < $70 million
[10] 50,000 to < 60,000
[11] $70 million to < $80 million
[12] 100,000 to < 200,000
[13] $200 million to < $300 million

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

7 PBAC Outcome

7.1 The PBAC recommended apalutamide for the treatment of metastatic hormone sensitive prostate cancer (mHSPC). The PBAC considered that apalutamide plus androgen deprivation therapy (ADT) provides a moderate clinical benefit for patients with mHSPC compared to ADT alone. While the resubmission had proposed that apalutamide be used in patients with low volume (LV) disease and those with high volume (HV) disease who were unsuitable for treatment with docetaxel, the PBAC recommended apalutamide for use in patients with mHSPC regardless of disease volume or suitability for docetaxel. The PBAC noted that although the economic model presented in the resubmission incorporated a number of revisions suggested by the PBAC in November 2021, the overall survival curves were not converged, and the

duration of NHA therapy for metastatic castrate resistant prostate cancer (mCRPC) was potentially overestimated. Incorporating these changes increased the incremental cost-effectiveness ratios (ICERs) and a price reduction is required for apalutamide to be considered cost-effective with ICERs within the range of $40,000 to $45,000 per QALY. The PBAC considered that the proposed risk sharing arrangement (RSA) with an % rebate for use above the expenditure caps adequately managed the risk that patients would remain on apalutamide for longer than estimated based on the TITAN trial and the risk that use in patients with HV disease suitable for docetaxel would not be cost-effective.

7.2 The PBAC noted the comments from consumers, prostate cancer support groups and the Medical Oncology Group of Australia, all of which supported the listing of apalutamide on the PBS for the treatment of mHSPC.

7.3 The PBAC recalled that in November 2021 it requested that any resubmission should revise the restriction to include all fit mHSPC patients and include docetaxel as a relevant comparator and present an economic analysis using docetaxel as a comparator for the chemotherapy suitable HV patients. The PBAC noted that the clinical algorithm proposed in the resubmission again excluded apalutamide as a treatment option for patients with HV disease who were considered fit for chemotherapy. The PBAC noted that although the proposed restriction better excluded use in patients with HV mHSPC who were suitable for docetaxel as the listed contraindications and comorbidities for docetaxel were more specific than in the November 2021 submission, some of the criteria remained qualitative (e.g. poor cognition that leads to decreased ability to understand treatment options) and thus assessment was necessarily subjective. Overall, the PBAC considered that a broad restriction allowing use in mHSPC patients regardless of volume of disease or suitability for chemotherapy was appropriate given that (i) the results from the TITAN trial supported use in LV patients and HV patients regardless of suitability for chemotherapy, (ii) it is difficult to define patients unsuitable for docetaxel and that clinically this is should be based on individual risk factors, and (iii) the sponsor's arguments that in clinical practice docetaxel will remain the treatment of choice in mHSPC for those patients who are suitable for chemotherapy even if apalutamide was available.

7.4 The PBAC reaffirm that treatment with a NHA should be restricted to once per lifetime and hence patients who receive apalutamide through the PBS in the hormone sensitive setting (mHSPC) will be unable to receive a NHA (enzalutamide, abiraterone) through the PBS in the castrate resistant setting (mCRPC).

7.5 The PBAC noted that no new clinical data were presented. The PBAC recalled that the TITAN trial was a head-to-head randomised controlled trial that compared apalutamide plus ADT with placebo plus ADT and that after a median follow up of 43.8 months, a statistically significant improvement in overall survival was reported in the intention to treat (ITT) population (HR = 0.651; 95% CI: 0.534, 0.793), and the LV (HR

= 0.525; 95% CI: 0.347, 0.794) and HV (HR = 0.699; 95% CI: 0.558, 0.875) subgroups. The PBAC recalled that the OS data were immature as median OS had not been reached in either arm of the subgroup populations. The PBAC recalled that the TITAN trial also demonstrated statistically significant improvements in radiographic progression-free survival in the ITT population and the LV and HV subgroups.

7.6 The PBAC considered that apalutamide plus ADT was superior in terms of efficacy and inferior in terms of safety compared to placebo plus ADT for LV and HV mHSPC patients.

7.7 In terms of the economic model, the PBAC noted that the resubmission addressed a number of the suggested changes from November 2021 including:

- Using the HV subgroup data to inform the HV model (in November 2021 the ITT population was used to inform the HV model);
- Reducing the time horizon in the LV model from 20 years to 10 years and in the HV model from 15 years to 5 years; and
- Applying Gompertz rather than Weibull extrapolations to the OS Kaplan-Meier curves in both models.

7.8 The PBAC noted that the resubmission did not apply OS convergence from Year 5 in the LV model or from 44 months in the HV model as advised in November 2021. The PBAC noted the arguments in the PSCR and pre-PBAC that convergence would unduly undervalue the benefits of apalutamide. However, the PBAC maintained that applying convergence was appropriate given the expected higher subsequent NHA use in the placebo arm (i.e., representing use in mCRPC) and lower subsequent NHAs in the apalutamide arm (since patients can only receive one NHA on the PBS in a lifetime) would reduce the extent of benefit over time, and the modelled gain in QALYs appeared more plausible for the scenario with convergence applied (see paragraph 6.24).

