

## 6.02 ENZALUTAMIDE, Capsule 40 mg, Xtandi<sup>®</sup>, Astellas Pharma Australia Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested Authority Required (telephone/online) listing for enzalutamide for the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC). An alternate population of mHSPC patients with low volume (LV) disease, and in high volume (HV) disease where the patient is unsuitable for docetaxel due to poor Eastern Cooperative Oncology Group ECOG performance status, comorbidities, or contraindications was also proposed.
- 1.2 Listing of enzalutamide in addition to androgen deprivation therapy (ADT) was requested on the basis of a cost-effectiveness analysis versus ADT alone, and on the basis of a cost-minimisation approach versus apalutamide (if apalutamide was PBS listed the time of PBAC consideration).

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	Patients with mHSPC, OR Patients with mHSPC who have (i) low volume disease or (ii) high-volume disease who are unsuitable for docetaxel due to either poor ECOG status, comorbidities or contraindications
Intervention	Enzalutamide is administered orally at a dose of 160 mg daily (as 4 x 40 mg capsules) in addition to ADT which is comprised of LHRH agonists or an antagonist or surgical ADT (i.e., orchidectomy)
Comparator	<u>Main comparator</u> : ADT alone, comprised of LHRH agonists or an antagonist or surgical ADT (i.e., orchidectomy). <u>Near market (secondary) comparator</u> : apalutamide, administered orally at a dose of 240 mg (as 4 x 60 mg tablets) in addition to ADT
Outcomes	rPFS, OS, time to initiation of cytotoxic chemotherapy, AEs, and HRQoL.
Clinical claim	<u>Main comparator (ADT alone)</u> : For patients with mHSPC, enzalutamide + ADT demonstrates superior comparative efficacy to ADT monotherapy, as assessed by statistically and clinically significant improvements in rPFS and OS. Enzalutamide + ADT is associated with some additional AEs compared to ADT monotherapy and thus has an inferior safety profile. However, AEs are mostly mild to moderate in severity, unlikely to impact HRQoL, and usually do not require the discontinuation of treatment. Enzalutamide + ADT has a well-understood safety profile and did not show any new safety signals in the key studies, ARCHES and ENZAMET. Clinicians are familiar with these AEs in the treatment of enzalutamide in its current PBS-listed indications. <u>Near market (secondary) comparator (apalutamide + ADT)</u> : For patients with mHSPC, enzalutamide +ADT is non-inferior to the near market comparator apalutamide + ADT for efficacy based on OS and rPFS, and with a similar AE profile.

Source: Table 1.1-1, p5 of the submission.

ADT=androgen deprivation therapy; AE=adverse effect; ECOG=Eastern Cooperative Oncology Group (ECOG) scale; HRQoL=health-related quality of life; LHRH=luteinising hormone releasing hormone; mHSPC=metastatic hormone sensitive prostate cancer; OS=overall survival; rPFS=radiographic progression free survival.

## 2 Background

### **Registration status**

2.1 Enzalutamide was TGA registered in April 2021 for the indication:

‘the treatment of patients with metastatic hormone-sensitive prostate cancer’

It is also indicated for:

- ‘the treatment of patients with non-metastatic castration-resistant prostate cancer.
- the treatment of patients with metastatic castration-resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated.
- the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.’

### **Previous PBAC consideration**

2.2 This was the first submission for enzalutamide for mHSPC. Enzalutamide is currently PBS-listed for castration resistant non-metastatic carcinoma of the prostate (mOCRPC) and for castration resistant metastatic carcinoma of the prostate (mCRPC).

2.3 The PBAC recommended listing apalutamide for mHSPC in July 2022. Apalutamide was recommended on a cost-utility basis versus placebo for use in patients with mHSPC regardless of disease volume or suitability for docetaxel<sup>1</sup>. At the time of the March 2023 PBAC meeting, this PBAC recommendation was yet to be implemented.

2.4 The PBAC also considered darolutamide, in combination with docetaxel and ADT, for mHSPC at the November 2022 PBAC meeting, with the PBAC’s recommendation deferred pending a TGA outcome<sup>2</sup>.

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

## 3 Requested listing

3.1 The submission indicated that the requested restriction was intended to be aligned with the restriction proposed by the PBAC in July 2022 for apalutamide. The submission also proposed an alternate listing for use in LV patients and HV patients who are intolerant to docetaxel which is not presented below.

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<sup>1</sup> PBAC outcomes July 2022, available from: <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2022-07/pbac-web-outcomes-07-2022-v3.pdf> [accessed 23/11/2022].

<sup>2</sup> PBAC outcomes November 2022, available from: <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2022-11/pbac-web-outcomes-11-2022.pdf> [accessed 03/01/2023].

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MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Enzalutamide 40 mg oral capsule	\$3,536.92 published \$ effective	1	112	5	XTANDI®, Astellas Australia Pty Ltd
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
<b>Administrative Advice:</b> 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					
<b>Condition:</b> Metastatic castration sensitive					
<b>Indication:</b> Carcinoma of the prostate					
<b>Clinical criteria:</b> The treatment must be/have been initiated within 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 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 Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug AND Patient must be undergoing concurrent androgen deprivation therapy					
<b>Administrative Advice:</b> Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide					

Source: Tables 1.4-4 and 1.4-2, p20-21 of the submission.

- 3.2 The submission requested a special pricing arrangement, with an effective dispensed price for maximum quantity (DPMQ) of \$ (approved ex-manufacturer price (AEMP) \$ ), based on the price in the base case modelled economic evaluation. This effective AEMP was reduced by % in the Pre-Sub-Committee Response (PSCR) to \$ (DPMQ = \$ ) and by a further % in the pre-PBAC response to \$ (DPMQ = \$ ) which is the current AEMP for enzalutamide in the mCRPC setting. If apalutamide achieves PBS listing for mHSPC prior to the March 2023 PBAC meeting or shortly thereafter, the submission indicated that it would like to request an effective price that is consistent with apalutamide for mHSPC based on the equi-effective daily dose of 160 mg enzalutamide is equivalent to 240 mg apalutamide (see cost-minimisation approach below).
- 3.3 The PBAC considered that the restriction should allow the use of enzalutamide as dual therapy (with ADT) or as triple therapy (with ADT and docetaxel) to increase clinician choice.
- 3.4 The submission also requested transitioning arrangements for patients enrolled in a Patient Assistance Program (PAP) for mHSPC planned to start in early 2023. In the financial estimates, the submission assumed there will be < 500 grandfathered

patients initiating treatment. No further details were provided in relation to the PAP including patient eligibility. The Secretariat advised that the proposed restriction had been phrased in such a way that it would not exclude non-PBS initiated treatment where all PBS eligibility criteria are otherwise met.

*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, the goal of treatment in this population is to delay progression from mHSPC to metastatic castration-resistant prostate cancer (mCRPC) and prolong survival. ADT (lowering the serum testosterone to castrate levels either surgically or pharmaceutically) 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 novel hormonal agents (NHAs, abiraterone, enzalutamide and apalutamide) in combination with ADT for initial therapy of men with advanced disease. These combination therapies have now become a preferred approach for men with locally advanced HSPC, both non-metastatic and metastatic disease (ASCO 2021 and NCCN 2021).
- 4.2 Results from a growing list of published network meta-analyses (NMAs) suggest the combination therapies (i.e., apalutamide, abiraterone, enzalutamide or docetaxel plus ADT) do not differ significantly with respect to overall survival (OS). All are more effective than ADT alone, and, where reported, abiraterone plus ADT was often ranked highest in terms of estimated overall survival (OS) benefit and abiraterone or enzalutamide plus ADT the highest in terms of delaying progression. However, no combination therapy has been clearly proven to be superior to another (Sathianathen 2020<sup>3</sup>, Marchioni 2019<sup>4</sup>, Chen 2020<sup>5</sup> Wang 2021<sup>6</sup>, Wenzel 2021<sup>7</sup>, Mori 2021<sup>8</sup>, Mutlu 2021<sup>9</sup>). In addition, all NHA plus ADT combinations (particularly apalutamide or

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<sup>3</sup> Sathianathen NJ, Koschel S, Thangasamy IA, et al., 2020. Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. *Eur Urol.*, 77(3):365-372.

<sup>4</sup> Marchioni M, Di Nicola M, Primiceri G, et al., 2020. New Antiandrogen Compounds Compared to Docetaxel for Metastatic Hormone Sensitive Prostate Cancer: Results from a Network Meta-Analysis. *J Urol.*, 203(4):751-759.

<sup>5</sup> Chen J, Ni Y, Sun G, et al., 2020. Comparison of Current Systemic Combination Therapies for Metastatic Hormone-Sensitive Prostate Cancer and Selection of Candidates for Optimal Treatment: A Systematic Review and Bayesian Network Meta-Analysis. *Frontiers in Oncology*, 10:519388.

<sup>6</sup> Wang L, Paller CJ, Hong H, et al., 2021. Comparison of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. *JAMA Oncol.*, 7(3):412-420.

<sup>7</sup> Wenzel M, Nocera L, Collà Ruvolo C, et al., 2021. 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*, 25(2):139-148.

<sup>8</sup> Mori K, Mostafaei H, Sari Motlagh R, et al., 2021. Systemic therapies for metastatic hormone-sensitive prostate cancer: network meta-analysis. *BJU International*, 129(4):423-433.

<sup>9</sup> Mutlu H and Bozcuk H, The optimal upfront therapy in metastatic hormone-sensitive prostate cancer: A network meta-analysis. *Journal of Cancer Research and Therapeutics* (online ahead of print, accessed 5 August 2021). DOI: 10.4103/jcrt.JCRT\_23\_20

enzalutamide) were associated with significantly fewer side effects compared to docetaxel plus ADT.

- 4.3 Evidence is also emerging for triple therapy of ADT plus docetaxel and NHA, but with mixed results. There is currently a lack of guidance on the choice between dual or triple therapy for mHSPC, and the preferred regimen may depend on patient and clinician preferences, including their considerations of disease extent, patient frailty, additional toxicities associated with docetaxel and access to subsequent therapies given patients are only able to access NHAs once in their lifetime on the PBS.
- 4.4 Patient preferences for NHAs over docetaxel have been consistently observed in prostate cancer. The PBS listings of enzalutamide and abiraterone for mCRPC were restricted to patients who failed treatment with docetaxel OR were unsuitable for docetaxel on the basis of predicted intolerance. Despite the restrictions, data provided by the DUSC Secretariat indicated that in 2020, 69% of use of abiraterone and enzalutamide in mCRPC was in patients who had not received a prior supply of docetaxel. This prompted the PBAC to review the PBS listings of enzalutamide and abiraterone for mCRPC, ultimately recommending the listings be amended to allow use of enzalutamide and abiraterone prior to docetaxel.
- 4.5 The proposed intervention was enzalutamide, at a recommended dose of 160 mg (four 40 mg tablets) once daily, in combination with ADT. Referred to herein as 'enzalutamide' for simplicity. Treatment is to continue until disease progression.
- 4.6 Following the PBAC's recommendation of apalutamide in mHSPC, the PSCR confirmed that the clinical place in therapy for enzalutamide was for use in combination with ADT irrespective of disease volume and patient suitability for docetaxel.
- 4.7 The sponsor requested that enzalutamide be listed for the same patient population as apalutamide. Enzalutamide has a similar chemical structure to apalutamide, but with greater penetration of the blood–brain barrier<sup>10</sup>.

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

## **5 Comparator**

- 5.1 The submission nominated ADT alone as the main comparator. The ESC considered that this was appropriate.
- 5.2 The submission appropriately identified apalutamide as a near-market comparator. Apalutamide has a similar chemical structure to enzalutamide and was recommended for PBS listing for mHSPC at the July 2022 PBAC meeting.
- 5.3 The submission argued that darolutamide was not a relevant near-market comparator because darolutamide sought PBS listing for use in combination with docetaxel and

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<sup>10</sup> Cattrini C, Caffo O, De Giorgi U, et al., 2022. Apalutamide, Darolutamide and Enzalutamide for Nonmetastatic Castration-Resistant Prostate Cancer (mCRPC): A Critical Review. *Cancers (Basel)*, 14(7):1792. DOI: 10.3390/cancers14071792.

ADT (i.e., triple therapy) for the treatment of chemotherapy eligible/selected mHSPC population (which would typically be high volume and/or high risk/de novo metastatic disease), whereas the current submission was for enzalutamide as dual therapy. Following the recent PBAC recommendation to list apalutamide + ADT on the PBS for all patients with mHSPC regardless of disease volume, suitability for docetaxel, or concomitant treatments (i.e., there was no impediment to giving apalutamide + ADT in combination with docetaxel) and given the enzalutamide submission sought the same PBS listing as apalutamide, darolutamide would also be a relevant comparator. The ENZAMET trial included evidence for enzalutamide in triple therapy (see Section 6 Consideration of the evidence). The listed TGA indications for the NHAs are sufficiently broad (e.g., enzalutamide is registered for use in the treatment of patients with mHSPC) to encompass use in either dual or triple therapy for mHSPC. The PSCR reiterated that darolutamide was not a relevant near-market comparator. The ESC considered that as the proposed apalutamide restriction did not preclude use with ADT and docetaxel, it was likely that, if recommended, the proposed enzalutamide restriction also would not preclude this combination, making darolutamide + ADT + docetaxel a relevant comparator.

- 5.4 Another NHA with evidence of benefit in mHSPC is abiraterone and may be a potential future comparator for enzalutamide. Abiraterone is currently TGA registered for use in newly diagnosed high risk mHSPC.

*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 the Medical Oncology Group of Australia (MOGA) which expressed its strong support for the enzalutamide submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the ARCHES and ENZEMET trials. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for enzalutamide, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>11</sup>, based on a comparison with placebo plus ADT.

### ***Clinical trials***

- 6.3 The submission was based on two RCTs. The main trial (ARCHES) compared enzalutamide + ADT to ADT alone (i.e., enzalutamide versus placebo) and the

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<sup>11</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

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supportive trial (ENZAMET) compared enzalutamide + ADT versus a non-steroidal anti androgen (NSAA) of either bicalutamide, nilutamide, or flutamide + ADT (i.e., enzalutamide versus NSAA).

- 6.4 Approximately 45% of patients in each treatment arm of ENZAMET were also pre-planned to receive concomitant docetaxel, thus the ENZAMET trial also provides evidence for enzalutamide in triple therapy (i.e., enzalutamide + docetaxel + ADT versus docetaxel + ADT). Although concomitant docetaxel was not permitted in ARCHES or TITAN, a proportion of patients in TITAN (n=205, 18.5%) and ARCHES (n=113, 10.7%) received prior docetaxel with the majority completing the full 6 cycles.
- 6.5 The submission also identified the TITAN trial as evidence for the nominated near market comparator apalutamide, comparing apalutamide + ADT versus ADT alone (i.e., apalutamide versus placebo). The PBAC had previously considered evidence from TITAN in the November 2021 and July 2022 apalutamide submissions for mHSPC.
- 6.6 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
ARCHES NCT02677896	A Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC) (ARCHES).	31 May 2019
	Armstrong AJ, Szmulewitz RZ, Petrylak DP et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer.	Journal of Clinical Oncology 2019; 37(32): 2974-2986.
	Armstrong AJ, Azad AA, Iguchi T et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer.	Journal of Clinical Oncology 2022; 40(15): 1616-1622.
ENZAMET NCT02446405	Randomized Phase 3 Trial of Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer: ENZAMET Interim Clinical Study Report	10 June 2019
	Davis ID, Martin AJ, Stockler MR et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. Davis ID, Martin AJ, Zielinski RR, et al. Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC).	NEJM 2019; 381(2): 121-131. Journal of Clinical Oncology 2022; 41, LBA5004-LBA5004.
TITAN NCT02489318	A Study of Apalutamide (JNJ-56021927, ARN-509) Plus Androgen Deprivation Therapy (ADT) Versus ADT in Participants With mHSPC	August 2013
	Chi KN, Chowdhury S, Bjartell A et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. Chi KN, Agarwal N, Bjartell A et al. Apalutamide for metastatic, castration-sensitive prostate cancer.	Journal of Clinical Oncology 2021; 39(20): 2294-2303. NEJM 2019; 381(1), pp.13-24.

Source: Table 2.2-1, pp 29-31 of the submission.

- 6.7 The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	Modelled evaluation
<b>Enzalutamide (plus ADT) vs placebo (plus ADT)</b>							
ARCHES	1150	R, MC, PC, DB, 14-44 mths <sup>a</sup> , OL extension	Low	- Enzalutamide 4 x 40 mg daily + ADT - Placebo daily + ADT	mHSPC	1°: rPFS 2°: OS	Yes (main analysis)
<b>Enzalutamide (plus ADT) vs NSAA (plus ADT)</b>							
ENZAMET	1125	R, MC, OL, 34-68 mths <sup>b</sup>	Unclear	- Enzalutamide 4 x 40 mg daily + ADT - NSAA (bicalutamide, nilutamide, or flutamide) + ADT After enrolment of the first 88 patients, a protocol amendment permitted initiation of early treatment with up 18 weeks (6 cycles) of docetaxel (75 mg/m <sup>2</sup> ) at the discretion of the treating clinician in 45% versus 44% in the enzalutamide and NSAA arms, respectively. Up to 2 cycles of docetaxel were also permitted prior to randomisation.	mHSPC	1°: OS 2°: PSA PFS, rPFS, all- cause mortality	Yes, (supportive analysis)
<b>Apalutamide (plus ADT) vs placebo (plus ADT)</b>							
TITAN	1052	R, MC, PC, DB, 22-44 mths <sup>c</sup> , OL extension	Low	- Apalutamide 4 x 60 mg daily + ADT - Placebo daily plus ADT	mHSPC	1°: rPFS, OS 2°: pain progression, SREs, initiation of chemotherapy	Not used

Compiled during the evaluation, based on information contained on pp32-34, 59-60, 74 and 83-84 of the submission and Armstrong et al. 2022.

ADT=androgen deprivation therapy; DB=double blind; MC=multi-centre; mHSPC=metastatic hormone sensitive prostate cancer; NSAA=nonsteroidal antiandrogen; OL=open label; OS=overall survival; PC=placebo-controlled; PFS=progression-free survival; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival; R=randomised; SRE=skeletal-related event.

<sup>a</sup> Median follow ups at time of primary and final data analyses were 14.4 and 44.6 months respectively. Following primary data analysis of rPFS in October 2018, all eligible patients could be treated on study with OL enzalutamide at the discretion of the patient and investigator in the OL extension phase. The final analyses were performed in May 2021.

<sup>b</sup> Median follow-up at time of interim analysis was 34 months and at time of latest data analysis was 68 months.

<sup>c</sup> Median follow-up at time of interim analysis was 22.7 months and at time of 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.

6.8 Overall survival (OS) and progression free survival (PFS) were the key outcomes in all trials (primary or key secondary). While OS was measured similarly across the trials, PFS measurement differed. PFS was measured as radiographic PFS (rPFS) in ARCHES and TITAN, and clinical PFS in ENZAMET. In ARCHES and TITAN, rPFS was defined similarly as soft tissue lesions using CT/MRI or by bone lesion progression on bone scans. Scans were performed at screening, week 13 and every 12 weeks thereafter. In ENZAMET, clinical progression was defined as the earliest sign of radiographic progression, the development of symptoms attributable to cancer progression, or the initiation of another anticancer treatment for prostate cancer. Clinic assessments and PSA levels were performed at baseline and every 12 weeks thereafter, while imaging was performed at baseline and at evidence of PSA or clinical progression.

- 6.9 The individual trials were generally well balanced with respect to baseline patient characteristics. There was however a lower proportion of patients with high volume disease (52.3%) in ENZAMET versus ARCHES or TITAN (approximately 60%). In ENZAMET, given the decision to initiate treatment with docetaxel was left up to the individual patients and their physicians, there was a higher concentration of high-volume disease patients in the pre-planned docetaxel subgroup versus those not planned to receive docetaxel (70.8% compared to 37.3%). A higher proportion of patients in TITAN had de novo disease compared to ARCHES or ENZAMET (81.0% classified as M1 versus 66.7% in ARCHES and 60.6% ENZAMET). In ENZAMET the proportion of patients with confirmed M1 status was also higher in the pre-planned docetaxel subgroup (71.8%) versus those without pre-planned docetaxel (51.6%).
- 6.10 Overall, there was a low risk of bias for ARCHES and TITAN however due to ENZAMET being an open label trial, there was a risk of bias in ENZAMET due to knowledge of treatment assignment. In ENZAMET, there was a higher proportion of patients with one or more major protocol deviations in the enzalutamide arm (16.2%) compared to NSAA (7.7%), largely related to receiving excluded concomitant treatment (6% compared to 0.4%) and not satisfying study entry criteria (5.5% compared to 3.7%). Protocol deviations in ARCHES and TITAN were similar between treatment groups. In all trials, discontinuation was lower in the intervention arm compared to the control. In all trials, the most frequently reported primary reason for permanent treatment discontinuation was progressive disease (clinical progression).
- 6.11 In ARCHES and TITAN, post the interim analysis reaching statistical significance, the trials were unblinded and patients who remained progression free switched to open label treatment with either enzalutamide or apalutamide. In ARCHES, 180 (31.3%) patients from the control arm crossed over and received treatment with enzalutamide plus ADT (median time to crossover, 21.5 months). In TITAN, 208 (39.5%) placebo patients switched to receive open-label apalutamide. The submission presented OS results unadjusted and adjusted for treatment switching. While this may be a source of bias, the submission has used the unadjusted results in the primary analysis and the modelled economic evaluation. This approach would also be consistent with the PBAC's prior recommendations for apalutamide and darolutamide in m0CRPC (see apalutamide Public Summary Document (PSD), November 2020 PBAC meeting and darolutamide PSD, March 2021 PBAC meeting) and the presentation of evidence for apalutamide in mHSPC (paragraph 6.14, apalutamide PSD, November 2021).
- 6.12 The submission also presented indirect treatment comparisons (ITCs) for enzalutamide versus apalutamide. The ITCs were conducted using the Bucher method, comparing data from: i) ARCHES for enzalutamide and TITAN for apalutamide (primary analysis), and ii) from ARCHES and the no planned docetaxel subgroup of ENZAMET versus TITAN (supportive analysis), all using the control arms as common reference.
- 6.13 The submission indicated that the reason for choosing the no planned docetaxel subgroup over ITT results from ENZAMET was because these patients were considered more comparable with those enrolled in ARCHES. However, given apalutamide was

recommended for PBS listing on an all-comers basis, the ITT population from ENZAMET is also relevant, a sensitivity analysis pooling results from the ITT ENZAMET population with ARCHES was additionally conducted during the evaluation.

***Comparative effectiveness***

- 6.14 Table 4, Figure 1 and Figure 2 summarise results of PFS and OS in ARCHES, ENZAMET and TITAN as well as the results of the indirect treatment comparisons presented in the submission and additional analysis conducted during the evaluation.
- 6.15 The OS and PFS results from ENZAMET and ARCHES were pooled using weighting by trial sample size rather than the more preferred inverse variance weighting method. ITC results were re-estimated during in the evaluation using inverse variance weighting and was found to have minimal impact on the ITC results.

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Table 4: PFS and OS in the included trials and results of ITC (unless specified, ITT data is reported)

	NHA	NHA arm		Control arm <sup>a</sup>		HR (95% CI)
		n/N (%)	Median mths (95% CI)	n/N (%)	Median mths (95% CI)	
<b>PFS<sup>b</sup></b>						
ARCHES <sup>c</sup>	ENZA	91/574 (15.9%) <sup>c</sup>	NR	201/576 (34.9%)	19.0 (16.6-22.2)	<b>0.39 (0.30, 0.50)<sup>c</sup></b>
ENZAMET		167/563 (29.7%)	NR	320/562 (56.9%)	NR	<b>0.40 (0.33, 0.49)</b>
No planned docetaxel <sup>c</sup>		76/309 (24.6%) <sup>c</sup>	NR	174/313 (55.6%) <sup>c</sup>	NR	<b>0.34 (0.26, 0.44)<sup>c</sup></b>
Planned docetaxel		91/254 (35.8%)	NR	146/249 (58.6%)	NR	<b>0.48 (0.37, 0.62)</b>
<b>Pooled ENZA(no docetaxel)</b>		167/883 (18.9%)	NR	375/889 (42.2%)	NR	<b>0.36 (0.30, 0.44)</b>
<b>Pooled ENZA (ITT)</b>		257/1137 (22.7%)	NR	521/1138 (45.8%)	NR	<b>0.40 (0.34, 0.46)</b>
TITAN <sup>c</sup>	APA	134/252 (25.5%) <sup>c</sup>	NE	231/527 (43.8%) <sup>c</sup>	22.1 (18.5-32.9)	<b>0.48 (0.39, 0.60)<sup>c</sup></b>
<b>ITC enzalutamide (ARCHES) vs apalutamide (TITAN)</b>						0.81 (0.58, 1.14)
<b>ITC enzalutamide (pooled ARCHES+ ENZAMET no docetaxel subgroup) vs apalutamide (TITAN)</b>						0.75 (0.56, 1.00)
<b>ITC enzalutamide (pooled ARCHES+ ENZAMET ITT) vs apalutamide (TITAN)</b>						0.83 (0.64, 1.08)
<b>OS</b>						
ARCHES (2022) <sup>c</sup> Median 44.6mths follow up	ENZA	154/574 (26.8%)	NR	202/576 (35.1%)	NR (49.7 to NR)	<b>0.66 (0.53, 0.81)<sup>c</sup></b>
ENZAMET (2019) Median 34mths follow up		102/563 (18.1%)	NR	143/562 (25.4%)	NR	<b>0.67 (0.52, 0.86)</b>
No planned docetaxel		50/309	NR	88/313	NR	<b>0.53 (0.37, 0.75)</b>
Planned docetaxel		52/254	NR	55/249	NR	0.90 (0.62, 1.31)
ENZAMET (2022) Median 68mths follow up		208/563 (36.9%)	NR	268/562 (47.7%)	NR	<b>0.70 (0.58, 0.84)</b>
No planned docetaxel <sup>c</sup>		100/310 <sup>d</sup> (32.4%)	NR	145/312 <sup>d</sup> (46.5%)	NR	<b>0.60 (0.47, 0.78)<sup>c</sup></b>
Planned docetaxel		108/253 <sup>d</sup> (42.7%)	NR	123/250 <sup>d</sup> (49.2%)	NR	<b>0.82 (0.63, 1.06)</b>
<b>Pooled ENZA (no docetaxel)</b>		254/884 (28.7%)	NR	347/888 (39.1%)	NR	<b>0.63 (0.54, 0.75)</b>
<b>Pooled ENZA (ITT)</b>		362/1137(31.8%)	NR	470/1138 (41.3%)	NR	<b>0.68 (0.59, 0.78)</b>
TITAN (2021) <sup>c</sup> Median 44mths follow up		APA	170/525 (32.4%)	NR	235/527 (44.6%)	52.2(41.9- NR)
<b>ITC enzalutamide (ARCHES) vs apalutamide (TITAN)</b>						1.02 (0.76, 1.36)
<b>ITC enzalutamide (pooled ARCHES+ ENZAMET no docetaxel subgroup) vs apalutamide (TITAN)</b>						0.97 (0.75, 1.26)
<b>ITC enzalutamide (pooled ARCHES+ ENZAMET ITT) vs apalutamide (TITAN)</b>						1.05 (0.82, 1.34)

**Bold** typography indicates statistically significant results. The submission's meta-analyses were rerun pooling using inverse variance weighting rather than by sample size using Cochrane review manager 5.4.1.

Source: compiled during the evaluation based on data presented in Tables 2.5-1, 2.5-13, 2.5-15, 2.5-2, 2.5-12, and 2.5-14 of the submission and the published trial reports.

ADT=androgen deprivation therapy; APA=apalutamide; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; ITC=indirect treatment comparison; n=number of participants reporting data; N=total participants in group; NE=not evaluable; NR=not reached; NSAA=nonsteroidal antiandrogen.

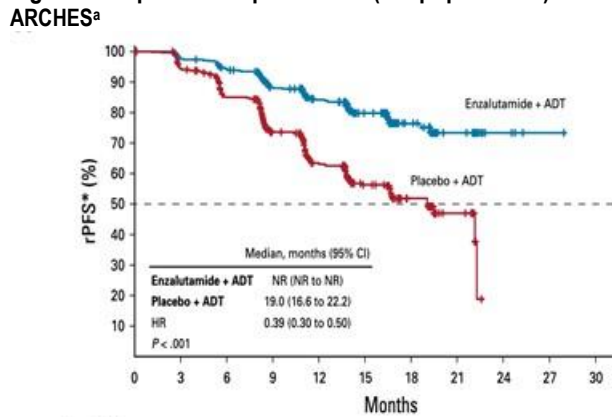
<sup>a</sup> placebo +ADT for ARCHES and TITAN and NSAA +ADT in ENZAMET.

<sup>b</sup> Radiographic PFS in ARCHES and TITAN and Clinical PFS in ENZAMET.

<sup>c</sup> Data used in the submission's butcher ITC.

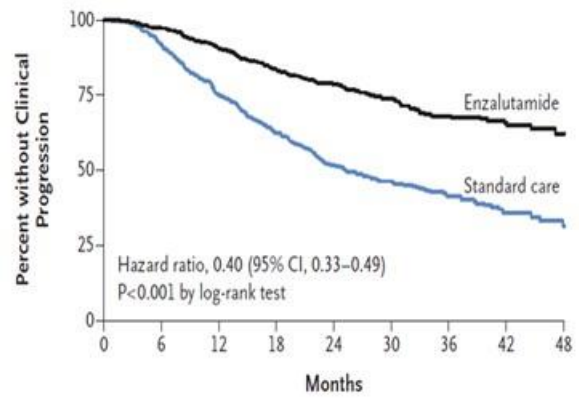
<sup>d</sup> From Davies et al 2019 published report for ENZAMET. These Ns were inconsistent with Ns reported in Davies 2019 which were 309 and 313 for the no planned docetaxel subgroup and 254 and 249 in the planned docetaxel subgroup in the enzalutamide +ADT and NSAA+ADT treatment arms respectively.

Figure 1: Kaplan-Meier plot of PFS (ITT populations) ARCHES<sup>a</sup>



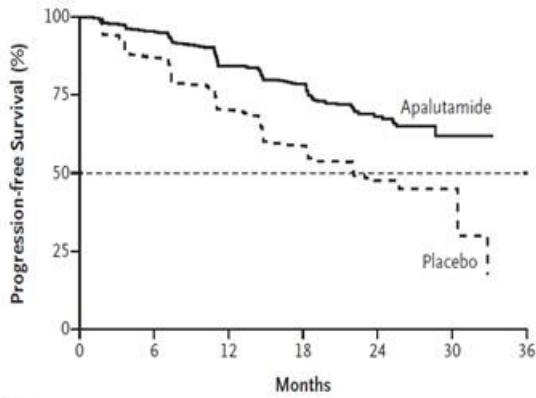
No. at risk	0	3	6	9	12	15	18	21	24	27	30
Enzalutamide + ADT	574	516	483	370	256	144	62	23	4	1	0
Placebo + ADT	576	511	445	314	191	106	38	10	0	0	0

ENZAMET<sup>b</sup>



No. at Risk	0	6	12	18	24	30	36	42	48
Enzalutamide	563	547	507	468	424	284	156	84	36
Standard care	562	512	418	346	272	182	96	50	17

TITAN<sup>a</sup>



No. at Risk	0	6	12	18	24	30	36
Apalutamide	525	469	389	315	89	2	0
Placebo	527	437	325	229	57	3	0

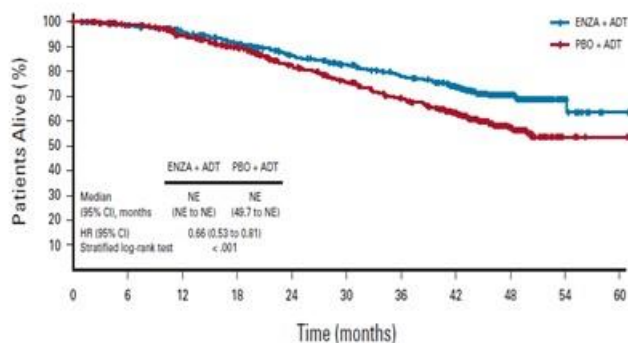
Source: Figures 2-3, 2-17 and 2-23 of the submission.