7.9 The PBAC noted that in the placebo arm of the economic model it was assumed that patients who progress to mCRPC would receive 15 months treatment with a NHA based on an analysis of the 10% PBS sample. The PBAC noted limited information was provided in the resubmission for this analysis, including whether the analysis accounted for treatment breaks or imperfect compliance. An analysis undertaken by the DUSC Secretariat using the 100% PBS data estimated the average duration of NHA treatment in the mCRPC setting to be 11.8 months. The PBAC noted the arguments in the PSCR and pre-PBAC response that the PBS data would not have fully captured the impact of the recent change to the PBS restrictions which removed the requirement for prior chemotherapy; however, considered based on the information presented, that a treatment duration of 12 months was the more reliable estimate for use in the economic model.

7.10 The PBAC noted that if convergence was applied and the time on NHA therapy in the

placebo arm reduced from 15 to 12 months, the ICERs increased to $55,000 to < $65,000 per QALY in the LV model and $55,000 to < $65,000 per QALY in the HV model. The PBAC recalled that in November 2021 it had considered apalutamide would be cost-effective for mHSPC if the ICERs were between $40,000 and $45,000 per QALY. For ICERs at the upper end of this range, the AEMP for apalutamide would need to be reduced to $ for the LV patients and to $ for the HV patients. Based on the weightings using the financial estimates included in the pre-PBAC response (% of prescriptions for LV and % for HV, (paragraph 3.1)), the weighted AEMP would need to be $ for the ICERs to be $45,000 per QALY.

7.11 The PBAC noted that the sponsor's request for excluding patients with HV disease suitable for chemotherapy from the PBS restriction was because of the implications for the apalutamide price. The PBAC also considered the suggestion in the pre-PBAC response for a PBS listing for apalutamide only in patients with LV disease. The PBAC noted that for this scenario the AEMP for apalutamide would be lower ($ versus $ for the LV and HV patients unsuitable for chemotherapy, paragraph 7.10) and hence, this suggestion did not address the sponsor's pricing concern. The PBAC noted that whether the population is that as proposed by PBAC, or as defined in the sponsor's submission (LV plus HV unsuitable for docetaxel) or as suggested in the pre-PBAC response (LV only), the requested ICER ranges would result in a similar price.

7.12 In the pre-PBAC response it was noted that with an % rebate for the RSA the effective AEMP for apalutamide for any use above the financial caps was $, and that this was at the lower end of the price range estimated for apalutamide in the cost minimisation approach versus docetaxel for the HV docetaxel suitable mHSPC patients ($ to $, see paragraph 6.18). Noting with the price reduction as outlined in paragraph 7.10 that the effective price for apalutamide for use above the caps would be approximately $, the PBAC considered that the proposed RSA adequately managed the risk of the use of apalutamide in the treatment of patients with HV mHSPC suitable for docetaxel not being cost-effective, and for the reasons outlined in paragraph 7.3 recommended that the restriction does not attempt to preclude use in these patients.

7.13 In terms of the financials, the PBAC noted that the pre-PBAC response presented revised estimates which applied DUSC data for patients who initiated docetaxel within 6 months of ADT and that this reduced the projected number of incident patients by 8%. In response to ESC's advice regarding the assumed uptake (paragraph 6.40), the uptake was also revised in the pre-PBAC estimates and overall, the net PBS cost of apalutamide was slightly increased in the pre-PBAC response ($300 million to < $400 million over 6 years versus $300 million to < $400 million). The PBAC considered some uncertainty remained regarding the uptake as well as the percentage of untreated patients remaining eligible for treatment in the subsequent year; however, considered that the use estimated in the pre-PBAC response together with the revised prices (paragraph 7.10) and the reduction of the time on subsequent NHA therapy to 12 months would provide a reasonable estimate of the likely PBS

expenditure.

7.14 The PBAC noted that the resubmission proposed an RSA with a rebate of [redacted]% for use beyond annual subsidisation caps which were based on estimated PBS/RPBS expenditure. The PBAC considered that an [redacted]% rebate for use beyond revised subsidisation caps calculated as outlined in paragraph 7.13 would be reasonable. The PBAC considered that the [redacted]% rebate was sufficient to mitigate the risk that patients would remain on apalutamide for longer than estimated based on the TITAN trial and the risk that use in patients with HV disease suitable for docetaxel would not be cost-effective. Using the PBAC recommended price ($[redacted]), the financial cap would be $[redacted] million over 5 years. The PBAC acknowledged that it may be reasonable to achieve the required ICERs with a combination of this cap as well as a price reduction; however, in this circumstance the rebate for use beyond the cap would need to be close to [redacted]% and the price should be no higher than that for apalutamide in m0CRPC.