ADT=androgen deprivation therapy; CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; KM=Kaplan-Meier; NR=not reached; PFS=progression free survival; rPFS=radiographic progression free survival.

<sup>a</sup> Radiographic progression free survival

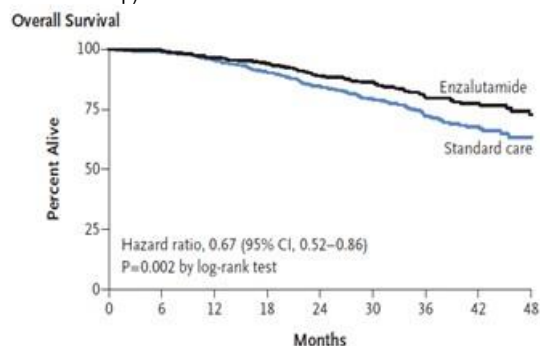
<sup>b</sup> Clinical progression free survival

Figure 2: Kaplan-Meier plot of OS (ITT populations)  
ARCHES 2022 median 44.6mth follow up



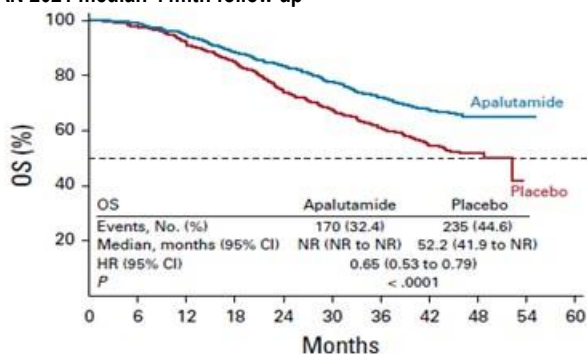
No. at risk:	ENZA + ADT	574	568	559	551	525	516	488	479	457	445	427	412	396	384	378	354	254	120	49	3	1
PBO + ADT	576	564	548	539	511	489	468	435	404	385	363	338	322	301	232	154	90	26	4	1	1	

ENZAMET 2019 Median 34mth follow up (KM plot was not provided in the submission for the latest 2022 data cut, after 68mth median follow up)



No. at Risk	Enzalutamide	563	558	541	527	480	340	189	106	45
Standard care	562	551	531	501	452	311	174	86	32	

TITAN 2021 median 44mth follow up



No. at risk:	Apalutamide	525	513	489	452	425	394	362	227	52	3	0
Placebo	527	510	474	436	374	339	301	181	43	0	0	

Source: Figures 2-4, 2-14 and 2-22 of the submission.

ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; ITT=intention-to-treat; KM=Kaplan-Meier; NE=not evaluable; NR=not reached; OS=overall survival; PBO=placebo.

6.16 All trials demonstrated superior PFS and OS for NHA versus standard of care. ARCHES showed statistically significantly better rPFS for enzalutamide versus placebo, with a 61% reduction in the risk of rPFS or death (HR = 0.39; 95% CI: 0.30, 0.50; p-value < 0.001). Similarly, in TITAN, there was a 52% lower risk of rPFS or death in the apalutamide + ADT arm (HR = 0.48; 95% CI: 0.39, 0.60; p-value < 0.001), compared to placebo + ADT. In ENZAMET, there was a 60% lower risk of clinical PFS (imaging, symptoms, signs) in the enzalutamide arm compared with NSAA (HR = 0.40; 95% CI: 0.33, 0.49; p-value < 0.001). Clinical PFS risk was significantly reduced in patients with and without planned docetaxel (HR = 0.48; 95% CI: 0.37, 0.62 and HR = 0.34; 95% CI: 0.26, 0.44 respectively). For OS, at all follow up assessment points, the NHAs demonstrated a 30-35% reduction in the risk of death versus control in the ITT populations.

6.17 There was no statistically significant improvement in OS for enzalutamide + ADT in the pre-planned docetaxel subgroup of ENZAMET (i.e., triple therapy). This differed to

results from trials for abiraterone (PEACE 1<sup>12</sup>) and darolutamide (ARARENS<sup>13</sup>) where triple therapy (NHA + ADT + docetaxel) was found to be superior to docetaxel + ADT for OS. The reason for the difference in the results for enzalutamide was uncertain, however may be influenced by differences in trial populations and trial design and a more actively managed control group in ENZAMET (NHA + ADT + docetaxel vs NSAA + ADT + docetaxel). For example, a higher proportion of, enrolled patients in ARASENS (86%) and PEACE 1 (100%) had confirmed M1 status indicating de-novo metastatic disease, whereas only 61% of patients from ENZAMET had confirmed M1 status (71.8% in the pre-planned docetaxel subgroup). Updated ENZAMET OS results after 68 months of follow-up showed the subgroup of patients with M1 status at diagnosis treated with triple therapy did experience a significant OS benefit (HR = 0.73; 95% CI: 0.55, 0.99)<sup>14</sup>. ENZAMET was also an open label study whereas PEACE 1 and ARASENS were double blind, this may have affected treatment choices of patients and clinicians in ENZAMET, particularly for patients in the control arms.

- 6.18 No significant differences were demonstrated between enzalutamide and apalutamide in terms of PFS or OS for any of the indirect treatment comparisons presented.
- 6.19 Results for secondary outcomes also either numerically and/or statistically favoured enzalutamide compared to placebo/NSAA groups. Treatment with NHAs was associated with significant improvements in PSA progression, time to next antineoplastic therapy, time to castration resistance, time to SSE/SRE (ARCHES only), but not for pain progression (defined as a 30% or greater increase in BPI-SF item scores).
- 6.20 Results of subgroup analyses were also generally consistent with the ITT analyses. Some of the subgroups had small number of patients and events, and results need to be taken with caution. Efficacy of enzalutamide in terms of OS in mHSPC patients was not affected by ECOG status, comorbidities or docetaxel contra-indications. The effect for enzalutamide for disease volume varied in ARCHES and ENZAMET, with similar effect by disease volume in ARCHES (HR = 0.66) for both high and low volume disease, however the difference in the low volume group did not reach statistical significance likely due to the smaller sample size. In ENZAMET, the effect of enzalutamide versus NSAA was larger in the low volume subgroup (HR = 0.43; 95% CI: 0.26, 0.72) versus in the high-volume group (HR = 0.80; 95% CI: 0.59, 1.07). This may be due to the different treatments received in these strata, as a larger proportion of high-volume patients

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<sup>12</sup> Fizazi K, Foulon S, Carles J, et al., 2022. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2×2 factorial design. *The Lancet*, 399(10336), pp.1695-1707.

<sup>13</sup> Smith MR, Hussain M, Saad F, et al., 2022. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *New England Journal of Medicine*, 386(12), pp.1132-1142.

<sup>14</sup> Davis ID, Martin AJ, Zielinski RR, et al., 2022. Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC). *Journal of Clinical Oncology*, 40:17\_suppl, LBA5004-LBA5004.

were selected for pre-planned docetaxel treatment. Apalutamide was effective against placebo for OS irrespective of disease volume, however the effect was numerically larger in the low volume group (HR = 0.52) versus in the high-volume group (HR = 0.72).

- 6.21 In ARCHES and TITAN, deterioration in quality of life was defined as a 10-point decrease in Functional Assessment of Cancer Therapy – Prostate (FACT-P) total score. Comparing enzalutamide and apalutamide groups to the placebo group, there was no difference in the time to deterioration of quality of life based on the FACT-P total score. In ENZAMET, Overall Health related Quality of Life (OHRQL) was measured using the European Organisation for Research and Treatment of Cancer (EORTC) core quality-of-life questionnaire and QLM-PR25 and EQ5D. Enzalutamide was associated with worsening of self-reported fatigue, cognitive function, and physical function, but not OHRQL. Enzalutamide was however associated with improved deterioration-free survival for OHRQL, physical function, and cognitive function because delays in disease progression outweighed early deteriorations in these aspects of health-related quality of life.

### Comparative harms

- 6.22 Table 5 summarises treatment emergent adverse events (TEAEs) in ARCHES, ENZAMET and TITAN.

**Table 5: Summary of key adverse events in the trials**

Trial ID	ARCHES			ENZAMET			TITAN		
	ENZA N=572 n (%)	PBO N=574 n (%)	RD (95% CI)	ENZA N=563 n (%)	NSAA N=558 n (%)	RD (95% CI)	APA N=524 n (%)	PBO N=527 n (%)	RD (95% CI)
Any TEAE	520 (90.9)	504 (87.8)	0.03 (-0.00, 0.07)	563 (100)	548 (98.2)	0.02 (0.01, 0.03)	507 (96.8)	509 (96.6)	0.00 (-0.02, 0.02)
Grade 3-4 TEAE	224 (39.2)	160 (27.9)	0.11 (0.06, 0.17)	315 (56.0)	234 (41.9)	0.14 (0.08, 0.20)	221 (42.2)	215 (40.8)	0.01 (-0.05, 0.07)
SAE	104 (18.2)*	112 (19.5)*	-0.01 (-0.06, 0.03)	235 (41.7)	189 (33.9)	0.08 (0.02, 0.14)	104 (19.8)	107 (20.3)	-0.00 (-0.05, 0.04)
TEAE leading to death	30 (5.2)	12 (2.1)	0.03 (0.01, 0.05)	8 (1.4)	13 (2.3)	-0.01 (-0.03, 0.01)	10 (1.9)	16 (3.0)	-0.01 (-0.03, 0.01)
TEAE leading to discontinuation	41 (7.2)*	30 (5.2)*	0.02 (-0.01, 0.05)	33 (5.9)	14 (2.5)	0.03 (0.01, 0.06)	42 (8.0)	28 (5.3)	0.03 (-0.00, 0.06)

Source: Table 2.5-18, 2.5-19, and 2.5-21 of the submission; Table 37, ARCHES CSR; Table 13, ENZAMET CSR.

AE=adverse event; CI=confidence interval; ENZA=enzalutamide; NSAA=nonsteroidal antiandrogen; PBO=placebo; RD=risk difference; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

\* Data cut-off 14 October 2018

- 6.23 Safety outcomes reported in ARCHES and ENZAMET were consistent with the known safety profile of enzalutamide. Enzalutamide has been available as a treatment for mCRPC since 2012 in the US and 2013 in Europe and more recently for mOCRPC.
- 6.24 ARCHES and TITAN had similar proportions of patients who experienced any TEAE, SAE and TEAE leading to discontinuation. However, in ARCHES, Grade 3 or 4 TEAEs and TEAEs leading to death were significantly higher in patients treated with enzalutamide compared to placebo. This was not the case in TITAN for apalutamide compared to

placebo. Compared to control, enzalutamide treatment was associated with significantly more frequently reported hot flushes, fatigue, arthralgia, hypertension, nausea, asthenia, dizziness and falls, whereas apalutamide treatment was associated with more hot flushes (similar to enzalutamide), greater weight gain, diarrhoea, pruritus and rash and a small increase in ischaemic heart disease and ischaemic cerebrovascular events.

- 6.25 The submission did not present any ITCs comparing safety outcomes across the trials. The submission noted that in mOCRPC, the PBAC had previously considered that a claim that darolutamide was non-inferior in terms of safety to apalutamide and enzalutamide was reasonable (Darolutamide PSD, March 2021).

### ***Benefits/harms***

- 6.26 A summary of the comparative benefits and harms for enzalutamide versus placebo is presented in Table 6.

Table 6: Summary of comparative benefits and harms for enzalutamide and placebo

<b>Benefits</b>					
<b>Trial</b>	<b>ENZA</b>	<b>Placebo</b>	<b>Absolute Difference</b>		<b>HR (95% CI)</b>
<b>Progression free survival</b>					
<b>ARCHES (2019)</b>					
Progressed, n/N (%)	91/574 (15.9%)	201/576 (34.9%)	-		<b>0.39 (0.30-0.50)</b>
Median rPFS, months (95% CI)	NR	19.0 (16.6-22.2)	NE		
% not progressed at 12 months (95% CI)	84.5 (NR)	63.7 (NR)	20.8%		
% not progressed at 18 months (95% CI)	76.5 (NR)	51.7 (NR)	24.8%		
<b>ENZAMET (2019)</b>					
Progressed, n/N (%)	167/563 (29.7%)	320/562 (56.9%)	-		<b>0.40 (0.33-0.49)</b>
Median clinical PFS, months (95% CI)	NR	NR	NE		
% not progressed at 12 months (95% CI)^	90	75	15%		
% not progressed at 18 months (95% CI)^	85	63	22%		
% not progressed at 48 months (95% CI)^	63	31	32%		
<b>Overall survival</b>					
<b>ARCHES (2022) - Median 44.6 months follow up</b>					
Deaths, n/N (%)	154/574 (26.8%)	202/576 (35.1%)	-		<b>0.66 (0.53-0.81)</b>
Median OS, months (95% CI)	NR	NR (49.7 to NR)	NE		
% Alive at 12 months (95% CI)	95.5 (NR)	93.9 (NR)	1.6%		
% Alive at 18 months (95% CI)	89.9 (NR)	89.4 (NR)	0.5%		
% Alive at 24 months (95% CI)	88.9 (NR)	83.3 (NR)	5.6%		
% Alive at 36 months (95% CI)^	82	69	13%		
% Alive at 48 months (95% CI)^	70	57	13%		
<b>ENZAMET (2022) – Median 68 months follow up</b>					
Deaths, n/N (%)	208/563 (36.9%)	268/562 (47.7%)	-		<b>0.70 (0.58-0.84)</b>
Median OS, months (95% CI)	NR	NR	NE		
% Alive at 12 months (95% CI)	96.6 (94.7, 97.8)	95.7 (93.6, 97.1)	0.9%		
% Alive at 24 months (95% CI)	89.1 (86.2, 91.4)	84.7 (81.4, 87.4)	4.4%		
% Alive at 36 months (95% CI)	79.7 (75.4, 83.3)	72.4 (67.8, 76.4)	7.3%		
% Alive at 48 months (95% CI)^	72	63	9%		
<b>Harms</b>					
<b>Key study drug related TEAEs</b>	<b>NHA n/N (%)</b>	<b>Placebo n/N (%)</b>	<b>Event rate/100 PY</b>		<b>RD (95% CI)</b>
			<b>ENZA</b>	<b>PBO</b>	
<b>ARCHES (2022)</b>					
Grade 3-4 TEAEs	224/572 (39.2)	160/574 (27.9)	14.7	21.8	0.113 (0.059, 0.167)
Grade 3-4 hypertension	30/572 (5.2)	13/574 (2.3)	2.0	1.8	0.030 (0.008, 0.052)
<b>ENZAMET (2019)</b>					
Grade 3-4 TEAEs	320/563 (56.8)	237/558 (42.5)	24.1	23.0	0.144 (0.086, 0.202)
Grade 3-4 hypertension	43/563 (7.6)	25/558 (4.5)	3.2	2.4	0.032 (0.004, 0.059)

**Bold** typography indicates statistically significant results.

Source: Table 19, p79; Table 29, p92 of the submission; ENZAMET CSR.

CI=confidence interval; ENZA=enzalutamide; mCRPC=metastatic castration-resistant prostate cancer; n=number of participants reporting data; NE=not estimable; OS=overall survival

^ estimated from published KM curves.

6.27 On the basis of direct evidence from ARCHES and ENZAMET for every 100 patients treated with enzalutamide in comparison with standard of care (placebo or NSAA):

- Approximately 15-21 additional patients at 12 months, 22-25 additional patients at 18 months and 32 patients at 48 months will remain progression-free.
- Approximately 9-13 additional patients will remain alive after 48 months.

- Approximately 11-14 additional patients will develop Grade 3 or 4 TEAEs related to enzalutamide, over a 12-month period.
- Approximately 3 additional patients will develop Grade 3 or 4 hypertension, over a 12-month period.

### ***Clinical claim***

- 6.28 The submission described enzalutamide + ADT as superior in terms of effectiveness and as inferior (but manageable) in terms of safety compared to ADT alone. The ESC and PBAC considered that these claims were adequately supported by the trial evidence presented.
- 6.29 The submission also described enzalutamide + ADT as non-inferior in terms of efficacy and safety compared to apalutamide + ADT for the treatment of mHSPC. The ESC considered that the evidence presented in the submission adequately supported the claim of non-inferior efficacy as there were no significant differences between enzalutamide and apalutamide for PFS or OS in all ITC comparison sets. Although the submission did not present any ITCs for safety outcomes, the ESC noted that in m0CRPC, the PBAC had previously considered enzalutamide, darolutamide and apalutamide were likely non-inferior in terms of safety (paragraph 7.7, Darolutamide PSD, March 2021). The reported AEs of enzalutamide and apalutamide from the included trials were consistent with their known safety profiles. The PBAC considered that the claims versus apalutamide were adequately supported by the data.

### ***Economic analysis***

- 6.30 Consistent with the clinical claim, the submission presented two economic evaluations for enzalutamide: i) a modelled economic evaluation versus standard of care and ii) a cost-minimisation approach versus apalutamide. These are described separately below.

#### **Modelled economic evaluation**

- 6.31 The submission presented a cost-utility analysis comparing enzalutamide in combination with ADT (enzalutamide arm) versus ADT alone (ADT arm). The primary analysis was based on ITT data from ARCHES. Scenario analyses were also presented using a similar model structure for the low volume (LV) and high volume (HV) subgroups of ARCHES and the subgroup of patients without docetaxel combination treatment from ENZAMET. Thus, the modelled evidence was limited to dual therapy of NHA + ADT versus standard of care.
- 6.32 The model used a combination partitioned survival and Markov state model with five health states: PFS (i.e., mHSPC), progressed disease first line (PD1), progressed disease second line (PD2), progressed disease third line (PD3), and death. PD1-3 were intended to represent mCRPC. The partitioned survival model estimated the movement between PFS, PD and death, and the Markov state model estimated movement within PD, i.e., from PD1 to PD2 to PD3.

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Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Type of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years, life years
Populations	<p>The economic evaluation was presented for mHSPC patients who did not receive docetaxel, based on the ITT population in ARCHES. It was reasonable to use ARCHES in preference to ENZAMET as there were several concerns with ENZAMET that could either bias the results or make it less comparable to other studies, including: it had a broader definition of PFS (i.e., not rPFS), may be subject to bias as it was unblinded for treatment assignments, the control arm was NSAA + ADT (rather than the ADT alone) and there were comparatively fewer patients with de novo metastasis.</p> <p>Results for the HV and LV populations from ARCHES were also presented. As these subgroups likely differ in prognosis and could vary in proportion across trials and the intended Australian population it was appropriate to also present these results. However, as model inputs for the HV and LV models were estimated independently of the ITT analysis, combining the HV and LV results would not give the base case, and therefore these results may not be reasonable. In particular, survival for both HV and LV patients receiving ADT alone was estimated to be worse than the ITT population at Year 15.</p> <p>Paras 7.15-16 apalutamide mHSPC PSD, November 2021, recommended that an economic analysis including patients suitable for docetaxel be performed, and therefore restricting the analysis to patients not receiving docetaxel may not be appropriate.</p>
Time horizon	15 years compared to median follow-ups of 44.6 months (3.7 years) in ARCHES (main analysis) and 68 months (5.7 years) in ENZAMET (sensitivity analysis). Paras 7.15-16 apalutamide mHSPC PSD, November 2021, recommended a time horizon of 10 years for LV and 5 years for HV patients. A shorter time horizon is likely more appropriate for an older population (median age of 70 years in ARCHES and ENZAMET and 74 years in the Victorian Prostate Cancer Registry with metastatic prostate cancer). The PSCR presented a revised base case in which the time horizon was reduced to 10 years.
Methods used to generate results	<p>Partitioned survival model with Markov health states in progressed disease.</p> <p>The Markov states within progressed disease were informed by multiple sources and was more complex than other recent submissions in mHSPC. However, only time on NHA use in PD1 appeared to drive the model cost and benefit offsets.</p>
Health states	<p>5 health states:</p> <ul style="list-style-type: none"> <li>- Progression free survival (PFS) = mHSPC</li> <li>- Progressed disease 1L</li> <li>- Progressed disease 2L</li> <li>- Progressed disease 3L</li> <li>- Death.</li> </ul> <p>This was reasonable; although modelling multiple lines of treatment in progressed disease required additional assumptions and additional data sources.</p>
Cycle length	Monthly, with half cycle correction.
Transition probabilities	<p>Transitions between PFS, PD and death health states derived from KM data in ARCHES for OS rPFS and time to treatment discontinuation (TTD) and extrapolated to 15 years.</p> <p>Monthly transition probabilities between PD1, PD2 and PD3 were derived from treatment durations described in PREVAIL<sup>a</sup>, TAX 327<sup>b</sup>, AFFIRM<sup>c</sup>, COU-AA-301<sup>d</sup>, TROPIC<sup>e</sup> and p23 of the apalutamide mHSPC PSD, Nov 2021.</p> <p>AEs and SREs were estimated from ARCHES in mHSPC, and PREVAIL, TAX 327, AFFIRM, COU-AA-301 and TROPIC in mCRPC.</p> <p>None of the trials included in the PD transitions for ADT, docetaxel or cabazitaxel were published in the last 10 years. However, the impact of ADT, docetaxel and cabazitaxel use in progressed disease had minimal impact upon the ICER.</p>
Costs	<p>The model included costs for enzalutamide, background ADT, management of AEs, SREs, monitoring disease progression (PSA tests, specialists, imaging), subsequent treatment post progression (docetaxel, cabazitaxel, abiraterone/enzalutamide, antiandrogens, prednisolone) and end of life costs. The model assumed patients treated with enzalutamide for mHSPC do not receive abiraterone/enzalutamide in PD.</p>

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	ADT costs in the enzalutamide arm appeared to be underestimated, only occurring in PFS when enzalutamide treatment ceased. As such, undiscounted PFS ADT costs were \$728 in the enzalutamide arm, compared with \$10,655 in the ADT arm. The PSCR presented a revised base case in which the cost of ADT was applied to all alive patients in both treatment arms.
Utilities	Health state utilities derived from post-hoc analysis of EQ-5D-5L data in ARCHES (PFS, PD1, EoL), AFFIRM <sup>c</sup> (PD3), NICE TA712 <sup>f</sup> and TA377 (AEs and SREs) <sup>g</sup> . The utilities assumed were generally reasonable, however the choice to include EoL as a distinct utility was different from recent submissions and may be double counted as utility estimates in the other health states did not exclude patients who died before the next follow up. Removing the EoL disutility had minimal impact upon the ICER.
Software package	Excel 2016

Source: compiled during the evaluation from Table 3.1-1 (p117), Sections 3.1.1-3.1.5 (pp118-119), Section 3.2.2 (pp130-135) of the submission

AE = adverse event; ADT = androgen deprivation therapy; APA = apalutamide; DARO=darolutamide; EoL= end of life; EQ5D-5L = EuroQoL 5 Dimension 5-Level; HV = high volume; ICER=incremental cost effectiveness ratio; ITT = intention to treat; KM = Kaplan-Meier; LV = low volume; mCRPC = non-metastatic castration resistant prostate cancer; mCRPC = metastatic castrate resistant prostate cancer; mHSPC = metastatic hormone sensitive prostate cancer; NHA = novel hormonal agent; OS = overall survival; PBO = placebo; PD = progressive death; PFS = progression free survival; PSA = prostate specific antigen; rPFS = radiographic progression free survival, TTD=time to treatment discontinuation; SRE=skeletal related event.

<sup>a</sup> Armstrong, A. J. et al. Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial. *Eur Urol* 78, 347-357 (2020)

<sup>b</sup> Tannock, I. F. et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 351, 1502-1512 (2004)

<sup>c</sup> Scher, H. I. et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *New England Journal of Medicine* 367, 1187-1197 (2012)

<sup>d</sup> Fizazi, K. et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 13, 983-992 (2012)

<sup>e</sup> De Bono, J. S. et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *The Lancet* 376, 1147-1154 (2010)

<sup>f</sup> NICE. National Institute for Clinical Excellence. Enzalutamide for treating hormone-sensitive metastatic prostate cancer. Technology appraisal guidance (TA712). Available from: <https://www.nice.org.uk/guidance/ta712>

<sup>g</sup> NICE. National Institute for Clinical Excellence. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Technology appraisal guidance [TA377] Published: 27 January 2016. Accessed at <https://www.nice.org.uk/guidance/ta377>

6.33 The partitioned survival approach allocated patients to PFS, PD and death. All patients started in PFS (i.e., mHSPC). Each cycle patients in PFS either remained progression-free, developed progressed disease (i.e., became castrate resistant, mCRPC) or died; and patients with progressed disease either remained with progressed disease or died. Time in each health state was based on PFS and OS KM data from ARCHES extrapolated to 15 years, with allocation to PD the difference between the PFS and OS curves. Time on treatment was modelled independently of the health states but could not exceed PFS.

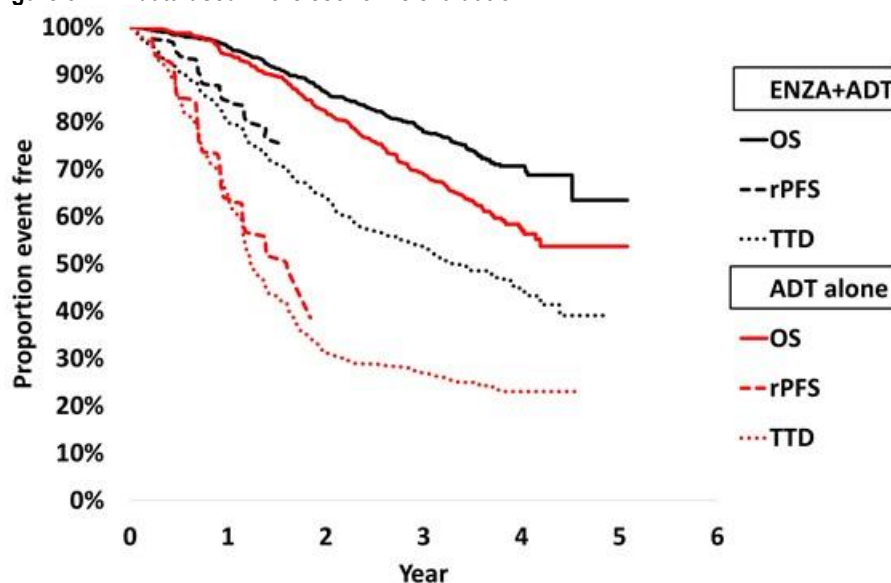
6.34 The Markov approach estimated movement between the PD health states. Upon entry to PD, patients entered the PD1 health state and each cycle patients in PD1 could remain on first-line PD treatment, move to second-line PD treatment (PD2) or die. Patients in PD2 could remain on second line treatment, move to third-line treatment (PD3) or die. Patients in PD3 could remain in PD3 or die. Patients in PD1 could not move directly to PD3 and patients could not go in reverse (e.g., PD3 to PD2). Monthly transition probabilities were based on treatment allocation upon entry to each PD health state and the expected duration of the treatment based upon trials in mCRPC

(PREVAIL, AFFIRM, TAX 327, TROPIC) and duration of NHA use in mCRPC reported in the apalutamide mHSPC PSD, November 2021.

6.35 The model estimated costs and benefits over the lifetime, with a time horizon of 15 years in the base case. The submission used modelled extrapolations of rPFS to justify the time horizon, which was not appropriate. The PBAC had previously recommended time horizons of 10 and 5 years in LV and HV patients respectively for mHSPC (paragraph 7.15-16, apalutamide PSD, Nov 2021 PBAC meeting). The model was sensitive to changes in time horizon, increasing to \$55,000 to < \$75,000 per QALY gained for a time horizon of 7.5 years, compared to \$35,000 to < \$45,000 per QALY gained in the submitted base case. The PSCR presented a revised base case in which the time horizon was reduced to 10 years. The ESC, noting that this was consistent with the time horizon applied for LV patients in the apalutamide July 2022 submission (Table 8, apalutamide PSD, July 2022 PBAC meeting), considered that it was reasonable.

6.36 KM data from ARCHES are presented in Figure 3.

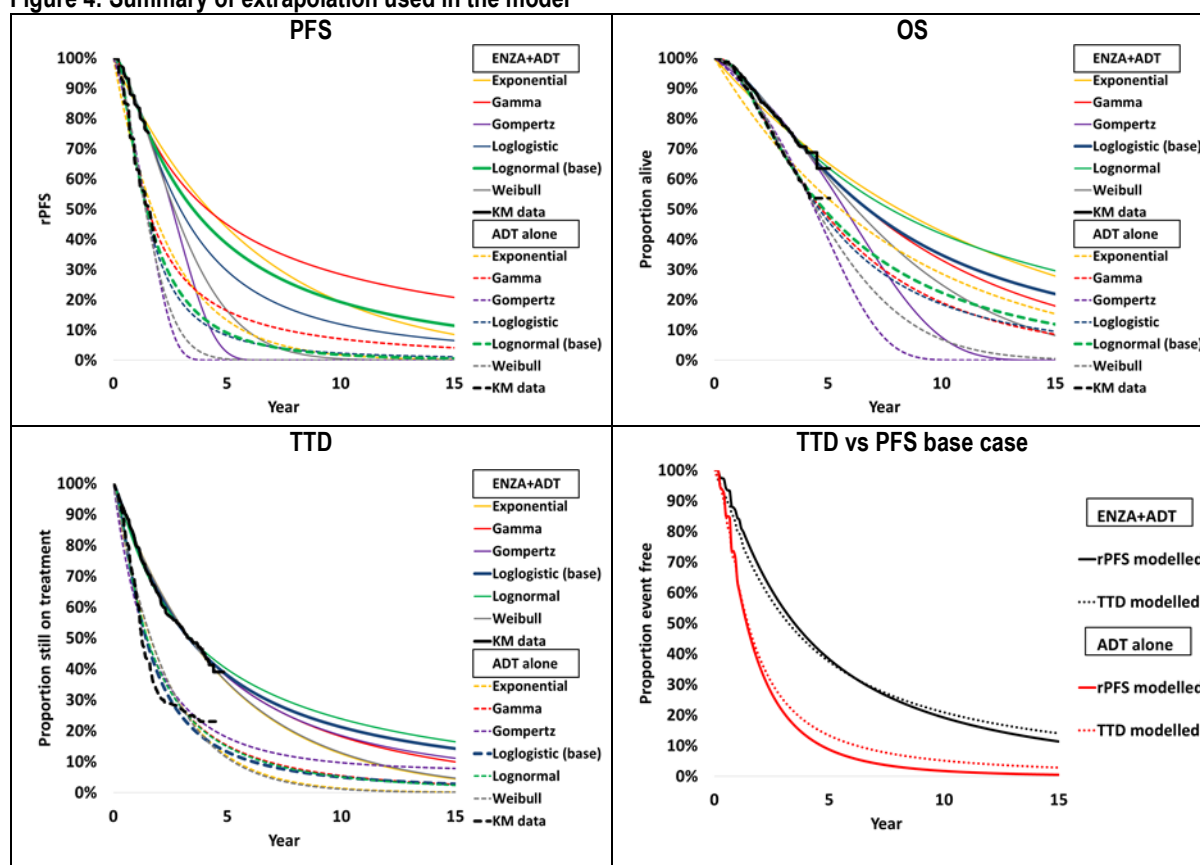
Figure 3 : KM data used in the economic evaluation



Source: compiled during the evaluation using Sheets 'rPFS', 'OS', 'TTD' of the Excel workbook 'Attachment 17 – Xtandi mHSPC Section 3A Cost-Eff Model\_vfinal.xlsm'  
 ADT=androgen deprivation therapy, ENZA=enzalutamide, OS=overall survival, rPFS=radiographic progression free survival, TTD=time to treatment discontinuation.