7.15 The PBAC advised that apalutamide is not suitable for prescribing by nurse practitioners.

7.16 The PBAC advised that apalutamide should not be exempt from the Early Supply Rule.

7.17 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for apalutamide:

- The treatment is expected to provide a moderate clinical benefit for patients with mHSPC compared to ADT alone;
- The treatment is not expected to address a high and urgent unmet clinical need as it, and other novel hormonal agents, are available on the PBS for patients with prostate cancer in a later line setting;
- It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
APALUTAMIDE					
apalutamide 60 mg tablet, 120	NEW	1	120	5	Erlyand

Restriction Summary / Treatment of Concept: [New 1]		
		Category / Program: GENERAL – General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
Prescribing rule		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
		Condition: Metastatic castration sensitive
		Indication: Carcinoma of the prostate
		~~**Treatment Phase:** Initial~~
		Clinical criteria:
		The treatment must ~~commence~~ be/have been initiated within 6 months of treatment initiation with androgen deprivation therapy
		AND
		Clinical criteria:
		Treatment must be used in combination with androgen deprivation therapy
		AND
		Clinical criteria:
		~~Patient must be untreated with a novel hormonal agent for this condition in non-metastatic disease; or~~
		~~Patient must have developed a severe intolerance to another novel hormonal agent~~
		Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or
		Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation
		AND
		Clinical criteria:
		Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
		~~**Treatment criteria:**~~
		~~Patient must be undergoing treatment with this drug for the first time~~
		~~**AND**~~
		~~**Treatment criteria:**~~
		~~Patient must not be undergoing simultaneous treatment with this drug under another PBS-listing (apply under either listing type, but not both simultaneously)~~
		AND
		Treatment criteria:

	Patient must be undergoing ~~concomitant~~ concurrent androgen deprivation therapy
	~~**Prescribing Instructions:**~~ ~~Novel hormonal agents include abiraterone, apalutamide, darolutamide and enzalutamide~~
	Administrative Advice: *Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide.*
~~**Restriction Summary / Treatment of Concept: [New 2]**~~	
	~~**Category / Program:** GENERAL – General Schedule (Code GE)~~
	~~**Prescriber type:** ☒ Medical Practitioners~~
	~~**Restriction type:** ☒ Authority Required (telephone/online PBS Authorities system)~~
	~~**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.~~
	~~**Administrative Advice:** No increase in the maximum number of repeats may be authorised.~~
	~~**Administrative Advice:** Special Pricing Arrangements apply.~~
	~~**Administrative Advice:**~~ ~~Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.~~
	~~**Condition:** Metastatic castration sensitive~~
	~~**Indication:** Carcinoma of the prostate~~
	~~**Treatment Phase:** Continuing~~
	~~**Clinical criteria:**~~
	~~Patient must not have developed disease progression while receiving treatment with this drug for this condition.~~
	~~**Treatment criteria:**~~
	~~Patient must be undergoing continuing PBS-subsidised treatment with this drug for this PBS indication, with treatment having commenced through one of: (i) the 'Initial treatment' listing, (ii) 'Grandfather' arrangements.~~
	~~**AND**~~
	~~**Treatment criteria:**~~
	~~Patient must not be undergoing simultaneous treatment with this drug under another PBS-listing (apply under either listing type, but not both simultaneously)~~
	~~**AND**~~
	~~**Treatment criteria:**~~
	~~Patient must be undergoing concomitant androgen deprivation therapy~~
~~**Restriction Summary / Treatment of Concept: [New 3]**~~	
	~~**Category / Program:** GENERAL – General Schedule (Code GE)~~
	~~**Prescriber type:** ☒ Medical Practitioners~~
	~~**Restriction type:** ☒ Authority Required (telephone/online PBS Authorities system)~~
~~**Prescribin**~~	~~**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.~~
	~~**Administrative Advice:** No increase in the maximum number of repeats may be authorised.~~
	~~**Administrative Advice:** Special Pricing Arrangements apply.~~
	~~**Administrative Advice:**~~

		Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
		Administrative advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
		Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
		Condition: Metastatic castration sensitive
		Indication: Carcinoma of the prostate
		Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
		Clinical criteria:
		Patient must be each of: (i) currently receiving non-PBS subsidised treatment with this drug for metastatic disease, (ii) commenced on non-PBS subsidised treatment with this drug for metastatic disease prior to [insert listing date here]
		Clinical criteria:
		The treatment must commence within 6 months of treatment initiation with androgen deprivation therapy
		AND
		Clinical criteria:
		Patient must be untreated with a novel hormonal agent prior to commencing non-PBS subsidised treatment with this drug for this condition in non-metastatic disease; or
		Patient must have developed a severe intolerance to another novel hormonal agent
		AND
		Clinical criteria:
		Patient must not have developed disease progression while receiving treatment with this drug for this condition.
		Treatment criteria:
		Patient must not be undergoing simultaneous treatment with this drug under another PBS-listing (apply under either listing type, but not both simultaneously)
		AND
		Treatment criteria:
		Patient must be undergoing concomitant androgen deprivation therapy
		Prescribing Instructions: Novel hormonal agents include abiraterone, apalutamide, darolutamide and enzalutamide

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.