6.37 Extrapolations based on ARCHES ITT are presented in Figure 4.

Figure 4: Summary of extrapolation used in the model



Source: compiled during the evaluation using Sheets 'rPFS', 'OS', 'TTD' of the Excel workbook 'Attachment 17 - Xtandi mHSPC Section 3A Cost-Eff Model\_vfinal.xlsx'

ADT=androgen deprivation therapy; ENZA=enzalutamide; HV=high volume disease; KM=Kaplan Meier; OS=overall survival; PFS=progression free survival, rPFS=radiographic progression free survival, TTD=time to treatment discontinuation

- 6.38 Extrapolations were chosen based on visual fit of the KM data, statistical fit (AIC/BIC), clinical plausibility and consistency with the other extrapolations. All extrapolations were fitted independently, and proportional hazards did not appear to be tested. If the proportional hazards assumption held then the use independent extrapolations may not be reasonable.
- 6.39 OS was modelled with KM data until 20% patients remained at risk (48 months enzalutamide arm, 45 months ADT arm) then log-logistic extrapolation for the enzalutamide arm and log-normal for the ADT arm. These extrapolations had the lowest AIC/BIC, but both had long tails and were therefore optimistic extrapolations of the KM data. OS benefit was also assumed to persist across the time horizon. The PBAC previously recommended that OS benefit converge from Year 5 in the LV model of the apalutamide mHSPC PSD, November 2021 PBAC meeting. If OS converged from Year 5, the ICER increased to \$75,000 to < \$95,000 per QALY gained (compared to the revised base case of \$55,000 to < \$75,000 per QALY gained). The PSCR presented a revised base case in which the more conservative Gompertz function was applied to both arms of the economic model, stating that the Gompertz function reasonably predicted observed survival rates at 4 years and resulted in the enzalutamide and ADT

arms converging at approximately 13 years. The PSCR stated that earlier convergence of the OS curves was not required as, despite crossover and subsequent NHA treatment for patients in the ADT arm of the ARCHES trial, the trial resulted in diverging OS Kaplan Meier curves at a median follow-up of 44.6 months which was suggestive of a sustained treatment benefit associated with enzalutamide. The PSCR presented further data from an open-label extension trial, PREVAIL, which suggested that the survival benefit of enzalutamide was maintained beyond 5 years, despite crossover. The ESC noted that the use of the Gompertz function was consistent with that accepted previously by the PBAC in consideration of apalutamide (Table 8, apalutamide PSD, July 2022 PBAC meeting). In terms of convergence, the ESC noted the arguments in the PSCR, but considered, given patients can only receive one NHA on the PBS in a lifetime, the extent of benefit associated with enzalutamide would reduce over time. Noting that the PBAC had previously considered that convergence of the OS curves was appropriate for apalutamide (paragraphs 7.8 and 7.10, apalutamide PSD, July 2022 PBAC meeting), the ESC considered that it would be reasonable for the enzalutamide and ADT curves to converge from 5 to 10 years.

- 6.40 PFS was modelled with rPFS KM data until 20% patients remained at risk (15 months enzalutamide arm, 12 months ADT arm) followed by independent log-normal extrapolations, restricted to not exceed OS. For the enzalutamide arm, AIC/BIC were nearly identical for the Gompertz function, which would result in a more conservative estimate of PFS, and the gamma function had the lowest AIC for the ADT arm. If Gompertz was used to extrapolate enzalutamide arm PFS and gamma to extrapolate ADT arm the ICER decreased to \$45,000 to < \$55,000 per QALY gained compared to the revised base case of \$55,000 to < \$75,000 per QALY gained, as both the incremental QALYs and costs were reduced. The PSCR noted that if the Gompertz extrapolation was applied to the enzalutamide arm and the gamma extrapolation to the ADT arm, there was a superior PFS trajectory for ADT alone over enzalutamide, which was not supported by the data. The PSCR therefore proposed that the Weibull function was applied to both arms as it was a more conservative extrapolation of PFS with 100% of enzalutamide patients experiencing progression at approximately 10 years (see Figure 4). The ESC, noting the crossover that occurred in the PFS arms of the model when the Gompertz and gamma extrapolations were applied, considered that the application of the Weibull function to both arms, although not well justified, was a more conservative option.
- 6.41 TTD was modelled as KM data until rPFS cut-off (15 months enzalutamide arm, 12 months ADT arm) followed by independent log-logistic extrapolations restricted to not exceed PFS or OS. There was less variability in the TTD extrapolations than the PFS and OS estimates. In the model, TTD always exceeded PFS in ADT alone arm (so patients in PFS in the ADT alone arm were always on treatment). In comparison, PFS was slightly longer than TTD in the enzalutamide arm, resulting in a period in which patients were progression free, not receiving enzalutamide but had switched to ADT alone (i.e. patients in the enzalutamide arm did receive ADT until enzalutamide was

discontinued). TTD was assumed to be time to discontinuation of enzalutamide in the enzalutamide plus ADT arm, and time to discontinuation of ADT in the ADT alone arm, making the interpretation inconsistent. This was revised for consistency during the evaluation such that both enzalutamide and ADT followed the TTD curve in the enzalutamide arm, similar to the ADT arm. This increased the ICER from \$35,000 to < \$45,000 in the submission to \$55,000 to < \$75,000 per QALY gained. The PSCR selected the Weibull function for both TTD arms as this reduced the trajectory, given the PFS adjustment. The ESC noted that the application of the Weibull function resulted in a treatment duration for enzalutamide of 35.8 months (as compared to 62.2 months in the base case – see Table 12), which was more comparable to what was accepted by the PBAC in July 2022 for apalutamide (39.8 months for LV disease and 30.2 months for HV disease; Table 14, apalutamide PSD, July 2022 PBAC meeting).

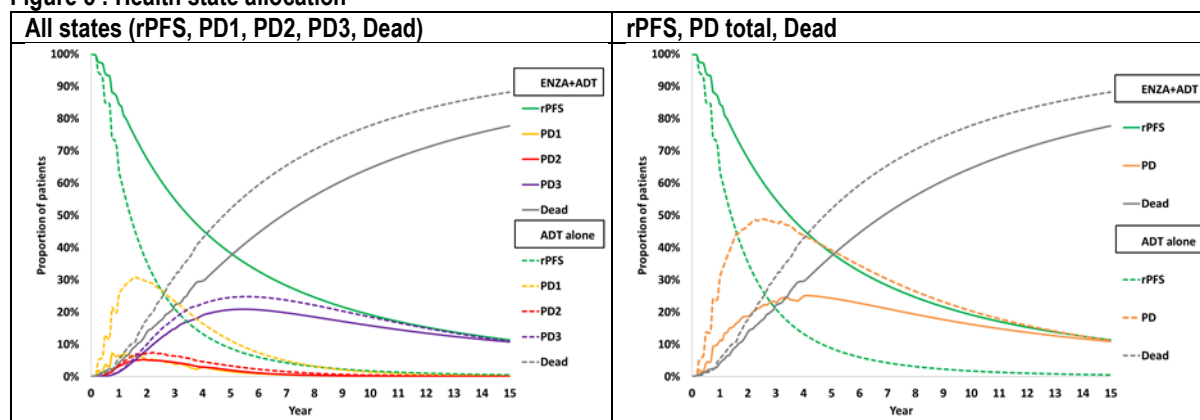
- 6.42 Figure 3 showed that TTD KM data followed a similar trajectory to PFS KM data. Although the TTD extrapolations were implemented from the same KM cut-off as PFS, the extrapolations were based on longer follow-up (~4 years TTD data versus <2 years rPFS data), and as such may be more reliable than the PFS extrapolations. When TTD was used as a proxy for PFS (i.e., treatment discontinuation was assumed to represent disease progression), the ICER increased to \$55,000 to < \$75,000 per QALY gained versus the revised base case ICER \$55,000 to < \$75,000 per QALY gained. In comparison, when PFS was used as a proxy for TTD (i.e., assuming patients discontinue treatment upon progression), the ICER increased only slightly to \$55,000 to < \$75,000 per QALY gained. The difference in these ICERs was driven by the change in health state allocation for the ADT arm (i.e., when TTD was used as a proxy for PFS, patients accrued more QALYs in mHSPC and fewer costs in PD1).
- 6.43 Of the three progressed disease health states, PD1 had the most influence on the ICER, as this was where the NHA cost-offsets in the ADT arm occurred. The duration of treatment with NHA in PD1 used to estimate the monthly transition probabilities was 15 months. The PBAC had previously considered that 12 months of subsequent NHA therapy would be more reliable as it was in line with data provided by the DUSC Secretariat (paragraphs 6.34 and 7.9, apalutamide PSD, July 2022 meeting). If NHAs in PD1 were given for 12 months, the ICER increased to \$55,000 to < \$75,000 per QALY gained from \$55,000 to < \$75,000 per QALY gained in the revised base case. The ESC noted that the duration of subsequent treatment (15 months) exceeded that previously accepted by the PBAC as reasonable (12 months).
- 6.44 Subsequent enzalutamide or abiraterone were assumed for 90% of patients in the ADT arm. In contrast, in ARCHES, docetaxel was the most commonly observed subsequent treatment for both treatment arms (36.1% and 31.6% in the enzalutamide and ADT arms respectively), and while subsequent treatment data for ARCHES was not split by progressed disease health states, the limited duration of the trial follow up suggested that it may be most representative of PD1.

- 6.45 Adverse events (AEs) and skeletal related events (SREs) were included in the model as per cycle probabilities based on health state and treatment received. The ICER was not sensitive to AEs or SREs.
- 6.46 Utilities in PFS and PD1 were sourced from ARCHES ITT EQ-5D-5L data pre- and post-progression, mapped to UK preference weights for the EQ-5D-3L, to give utility value of 0.806 in PFS, 0.723 in PD1. For PD3, baseline EQ-5D-3L data from AFFIRM were converted to a utility of 0.688 with UK preference weights. PD2 was assumed to have the average utility of PD2 and PD3: 0.706. The estimated utility difference between PFS and PD ranged from -0.083 (PFS to PD1) to -0.118 (PFS to PD3), which was similar to the -0.113 difference from PFS to PD for TITAN ITT population (Table 9, apalutamide PSD, July 2022 PBAC meeting).
- 6.47 Enzalutamide was costed at a dose of 4 x 40 mg once daily, with 98.94% compliance, based on a pack of 112 x 40 mg capsules at \$1 (requested effective DPMQ). The cost per month of enzalutamide was estimated at \$1.
- 6.48 For ADT, the submission calculated a weighted average price for all available ADTs based on their recommended dosages and weighted by PBS utilisation (Medicare statistics 2022 calendar year and PBS 10% sample), resulting in a monthly cost of \$412.42 in both treatment arms. The cost of ADT was applied according to the TTD extrapolation for patients in the ADT alone arm, and to 10% of those patients who progressed to PD1. In the enzalutamide arm, the cost of ADT was applied to patients who had discontinued enzalutamide but not yet progressed and to 90% of those patients who progressed to PD1. As discussed, this was inconsistent with the expectation that enzalutamide would be used in combination with ADT. For consistency a revised based case considered ADT to be given and discontinued in line with enzalutamide TTD in the enzalutamide arm. As ADT is often continued into mCRPC, a sensitivity analysis conducted during the evaluation also applied the cost of ADT to all alive patients in both arms, which gave an ICER of \$55,000 to < \$75,000 per QALY gained. The PSCR presented a revised base case in which the cost of ADT was applied to all alive patients in both treatment arms.
- 6.49 In PD1, 90% of patients in the ADT alone arm were assumed to receive a NHA (60% enzalutamide, 30% abiraterone), whereas 90% of patients in the enzalutamide arm received ADT only. Patients who received enzalutamide in PD1 were assumed a daily dose of 4 x 40 mg capsules with 100% compliance, where 112 x 40 mg capsules cost \$1 (effective DMPQ), equivalent to a monthly cost of \$1. The submission was not privy to the confidential effective price for abiraterone, therefore abiraterone was costed at its published DPMQ of \$3,442.14 for 120 x 250 mg tablets for a once daily dose of 4 x 250 mg, equal to a monthly cost of \$3,492.34. This cost was higher than the DPMQ assumed for abiraterone in the financial analysis (\$1), which was estimated in the submission as equal to the effective price of enzalutamide (\$1/28\*30). If assuming all NHA use in PD1 was for enzalutamide (i.e., 90% enzalutamide, 0% abiraterone), as proxy for analysis using confidential effective price for abiraterone, similar to the approach taken in the financial analysis section of the submission, the ICER increased

to \$55,000 to < \$75,000 per QALY gained compared to \$55,000 to < \$75,000 per QALY gained in the revised base case. The cost of subsequent abiraterone treatment was assumed to be the same as enzalutamide in the mCRPC setting in the revised base case presented in the PSCR.

- 6.50 Costs of other subsequent treatments and health state costs were sourced from PBS, MBS and National Hospital Cost Data Collection (NHCDC). These did not have a large impact on the ICER. Similarly, terminal care costs were costed from the literature, but had minimal impact on the ICER.
- 6.51 Health state allocation plots are presented in the following figure. Both the full set of health states (PFS, PD1, PD2, PD3, Dead) and an abridged set (PFS, PD, Dead) are presented.

Figure 5 : Health state allocation



Source: compiled during the evaluation from the Excel workbook 'attachment 17 – Xtandi mHSPC Section 3A Cost-Eff Model\_vfinal.xlsx' rPFS=radiographic progression free survival, PD=progressed disease, ENZA=enzalutamide, ADT=androgen deprivation therapy

- 6.52 Within PD, the majority of patients in the ADT arm were in PD1 until year 3.5, after which, PD3 was the majority health state. For the enzalutamide arm, very few patients spent time in PD1 and 2, with PD3 the largest PD health state by Year 1.5. The proportion of patients in PFS exceeded PD for the entire time horizon for enzalutamide patients with ~10% in PFS and ~10% in PD by Year 15. In comparison, 1% patients in the ADT arm were expected to remain in PFS by Year 15.
- 6.53 At the end of the model time horizon, only 12% of patients in the ADT arm were alive, compared to 22% in the enzalutamide arm, representing a significant sustained survival benefit for enzalutamide.
- 6.54 For mHSPC patients receiving ADT alone, OS in the model and ARCHES were higher than survival in other published literature. This may be a result of the heterogeneous populations across the trials. There was limited recent data that extended beyond 5 years and therefore it was uncertainty how well the model captured long term survival.
- 6.55 Key drivers of the model are presented in the following table.

Table 8: Key drivers of the model

Description	Method/Value	Impact Revised base case: <sup>1</sup> /QALY
Time horizon	15 years compared to 3.7 years of data in ARCHES	High, favoured enzalutamide arm. If time horizon was reduced to 7.5 years, the ICER increased to <sup>2</sup> /QALY.
Data source for inputs	ARCHES ITT for rPFS, OS and TTD	Moderate, favoured ADT arm. If ENZAMET (subgroup without docetaxel) was used as data source, ICER decreased to <sup>1</sup> /QALY.
PFS extrapolation	rPFS KM data until 20% patients remained at risk (ENZA 15 mths, ADT 12 mths) then <u>independent</u> log-normal extrapolation, restricted to not exceed OS.	High, favoured ADT arm. PFS was where the enzalutamide arm gained the most QALYs but also where most costs were accrued. Such that if incremental PFS was reduced but OS was unchanged, the ICER would decrease, i.e., if second best fitting extrapolations were used (enzalutamide Gompertz, ADT gamma), the ICER decreased to <sup>3</sup> /QALY.
OS extrapolation	Enzalutamide arm: KM data until 20% patients remained at risk (48 mths) then log-logistic extrapolation. ADT arm: KM data until 20% patients remained at risk (45 mths) then log-normal extrapolation.	High, favoured enzalutamide arm. If OS converged from Year 5, the ICER increased to <sup>2</sup> /QALY.
TTD extrapolation	KM data until rPFS cut-off (ENZA 15 mths, ADT 12 mths) then <u>independent</u> log-logistic extrapolation restricted to not exceed PFS or OS. TTD assumed to represent time to discontinuation of enzalutamide and ADT in the revised base case.	High, favoured enzalutamide arm (TTD in enzalutamide arm did not exceed PFS, but TTD in ADT arm did). However, if ADT costs were assumed for all <u>alive</u> patients each cycle, the ICER decreased to <sup>1</sup> /QALY.
Subsequent NHA use	Included for 90% of patients in ADT arm who progress to PD1 (60% enzalutamide, 30% abiraterone). Assumed to require 15 months of treatment.	High, favoured enzalutamide, as this was the main cost offset in the model. If all patients receiving NHA second line received enzalutamide, ICER increased to <sup>1</sup> /QALY.
Utilities	Health state utilities based on ARCHES and AFFIRM (PFS, PD1, PD2 and PD3, and EoL disutility). Utilities did not differ based on treatment received. Disutilities for AEs and SREs based on literature.	Moderate, favoured enzalutamide, as the majority of incremental QALYs were accrued in PFS where utility was highest. If utility in PD1 increased by 3% (from 0.72 to 0.75) the ICER increased to <sup>1</sup> /QALY (2% increase).

Source: compiled during the evaluation.

PFS= progression free survival, PD=progressed disease, ENZA=enzalutamide, ADT=androgen deprivation therapy; ITT = intention-to-treat; OS = overall survival; PD = progressed disease; TTD = time to treatment discontinuation, mth=month, ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$45,000 to < \$55,000

6.56 Table 9 summarises the results of the stepped economic analysis. The majority of the benefits were accrued in the extrapolation from 44 months to 15 years, compared to the majority of the incremental costs which occurred during the trial period. The submitted ICER was \$35,000 to < \$45,000 per QALY gained. Once ADT costs were revised in the enzalutamide arm to be in combination with enzalutamide, the ICER increased to \$55,000 to < \$75,000 per QALY gained. Enzalutamide cost was the largest contributor to the incremental costs (123.6%). The largest cost offset (equivalent to -35.2% of the incremental costs) were subsequent treatment costs in PD1, due to the

high utilisation and cost of subsequent NHAs in the ADT arm. The total incremental QALY gain was 1.47 years undiscounted (1.04 discounted), this far exceeded the 0.56 QALY gain (weighted across the HV and LV models) for apalutamide versus ADT presented in the July 2022 apalutamide resubmission (paragraph 6.24, apalutamide PSD, July 2022 PBAC meeting), primarily due to differences in the model time horizon (shorter in the apalutamide submission).

6.57 The results of the revised base case presented in the PSCR and pre-PBAC response are also included in the table below. The changes included:

- Reduction of the time horizon to 10 years (from 15);
- Application of the Gompertz function to OS in both arms (previously a log-logistic function was applied to the enzalutamide arm and a log-normal function to the ADT arm);
- Application of the Weibull function to PFS in both arms (previously a Gompertz function was applied to the enzalutamide arm and a gamma function to the ADT arm);
- Application of the Weibull function to TTD in both arms (previously independent log-logistic functions were applied to both arms);
- ADT costs were applied to all alive patients in both arms (previously ADT costs were only applied to patients in the enzalutamide arm once they had ceased treatment with enzalutamide);
- The cost of subsequent abiraterone treatment was assumed to cost the same as enzalutamide in the mCRPC setting (previously the published higher DPMQ was used for abiraterone); and
- The effective AEMP of enzalutamide was reduced from \$| to \$|. This was further reduced to \$| in the pre-PBAC response.

6.58 The ESC noted that the PSCR revised base case ICER was \$45,000 to < \$55,000 per QALY gained. The ESC considered that the changes to the costs for ADT and subsequent therapies were appropriate. The ESC considered that the reduction in the time horizon was appropriate. The ESC considered that although the revised functions for the extrapolation of PFS and TTD were not well justified, they resulted in time on treatment outcomes that appeared more consistent with those previously accepted by the PBAC for apalutamide. For OS, the ESC noted that the application of the Gompertz function to both arms was consistent with that accepted by the PBAC previously for apalutamide, but that convergence was not applied. Overall, the ESC noted that the modelled QALY gain in the revised base case (0.83) remained higher than that previously accepted by the PBAC for apalutamide (0.56, weighted across the LV and HV models with convergence applied; paragraph 6.24, apalutamide PSD, July 2022 PBAC meeting).

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- 6.59 The ESC noted that the duration of subsequent NHA treatment (15 months) continued to exceed that previously accepted by the PBAC (12 months) in the revised base case presented in the PSCR.
- 6.60 The revised base case presented in the pre-PBAC response, which reduced the AEMP to \$, was \$35,000 to < \$45,000 per QALY gained.

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Table 9: Results of the stepped economic evaluation

Step and component	Submission			Revised		
	ENZA	ADT	Increment	ENZA	ADT	Increment
<b>Step 1: Time horizon, trial based (44 months), treatment costs only</b>						
Costs (\$)	█	█	█	█	█	█
PFLYs	2.63	1.70	0.93	2.63	1.70	0.93
LYs	3.21	3.05	0.17	3.21	3.05	0.17
Incremental cost/extra PFLY gained (\$)			█ <sup>1</sup>			█ <sup>3</sup>
Incremental cost/extra LY gained (\$)			█ <sup>2</sup>			█ <sup>2</sup>
<b>Step 2: Time horizon, trial based (44 months), all costs</b>						
Costs (\$)	█	█	█	█	█	█
PFLYs	2.63	1.70	0.93	2.63	1.70	0.93
LYs	3.21	3.05	0.17	3.21	3.05	0.17
Incremental cost/extra PFLY gained (\$)			█ <sup>1</sup>			█ <sup>3</sup>
Incremental cost/extra LY gained (\$)			█ <sup>2</sup>			█ <sup>2</sup>
<b>Step 3: Time horizon, trial based (44 months), all costs and utilities</b>						
Costs (\$)	█	█	█	█	█	█
QAPFLYs	2.12	1.37	0.75	2.12	1.37	0.75
QALYs	2.53	2.32	0.21	2.53	2.32	0.21
Incremental cost/extra QAPFLY gained (\$)			█ <sup>3</sup>			█ <sup>3</sup>
Incremental cost/extra QALY gained (\$)			█ <sup>4</sup>			█ <sup>2</sup>
<b>Step 4: Time horizon, 15 years, all costs and utilities (base case)</b>						
Costs	█	█	█	█	█	█
LYs	6.28	5.14	1.14	6.28	5.14	1.14
QALYs	4.78	3.74	1.04	4.78	3.74	1.04
Incremental cost/extra LY gained (\$)			█ <sup>5</sup>			█ <sup>3</sup>
Incremental cost/extra QALY gained (\$)			█ <sup>5</sup>			█ <sup>3</sup>
<b>PSCR revised base case</b>						
Costs (\$)	█	█	█			
LYs	4.93	3.90	1.03			
QALYs	3.66	2.83	0.83			
Incremental cost/extra LY gained (\$)			█ <sup>5</sup>			
Incremental cost/extra QALY gained (\$)			█ <sup>1</sup>			
<b>Pre-PBAC revised base case</b>						
Costs (\$)	█	█	█			
LYs	4.93	3.90	1.03			
QALYs	3.66	2.83	0.83			
Incremental cost/extra LY gained (\$)			█ <sup>6</sup>			
Incremental cost/extra QALY gained (\$)			█ <sup>5</sup>			

Source: Table 3.8-1 of the submission and compiled during the evaluation

QAPFLY=quality adjusted progression free life year, PFLY= progression free life year, QALY=quality adjusted life year, LY= life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$255,000 to < \$355,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$155,000 to < \$255,000

<sup>5</sup> \$35,000 to < \$45,000

<sup>6</sup> \$25,000 to < \$35,000

6.61 The results of key sensitivity analyses are summarised in Table 10. The ICER was most sensitive to time horizon, OS extrapolation and convergence, PFS extrapolation, TTD extrapolation and cost of NHA.

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Table 10: Sensitivity analyses

Analyses	Incremental		ICER	% Δ ICER
	Cost (\$)	QALY		
<b>Base case</b>	█	1.04	█ <sup>1</sup>	-
Discount rate (base case: 5%)				
0%	█	1.47	█ <sup>1</sup>	-10.6%
3.5%		1.15	█ <sup>1</sup>	-3.4%
Time horizon (base case: 15 years)				
5 years	█	0.33	█ <sup>2</sup>	80.7%
7.5 years		0.57	█ <sup>3</sup>	32.1%
10 years		0.77	█ <sup>1</sup>	14.6%
Efficacy data source for PFS, OS, TTD (base case: ARCHES ITT)				
ARCHES HV subgroup	█	0.96	█ <sup>4</sup>	-20.4%
ARCHES LV subgroup		1.61	█ <sup>5</sup>	-32.8%
ENZAMET w/o docetaxel subgroup		1.96	█ <sup>1</sup>	-6.8%
OS extrapolation (base case: ENZA log-log, ADT log-normal, no convergence)				
ENZA Weibull, ADT log-logistic	█	0.81	█ <sup>3</sup>	24.1%
OS converge from Year 5*		0.80	█ <sup>3</sup>	24.4%
OS converge from 44 months*		0.63	█ <sup>6</sup>	53.8%
PFS extrapolation (base case: independent log-normal)				
ENZA Gompertz, ADT Gamma	█	0.76	█ <sup>4</sup>	-17.9%
PFS=TTD		1.00	█ <sup>1</sup>	12.9%
TTD extrapolation (base case: independent log-logistic)				
ENZA exponential, ADT log-normal	█	1.04	█ <sup>4</sup>	-15.3%
TTD=PFS		1.04	█ <sup>1</sup>	5.1%
ADT all patients (base case: % follows TTD curve in PFS, 90% ENZA pts in PD1, 10% ADT pts in PD1), NB: AE/SRE/health state costs not adjusted	█	1.04	█ <sup>1</sup>	-9.4%
Subsequent NHA 12 months (base case: 15 months)	█	1.04	█ <sup>1</sup>	4.6%
Subsequent tx in ADT arm 90% ENZA, 0% ABI, 10% ADT (base case: 60% ENZA, 30% ABI, 10% ADT) - proxy for analysis using effective price of abiraterone.	█	1.04	█ <sup>1</sup>	13.8%
<b>PSCR revised base case</b>	█	<b>0.83</b>	█ <sup>4</sup>	-
OS extrapolation (base case ENZA and ADT Gompertz, no convergence)				
OS converge from Year 5*	█	0.50	█ <sup>1</sup>	40.4%
Subsequent NHA 12 months (base case: 15 months)	█	0.84	█ <sup>4</sup>	3.7%
Multivariate analysis				
OS converge from Year 5* and subsequent NHA 12 months	█	0.50	█ <sup>1</sup>	45.9%

Source: compiled during the evaluation based on Table 3.9.2 (pp211-212) of the submission and additional analyses generated during the evaluation.

ADT=androgen deprivation therapy; ENZA=enzalutamide, EOL=end of life, MA=multivariate analysis, ICER=incremental cost-effectiveness ratio, ITT = intention-to-treat; mth=month, OS = overall survival; PFS= progression free survival, PD=progressed disease, PD = progressed disease; TTD = time to treatment discontinuation, tx=treatment; QALY=quality adjusted life year.

\* Convergence is modelled as OS HR = 1 from point convergence is assumed to begin

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$115,000 to < \$135,000

<sup>3</sup> \$75,000 to < \$95,000

<sup>4</sup> \$45,000 to < \$55,000

<sup>5</sup> \$35,000 to < \$45,000

<sup>6</sup> \$95,000 to < \$115,000

6.62 The ESC noted that when convergence from 5 years was applied to the revised model presented in the PSCR, the QALY gain was 0.50, which was more consistent with that accepted by the PBAC for apalutamide in July 2022 (QALY gain = 0.56, weighted across the HV and LV models). The ESC noted that reducing the duration of subsequent NHA therapy from 15 to 12 months in the ADT arm had a modest effect on the ICER. The

ESC considered that the PSCR revised base case could therefore be further updated to include convergence from 5 years and a reduction in the duration of subsequent NHA therapy. As this multivariate analysis, presented in Table 10, resulted in an ICER of \$55,000 to < \$75,000 per QALY gained, the ESC noted that a price reduction would be required to attain an ICER of < \$45,000 per QALY.

### Cost minimisation approach

6.63 The results of the submission’s cost-minimisation approach are presented below. The only costs included were direct medicine costs, no other costs or cost offsets were included. The ESC considered that this was appropriate. The price for apalutamide in mHSPC was unknown to the sponsor, so the submission instead estimated the price for apalutamide based on the requested AEMP for enzalutamide.

6.64 The approach assumed the equi-effective doses for enzalutamide and apalutamide (based on those reported in ARCHES and TITAN) to be:

- Enzalutamide: 4 x 40 mg capsules daily, ARCHES
- Apalutamide: 4 x 60 mg tablets daily, TITAN

**Table 11: Results of the cost-minimisation approach**

Component	Enzalutamide	Apalutamide
AEMP	\$	\$
Pack size	112	120
Treatment days per pack	28 days	30 days
Cost per day	\$	\$
Dose duration	Until discontinuation (assumed similar to apalutamide)	Until discontinuation
Administrations per week	7 (4 x 40 mg daily)	7 (4 x 60 mg daily)
Total medicine cost per week	\$	\$
Difference in cost per week	\$0	-

Source: Section 3.10.3 p213, Table 3.11-1 p214, and compiled during the evaluation

6.65 The submission’s calculations were arithmetically correct. While the cost minimisation approach was generally appropriate, a number of differences were noted between enzalutamide and apalutamide that could potentially impact the results:

- While median time on treatment was similar for enzalutamide (40.2 months) and apalutamide (39.3 months) based on a median duration of follow up of 44.6 months in ARCHES and 44.0 months in TITAN, the modelled mean treatment durations differed significantly. Mean treatment duration for enzalutamide in the submission’s model was estimated to be 62.2 months for enzalutamide, compared to 30.2 months (HV subgroup) and 39.8 months (LV subgroup) for apalutamide (Table 14, p29, apalutamide PSD, July 2022 PBAC meeting). The ESC noted that the treatment duration for enzalutamide was reduced to 35.8 months in the revised base case model presented in the PSCR (see Table 12). The ESC considered that it was reasonable to assume a similar time on treatment for enzalutamide and apalutamide in mHSPC.

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- The proposed equi-effective doses were reasonable but did not account for the small difference in trial dose intensity between the drugs (98.94% for enzalutamide in ARCHES and 95.8% for apalutamide in TITAN).
- The cost minimisation analysis assumed no difference in adverse event costs between enzalutamide and apalutamide. This may not be entirely appropriate as some differences in AEs were noted between enzalutamide and apalutamide (see Comparative harms).

6.66 Overall, given that the benefit associated with enzalutamide treatment was expected to be similar to that with apalutamide treatment, the ESC considered that the prices should be similar.

**Enzalutamide cost/patient/course**

Table 12: Drug cost per patient for proposed and comparator drugs

	Trial dose and duration	Model			Financial estimates		
		Submission	PSCR	Pre-PBAC	Submission	PSCR	Pre-PBAC
Mean dose	158.3 mg/day <sup>a</sup>	158.3 mg/day <sup>a</sup>			158.3 mg/day <sup>a</sup>		
Mean duration	Median: 40.2 months (44.6 month follow up) Mean: not reported	62.2 months	35.8 months	35.8 months	Dose (160 mg/day), dose intensity (98.94%), cost per script (\$████) and duration (TTD based on ARCHES time on treatment KM data extrapolated) assumptions consistent with the economic model.	Dose (160 mg/day), dose intensity (98.94%), cost per script (\$████) consistent with the economic model. Duration equivalent to apalutamide PSD, July 2022 <sup>b</sup>	Dose (160 mg/day), dose intensity (98.94%), cost per script (\$████) consistent with the economic model. Duration equivalent to apalutamide PSD, July 2022 <sup>b</sup>
Cost/patient/month	-	\$████	\$████	\$████			
Cost/patient/course	-	\$████	\$████	\$████			

Source: compiled during the evaluation

HV = high volume; KM = Kaplan Meier; LV = low volume; TTD = time to treatment discontinuation

a prescribed dose of 160mg/day adjusted for 98.94% dose intensity from ARCHES

b From Table 15 of the apalutamide PSD, applying the weighted average of the HV and LV subgroups

**Estimated PBS usage & financial implications**

6.67 This submission was not considered by DUSC. The submission applied an epidemiological approach to the financial estimates, based on the July 2022 apalutamide resubmission for mHSPC. Detail of the approach is outlined in Table 13.

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Table 13: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment																																								
<b>Eligible population</b>																																											
Proportion of HV patients ineligible for chemotherapy; ineligible for docetaxel	25%	Based on the apalutamide mHSPC July 2022 PSD.	Corresponds to PBAC recommendation for apalutamide.																																								
Incident mHSPC patients - all	<table border="1"> <thead> <tr> <th></th> <th>LV</th> <th>HV</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Yr 1:</td> <td>█ 1</td> <td>█ 1</td> <td>█ 1</td> </tr> <tr> <td>Yr 2:</td> <td>█ 1</td> <td>█ 1</td> <td>█ 1</td> </tr> <tr> <td>Yr 3:</td> <td>█ 1</td> <td>█ 1</td> <td>█ 1</td> </tr> <tr> <td>Yr 4:</td> <td>█ 1</td> <td>█ 1</td> <td>█ 1</td> </tr> <tr> <td>Yr 5:</td> <td>█ 1</td> <td>█ 1</td> <td>█ 1</td> </tr> <tr> <td>Yr 6:</td> <td>█ 1</td> <td>█ 1</td> <td>█ 1</td> </tr> <tr> <td></td> <td></td> <td>█ 1</td> <td></td> </tr> <tr> <td></td> <td></td> <td>█ 1</td> <td></td> </tr> <tr> <td></td> <td></td> <td>█ 1</td> <td></td> </tr> </tbody> </table>		LV	HV	Total	Yr 1:	█ 1	█ 1	█ 1	Yr 2:	█ 1	█ 1	█ 1	Yr 3:	█ 1	█ 1	█ 1	Yr 4:	█ 1	█ 1	█ 1	Yr 5:	█ 1	█ 1	█ 1	Yr 6:	█ 1	█ 1	█ 1			█ 1				█ 1				█ 1		Based on the apalutamide mHSPC July 2022 PSD, which estimated █ 1 patients in 2023 plus yearly growth of 68.95 patients. Thus █ 1 patients in Year 1. The estimates were sourced from a regression model fit to historical estimates. Proportion of LV (47.7%) and HV (52.3%) patients based on the ENZAMET trial, as in the apalutamide PSD.	Apalutamide PSD, July 2022 (Table 15) indicated this approach was generally reasonable, although the predictions were likely overestimated as the historical patients were likely overestimated compared to DUSC data. With regard to the proportion of patients with LV and HV disease, the apalutamide PSD (Table 15) indicated the PBAC considered the split proposed in the apalutamide resubmission to be a reasonable estimate.
	LV	HV	Total																																								
Yr 1:	█ 1	█ 1	█ 1																																								
Yr 2:	█ 1	█ 1	█ 1																																								
Yr 3:	█ 1	█ 1	█ 1																																								
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Eligible incident mHSPC patients	<table border="1"> <thead> <tr> <th></th> <th>LV</th> <th>HV</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Yr 1:</td> <td>█ 1</td> <td>█ 2</td> <td>█ 1</td> </tr> <tr> <td>Yr 2:</td> <td>█ 1</td> <td>█ 2</td> <td>█ 1</td> </tr> <tr> <td>Yr 3:</td> <td>█ 1</td> <td>█ 2</td> <td>█ 1</td> </tr> <tr> <td>Yr 4:</td> <td>█ 1</td> <td>█ 2</td> <td>█ 1</td> </tr> <tr> <td>Yr 5:</td> <td>█ 1</td> <td>█ 2</td> <td>█ 1</td> </tr> <tr> <td>Yr 6:</td> <td>█ 1</td> <td>█ 2</td> <td>█ 1</td> </tr> <tr> <td></td> <td></td> <td>█ 2</td> <td></td> </tr> <tr> <td></td> <td></td> <td>█ 2</td> <td></td> </tr> </tbody> </table>		LV	HV	Total	Yr 1:	█ 1	█ 2	█ 1	Yr 2:	█ 1	█ 2	█ 1	Yr 3:	█ 1	█ 2	█ 1	Yr 4:	█ 1	█ 2	█ 1	Yr 5:	█ 1	█ 2	█ 1	Yr 6:	█ 1	█ 2	█ 1			█ 2				█ 2		All LV patients (47.7% of the incident population) were considered eligible for treatment. As per the July 2022 apalutamide mHSPC PSD, for HV patients (52.3% of the population), only those ineligible for docetaxel (25%) were included in the estimates.	This was consistent with the apalutamide mHSPC July 2022 PSD in which the PBAC recommended that use in HV patients suitable for docetaxel should be managed through a RSA.				
	LV	HV	Total																																								
Yr 1:	█ 1	█ 2	█ 1																																								
Yr 2:	█ 1	█ 2	█ 1																																								
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Data	Value			Source	Comment	
Prevalent mHSPC patients – all are eligible		<u>LV</u>	<u>HV</u>	<u>Total</u>	<p>Prevalent patients in Year 2 onward were estimated as a proportion of untreated patients from the previous year who remain mHSPC. These patients will be receiving ADT only and therefore will be eligible to receive treatment. The proportion was based on median time to progression (11.7 months) in the ADT arm of CHARTED (49.12% = <math>0.5^{(1/(11.7/12))}</math>).</p> <p>Prevalent patients in Year 1 were estimated using the same methodology, and patient numbers were based on a historical cohort of mHSPC incident patients from five years prior to the requested listing of enzalutamide.</p>	<p>The submission applied the same methodology to estimate prevalent patients as used in the July 2022 apalutamide resubmission (and the November 2021 submission), although the apalutamide resubmission included prevalent patients in Year 1 only. This has a considerable impact on patient numbers, and resultant cost. For apalutamide, the PBAC had considered prevalent patient estimation was uncertain as the method assumed an exponential extrapolation of time to progression that was unrelated to patient characteristics such as HV and LV disease. The submission provided no discussion around the identified uncertainty with the method used. The PSCR presented a revised base case in which prevalent patients were excluded from Year 2 onwards.</p>
	Yr 1:	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>		
	Yr 2:	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>1</sup>		
	Yr 3:	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>1</sup>		
	Yr 4:	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>		
	Yr 5:	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>		
	Yr 6:	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>		
<b>Treatment utilisation</b>						
Uptake rate		<u>LV</u>	<u>HV</u>	<p>Sourced from apalutamide July 2022 PSD. The same uptake rates were applied for incidence and prevalence.</p> <p>Used to calculate eligible incident and prevalent patients initiating treatment.</p>	<p>The submission did not justify the use of the same uptake rates for incident and prevalent patients. For apalutamide the PBAC had stated this may not be reasonable as incident patients may be more likely to get treated (Table 15, July 2022 PSD). In addition, the submission did not justify the higher uptake rates used for HV disease patients.</p>	
Yr 1: 40% Yr 2: 50% Yr 3: 55% Yr 4: 57% Yr 5: 59% Yr 6: 60%	Yr 1: 60% Yr 2: 75% Yr 3: 82% Yr 4: 90% Yr 5: 90% Yr 6: 90%	<p>Patient Assistance Program is to be initiated in early 2023. Submission estimated there will be █<sup>2</sup> grandfathered patients in Year 1.</p>	<p>Submission provided no discussion or rationale for estimation of █<sup>2</sup> grandfathered patients.</p>			
Grandfathered patients	Yr 1: █ <sup>2</sup> Yr 2 to 6: █ <sup>2</sup>					

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Data	Value	Source	Comment																					
Treatment duration – proportion on treatment each year	<table border="1"> <thead> <tr> <th></th> <th>Submission</th> <th>PSCR</th> </tr> </thead> <tbody> <tr> <td>Yr 1:</td> <td>91.59%</td> <td>90.15%</td> </tr> <tr> <td>Yr 2:</td> <td>72.04%</td> <td>73.47%</td> </tr> <tr> <td>Yr 3:</td> <td>58.06%</td> <td>56.40%</td> </tr> <tr> <td>Yr 4:</td> <td>48.12%</td> <td>42.04%</td> </tr> <tr> <td>Yr 5:</td> <td>40.74%</td> <td>23.18%</td> </tr> <tr> <td>Yr 6:</td> <td>35.13%</td> <td>9.28%</td> </tr> </tbody> </table>		Submission	PSCR	Yr 1:	91.59%	90.15%	Yr 2:	72.04%	73.47%	Yr 3:	58.06%	56.40%	Yr 4:	48.12%	42.04%	Yr 5:	40.74%	23.18%	Yr 6:	35.13%	9.28%	Proportions were sourced from the 'TTD' worksheet of the economic model. The submission claimed this was consistent with the approach used to estimate treatment duration for apalutamide in mHSPC (July 2022), with the only difference being that time on treatment was not applied to LV and HV patients separately. Modelled mean treatment duration was significantly higher for enzalutamide versus apalutamide (62.2 months for enzalutamide, compared to 30.2 months (HV subgroup) and 39.8 months (LV subgroup) for apalutamide (Table 14, p29, apalutamide PSD, July 2022). This is reflected as higher proportions on treatment each year for enzalutamide versus apalutamide (Data for apalutamide is available in Table 15, p31, apalutamide PSD, July 2022).	May not be reasonable as treatment duration (proportion on treatment) relies on the economic model, which is influenced by the extrapolation curve selected. The use of proportions for all patients combined instead of LV and HV populations separately may be reasonable, although separate groups could be set up with different durations applied. The PSCR presented revised base case estimates in which the proportion of patients remaining on enzalutamide in the mHSPC setting were based on those reported in Table 15 of the apalutamide PSD.
	Submission	PSCR																						
Yr 1:	91.59%	90.15%																						
Yr 2:	72.04%	73.47%																						
Yr 3:	58.06%	56.40%																						
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Total treated each year	<table border="1"> <tbody> <tr> <td>Yr 1:</td> <td>1</td> </tr> <tr> <td>Yr 2:</td> <td>1</td> </tr> <tr> <td>Yr 3:</td> <td>1</td> </tr> <tr> <td>Yr 4:</td> <td>1</td> </tr> <tr> <td>Yr 5:</td> <td>1</td> </tr> <tr> <td>Yr 6:</td> <td>3</td> </tr> </tbody> </table>	Yr 1:	1	Yr 2:	1	Yr 3:	1	Yr 4:	1	Yr 5:	1	Yr 6:	3	Number of patients initiating treatment × proportion on treatment each year.	Accuracy may be limited by the accuracy of the proportion on treatment each year.									
Yr 1:	1																							
Yr 2:	1																							
Yr 3:	1																							
Yr 4:	1																							
Yr 5:	1																							
Yr 6:	3																							
Scripts dispensed	12.91 scripts per year	13.01 scripts per year × compliance of 98.94% from the ARCHES trial which equals 12.91 scripts per year.	Calculation of script numbers was reasonable, although it is questionable whether compliance from ARCHES will be realised in clinical practice, and the number of patients treated is not likely to be accurate.																					
Substituted therapy – proportion in mCRPC health state over time assuming treatment with ADT-only for mHSPC	<table border="1"> <tbody> <tr> <td>Yr 1:</td> <td>11.1%</td> </tr> <tr> <td>Yr 2:</td> <td>25.6%</td> </tr> <tr> <td>Yr 3:</td> <td>30.7%</td> </tr> <tr> <td>Yr 4:</td> <td>34.2%</td> </tr> <tr> <td>Yr 5:</td> <td>31.5%</td> </tr> <tr> <td>Yr 6:</td> <td>26.1%</td> </tr> </tbody> </table>	Yr 1:	11.1%	Yr 2:	25.6%	Yr 3:	30.7%	Yr 4:	34.2%	Yr 5:	31.5%	Yr 6:	26.1%	Abiraterone and enzalutamide for treatment of mCRPC. The estimated decrease in abiraterone and enzalutamide scripts used the same methodology as applied in the July 2022 apalutamide PSD. The submission calculated the patient years with mCRPC, assuming patients had received ADT-only treatment for mHSPC.	The November 2021 apalutamide PSD noted that these proportions were consistent with the modelled economic evaluation for apalutamide. The submission did not provide any discussion as to whether apalutamide-sourced proportions would also be applicable to enzalutamide.									
Yr 1:	11.1%																							
Yr 2:	25.6%																							
Yr 3:	30.7%																							
Yr 4:	34.2%																							
Yr 5:	31.5%																							
Yr 6:	26.1%																							

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Data	Value	Source	Comment
Proportion of time in mCRPC health state spent on ENZA or ABI	55.24%	Assumes 15 months of treatment with NHAs for mCRPC. Based on the July 2022 apalutamide PSD. Submission stated the 15 month duration of NHA treatment also aligns with analysis of 10% PBS sample data.	The July 2022 apalutamide PSD indicated that the average of 15 months treatment with NHAs for mCRPC remained uncertain, and the PBAC considered 12 months to be an appropriate estimate for the apalutamide economic model and should also be revised for financial estimates. The submission argued that 15 months is a more appropriate and accurate estimate, although the 10% PBS sample indicates just over 30% persistence at 15 months.
Script volume of NHAs in the mCRPC setting	Enzalutamide: 66% Abiraterone 250mg: 5% Abiraterone 500mg: 29%	Based on PBS utilisation in calendar year 2021, which the submission stated was in line with the market share reported in the July 2022 apalutamide PSD (66.3% for enzalutamide; 33.7% for abiraterone).	-
Compliance and scripts per year	100%; 13.04 scripts for enzalutamide and 12.18 scripts for abiraterone	Consistent with the apalutamide July 2022 PSD.	-
Cost offsets for substituted therapy	Abiraterone for mCRPC effective price: \$ Enzalutamide for mCRPC effective price \$	Based on effective prices sourced from the sponsor's deed agreement for enzalutamide.	-
<b>Costs</b>			
DPMQ Enzalutamide mHSPC	\$	Requested price	Reduced to \$ in the PSCR and \$ in the pre-PBAC response.
DPMQ Abiraterone	\$	Effective price	-
DPMQ Enzalutamide mCRPC	\$	Effective price, PBS item 10174L	-
Patient co-payment	PBS: \$11.99 RPBS: \$4.66	PBS/RPBS split: 96.55%/3.45% Based on enzalutamide utilisation in mCRPC (PBS item 10174L)	-

Source: Table 4.1-1, p222-226; Table 4.2-3, p231 of the submission; Excel workbook 'Attachment 20 – Xtandi mHSPC Section 4 Financial Model\_vfinal'.

ABI=abiraterone, ADT=androgen deprivation treatment, ENZA=enzalutamide, HV=high volume; LV=low volume; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=novel hormonal agent; PSD=public summary document; TTD=time to treatment discontinuation, Yr=year.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500

<sup>3</sup> 5,000 to < 10,000

6.68 Table 14 summarises the estimated net financial implications to the PBS/RPBS for the proposed listing of enzalutamide over the first six years. While the submission provided estimated numbers of incident and prevalent patients categorised by LV and

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HV disease (Table 13), the number of treated patients and estimated costs were based on these two patient groups combined, hence all estimates in the table below are for the incident and prevalent patients that make up the total population. As per the July 2022 apalutamide submission, enzalutamide use in patients with HV disease who were suitable for docetaxel were excluded from the utilisation and financial impact estimates. For apalutamide, in July 2022 the PBAC proposed that HV patients who were suitable for docetaxel should be managed via the proposed risk sharing arrangement (RSA).

6.69 The results of the revised estimates presented in the PSCR and pre-PBAC response are also included in the table below. The changes included:

- The exclusion of prevalent patients from Year 2 onwards;
- The proportion of mHSPC patients remaining on enzalutamide treatment was revised to be based on those in the apalutamide PSD (Year 1: 91.15%; Year 2: 73.47%; Year 3: 56.40%; Year 4: 42.04%; Year 5: 23.18%; Year 6: 9.28%); and
- The effective DPMQ of enzalutamide was reduced from \$| to \$|. This was further reduced to \$| in the pre-PBAC response.

Table 14: Estimated use and financial implications to the PBS/RPBS for the proposed listing of enzalutamide

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
<b>Number of patients with mHSPC</b>							
Incident patients	1	1	1	1	1	1	3
Prevalent patients	1	1	1	2	2	2	1
Total patients mHSPC	1	1	1	1	1	1	10
<b>Estimated number of patients eligible for the requested restriction</b>							
Incident patients	1	1	1	1	1	1	3
Prevalent patients	1	1	1	2	2	2	1
Total eligible	1	1	1	1	1	1	3
<b>Estimated number of patients treated</b>							
Incident patients	1	1	1	1	1	1	14
Prevalent patients	1	1	2	2	2	2	1
Grandfathered	2						2
Total patients initiated on treatment	1	1	1	1	1	1	14
Total patients treated each year <sup>a</sup>	1	1	1	1	1	14	10
<b>Estimated use and net cost of enzalutamide to PBS/RPBS (DPMQ \$ )</b>							
Number of scripts	3	7	12	15	18	18	22
Cost PBS/RPBS (\$)	4	8	13	16	19	21	23
Net cost <sup>a</sup> PBS/RPBS (\$)	4	8	13	16	19	21	23
<b>Estimated changes in use and financial impact of currently listed treatments</b>							
Enzalutamide	1	1	14	14	14	3	7
Abiraterone	1	1	1	1	1	14	3
Total	1	1	14	3	3	3	15
Cost PBS/RPBS (\$)	5	5	5	5	5	5	5
Net cost <sup>b</sup> PBS/RPBS (\$)	5	5	5	5	5	5	5
<b>Net financial implications to government</b>							
Total cost PBS/RPBS (\$)	4	8	13	16	19	21	23

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
<b>Number of patients with mHSPC</b>							
<b>Total net cost PBS/RPBS (\$)</b>	■ <sup>4</sup>	■ <sup>9</sup>	■ <sup>8</sup>	■ <sup>13</sup>	■ <sup>20</sup>	■ <sup>14</sup>	■ <sup>24</sup>
<b>Revised estimates presented in the PSCR (DPMQ \$■ )</b>							
Total patients	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>14</sup>
Number of enzalutamide scripts	■ <sup>3</sup>	■ <sup>10</sup>	■ <sup>7</sup>	■ <sup>12</sup>	■ <sup>12</sup>	■ <sup>12</sup>	■ <sup>22</sup>
Net cost of enzalutamide (\$)	■ <sup>4</sup>	■ <sup>11</sup>	■ <sup>9</sup>	■ <sup>8</sup>	■ <sup>13</sup>	■ <sup>13</sup>	■ <sup>25</sup>
Net cost offsets (\$)	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>17</sup>	■ <sup>17</sup>	■ <sup>17</sup>	■ <sup>8</sup>
<b>Total net cost PBS/RPBS (\$)</b>	■ <sup>4</sup>	■ <sup>11</sup>	■ <sup>11</sup>	■ <sup>9</sup>	■ <sup>9</sup>	■ <sup>9</sup>	■ <sup>25</sup>
<b>Revised estimates presented in the pre-PBAC response (DPMQ \$■ )</b>							
Net cost of enzalutamide scripts (\$)	■ <sup>4</sup>	■ <sup>11</sup>	■ <sup>9</sup>	■ <sup>8</sup>	■ <sup>8</sup>	■ <sup>8</sup>	■ <sup>25</sup>
Net cost offsets (\$)	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>17</sup>	■ <sup>17</sup>	■ <sup>17</sup>	■ <sup>8</sup>
<b>Total net cost PBS/PBS (\$)</b>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>11</sup>	■ <sup>11</sup>	■ <sup>9</sup>	■ <sup>9</sup>	■ <sup>25</sup>

Source: Table 4.2-3, p231; Table 4.2-8, p233; Table 4.2-10, p235; Table 4.3-4, p239; Table 4.4-1, p241 of the submission; Excel workbook Attachment 20 – Xtandi mHSPC Section 4 Financial Model\_vfinal’.

mHSPC=metastatic hormone sensitive prostate cancer.

<sup>a</sup> Based on the number of patients initiating treatment each year × the proportion on treatment each year, which was sourced from the ‘TTD’ worksheet of the economic model.

<sup>b</sup> Net of patient copayments.

The redacted values correspond to the following ranges:

- |  |  |
|--|--|
| <sup>1</sup> 500 to < 5,000                  | <sup>14</sup> 5,000 to < 10,000                |
| <sup>2</sup> < 500                           | <sup>15</sup> 50,000 to < 60,000               |
| <sup>3</sup> 10,000 to < 20,000              | <sup>16</sup> \$80 million to < \$90 million   |
| <sup>4</sup> \$20 million to < \$30 million  | <sup>17</sup> \$10 million to < \$20 million   |
| <sup>5</sup> net cost saving                 | <sup>18</sup> 60,000 to < 70,000               |
| <sup>6</sup> \$0 to < \$10 million           | <sup>19</sup> \$90 million to < \$100 million  |
| <sup>7</sup> 30,000 to < 40,000              | <sup>20</sup> \$70 million to < \$80 million   |
| <sup>8</sup> \$50 million to < \$60 million  | <sup>21</sup> \$100 million to < \$200 million |
| <sup>9</sup> \$40 million to < \$50 million  | <sup>22</sup> 200,000 to < 300,000             |
| <sup>10</sup> 20,000 to < 30,000             | <sup>23</sup> \$400 million to < \$500 million |
| <sup>11</sup> \$30 million to < \$40 million | <sup>24</sup> \$300 million to < \$400 million |
| <sup>12</sup> 40,000 to < 50,000             | <sup>25</sup> \$200 million to < \$300 million |
| <sup>13</sup> \$60 million to < \$70 million |  |

6.70 The net cost to the PBS/RPBS for the proposed listing of enzalutamide in mHSPC was estimated to be \$300 million to < \$400 million over the first six years of listing. This differed considerably from the estimated net cost to the PBS/RPBS for apalutamide for mHSPC in July 2022, which was reported as \$200 million to < \$300 million over the first six years of listing in the PSD. The revised estimates presented in the PSCR resulted in a net cost to the PBS/RPBS of \$200 million to < \$300 million over the first 6 years of listing. This was further reduced in the pre-PBAC response to \$200 million to < \$300 million over the first 6 years of listing.

6.71 Since the enzalutamide submission applied essentially the same data sources and approaches used in the July 2022 apalutamide resubmission, the main reasons for the difference in estimated net cost were:

- Modelled mean treatment duration was significantly higher for enzalutamide versus apalutamide (62.2 months for enzalutamide, compared to 30.2 months (HV subgroup) and 39.8 months (LV subgroup) for apalutamide (Table 14, p29, apalutamide PSD, July 2022). This was reflected in the financial estimates as higher proportions on treatment each year for enzalutamide (91.59% in Yr 1 to 35.13% in Yr 6) versus apalutamide (LV: 92.4% in Yr 1 to 6.3% in Yr 6 and for HV: 88.1% in Yr 1 to 12% in Yr 6) (see Table 15, p31, apalutamide PSD, July 2022). This contributed to the higher patient and script number in this submission versus the July 2022 apalutamide submission. The duration of treatment was amended in the revised base case calculations in the PSCR and pre-PBAC response.
- Table 16 in the July 2022 apalutamide PSD showed there were no estimated prevalent mHSPC patients from Years 2 to 6. While all estimated patient numbers were redacted from the July 2022 PSD, it would be reasonable to assume there are a greater number of prevalent mHSPC patients estimated in the enzalutamide submission, resulting in a greater total number of mHSPC patients. The revised base case estimations in the PSCR and pre-PBAC response removed prevalent patients from Year 2.

### **Quality Use of Medicines**

- 6.72 The submission indicated that the sponsor's presentation of educational material and activities always complies with the Medicines Australia code of conduct, and the patient brochure for patients who commence enzalutamide has a QR code to navigate patients to the consumer medicines information.

### **Financial Management – Risk Sharing Arrangements**

- 6.73 The submission stated that given the uncertainty on the timing of apalutamide being listed on the PBS for mHSPC, the sponsor was not outlining a RSA for enzalutamide. The submission added that if apalutamide is listed by the time of the March 2023 PBAC meeting, there may be implications of the RSA negotiated for that which would impact the enzalutamide listing.
- 6.74 The submission also stated that the sponsor understands an RSA will be a condition of listing of apalutamide for mHSPC and thus expects that should enzalutamide be recommended for treatment of mHSPC, the sponsor would need to agree to an RSA in its own right, or would be required to participate in the existing RSA for apalutamide. The sponsor acknowledged that the RSA would encompass an annual subsidisation cap based on estimated PBS/RPBS expenditure for enzalutamide, and that a percentage rebate for the Commonwealth payment above the annual subsidisation cap would be required. The Secretariat advised that if there was to be an RSA in place specifically for the proposed indication, separate PBS item codes would be required to allow the Department to more easily track expenditure in a transparent manner.

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

## 7 PBAC Outcome

- 7.1 The PBAC recommended listing enzalutamide for the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) irrespective of disease volume or suitability for docetaxel. The PBAC considered that enzalutamide, in combination with androgen deprivation therapy (ADT), provides a moderate clinical benefit compared to ADT alone. The PBAC advised that changes should be made to the economic model and that for enzalutamide to be considered cost effective, the price should be reduced such that the incremental cost-effectiveness ratio (ICER) was no more than \$45,000 per quality adjusted life year (QALY) gained. The PBAC considered that the utilisation estimates were reasonable, but that a risk sharing arrangement (RSA) would mitigate the risks that (i) patients would remain on enzalutamide for longer than estimated, and (ii) enzalutamide use in patients with high volume disease who were suitable for docetaxel may not be cost-effective.
- 7.2 The PBAC noted the input from the Medical Oncology Group of Australia (MOGA) which strongly supported the listing of enzalutamide on the PBS for the treatment of mHSPC.
- 7.3 The PBAC considered that the proposed place in therapy and associated requested listing, which was for all patients with mHSPC and mirrored that proposed for apalutamide, were appropriate. The PBAC reiterated that treatment with a novel hormonal agent (NHA) should be restricted to once per lifetime and hence, patients who receive enzalutamide through the PBS for mHSPC should not receive subsidy for a NHA through a non-metastatic disease indication. The PBAC also considered that the restriction should allow the use of enzalutamide as dual therapy (with ADT) or as triple therapy (with ADT and docetaxel) to increase clinical choice.
- 7.4 The PBAC considered that the nominated comparator, placebo in combination with ADT, was appropriate. The PBAC considered that the nomination of apalutamide as a near market comparator was reasonable. The PBAC considered that darolutamide could also be considered a near market comparator but noted that there were significant differences between the primary trials presented for darolutamide (ARASENS) and enzalutamide (ARCHES) that would make a comparison difficult.
- 7.5 The PBAC noted that the submission was primarily based on the ARCHES randomised trial which compared enzalutamide + ADT to ADT alone. The PBAC noted that supportive evidence was presented from the ENZAMET trial that compared enzalutamide + ADT with a non-steroidal anti androgen (either bicalutamide, nilutamide or flutamide) + ADT, with or without early docetaxel.
- 7.6 The ARCHES trial demonstrated significant improvements for enzalutamide compared with placebo in terms of radiographic progression free survival (rPFS; HR = 0.39; 95% CI: 0.30, 0.50) and overall survival (OS; HR = 0.66; 95% CI: 0.66, 0.81). The PBAC considered that the claim that enzalutamide was superior to placebo in terms of effectiveness was supported.

- 7.7 Although there were no significant differences in any treatment emergent adverse events (AEs), serious AEs, or AEs leading to discontinuation of study drug in the ARCHES trial, the PBAC noted that enzalutamide was associated with significantly higher rates of Grade 3-4 AEs and AEs leading to death compared to placebo. The PBAC considered that the claim that enzalutamide was inferior in terms of safety to placebo was supported.
- 7.8 The PBAC noted that the submission also presented a series of indirect treatment comparisons (ITCs) between enzalutamide (using data from the ARCHES and ENZAMET trials) and apalutamide (using data from the TITAN trial). The PBAC noted that no significant differences were demonstrated between enzalutamide and apalutamide in terms of PFS or OS. The PBAC considered that enzalutamide was likely non-inferior in terms of efficacy compared to apalutamide.
- 7.9 Although no ITCs were presented for safety outcomes, the PBAC considered that enzalutamide was likely to be non-inferior in terms of safety compared to apalutamide in mHSPC.
- 7.10 The PBAC noted that the submission presented two economic approaches, (i) a cost-utility analysis versus placebo, and (ii) a cost-minimisation approach versus apalutamide.
- 7.11 In terms of the cost-utility analysis, the PBAC noted that the submission presented a combination partitioned survival and Markov state model based on the intention-to-treat (ITT) population from the ARCHES trial. The PBAC noted that the Pre-Sub-Committee Response (PSCR) presented revisions to the model which better aligned the model outcomes to those from the apalutamide model which was accepted in July 2022 (see paragraph 6.57). However, the PBAC noted the outstanding concerns raised by ESC regarding the model, including that:
- the modelled QALY gain in the revised base case (0.83) remained higher than that previously accepted by the PBAC for apalutamide (0.56, weighted across the low and high volume models);
  - convergence was not applied to the OS arms from 5 to 10 years. The PBAC noted that if convergence was applied as it was in the apalutamide model, then the modelled QALY gain for enzalutamide was reduced to 0.50; and
  - subsequent NHA use was assumed to be 15 months. The PBAC noted that 12 months of subsequent NHA use was accepted in the apalutamide model.
- 7.12 Based on the above, the PBAC considered that the revised model presented in the PSCR was more reliable after: (i) applying convergence to OS from 5 to 10 years; and (ii) reducing subsequent NHA use from 15 months to 12 months. The PBAC noted that the ICER for this scenario (using the proposed ex-manufacturer price proposed in the pre-PBAC response of \$1 ) was \$55,000 to < \$75,000 per QALY gained. The PBAC considered that enzalutamide is cost-effective if the ICER is no more than \$45,000 per QALY gained and noted that a further price reduction would be required to achieve

this.

- 7.13 The PBAC considered for the purpose of Section 101(3B) of the *National Health Act 1953*, that enzalutamide was an alternative therapy to apalutamide, and that enzalutamide does not provide a significant improvement in efficacy and/or reduction of toxicity over apalutamide. The PBAC advised that the price of enzalutamide should therefore be not higher than the price of apalutamide, based on the daily cost at recommended doses (enzalutamide 160 mg daily is equi-effective to apalutamide 240 mg daily), should apalutamide be PBS listed for mHSPC.
- 7.14 In terms of the utilisation and financial impact estimates, the PBAC considered that it was appropriate that these were based on patients with either (i) low volume disease or (ii) high volume disease and were not suitable for docetaxel, as there was a risk that enzalutamide use in patients with high volume disease who were suitable for docetaxel may not be cost-effective and this use, like in the July 2022 submission for apalutamide, would be managed through the RSA. The PBAC noted that the PSCR and pre-PBAC response presented revised utilisation estimates which excluded prevalent patients from Year 2, reduced the proportion of mHSPC patients remaining on enzalutamide and reduced the effective price of enzalutamide (see paragraph 6.69). The PBAC noted that some uncertainty remained regarding the mean treatment duration for enzalutamide; however, considered that the use estimated in the revised estimates together with the revised price (see paragraph 7.12) would provide a reasonable estimate of the likely PBS expenditure.
- 7.15 The PBAC considered that an RSA would be required to mitigate the risks that (i) patients would remain on enzalutamide for longer than estimated, and (ii) enzalutamide use in patients with high volume disease who were suitable for docetaxel treatment may not be cost-effective. The PBAC recalled that for apalutamide in July 2022 it 'acknowledged that it may be reasonable to achieve the required ICER through a combination of the RSA expenditure caps as well as a price reduction; however, the price for apalutamide should be no higher than that in the mOCRPC setting' and considered that this would also be appropriate for enzalutamide. The PBAC advised that enzalutamide should join the apalutamide RSA should apalutamide have progressed to PBS listing for mHSPC.
- 7.16 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 enzalutamide:
- 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;

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- 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.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add indication as follows:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ENZALUTAMIDE					
enzalutamide 40 mg capsule, 112	NEW <small>MP (do not add to 13118K)</small>	1	112	5	Xtandi
Safety Net Rule Penalty Applies: Yes					
<b>Restriction Summary [New 1] / Treatment of Concept: [New 1.1] : Authority Required</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber Type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
<b>Episodicity:</b> [blank]					
<b>Severity:</b> Metastatic, castration sensitive					
<b>Condition:</b> carcinoma of the prostate					
<b>Indication:</b> Metastatic, castration sensitive carcinoma of the prostate					
<b>Clinical criteria:</b>					
The treatment must be/have been initiated within 6 months of treatment initiation with androgen deprivation therapy					
<b>AND</b>					
<b>Clinical criteria:</b>					
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					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug					
<b>Treatment criteria:</b>					
Patient must be undergoing concurrent treatment with androgen deprivation therapy with/without docetaxel					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply.					

	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
	<b>Administrative Advice:</b> Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide.

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

8.2 Flow-on changes are required to align the apalutamide restriction, which was recommended by the PBAC in July 2022, with the above restriction.

## **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**

Astellas Pharma Australia welcomes the PBAC decision to recommend the PBS listing of enzalutamide (Xtandi®) for metastatic hormone sensitive prostate cancer (mHSPC). Astellas will continue to work with the Department of Health to ensure a timely PBS listing.