

7.03 DAROLUTAMIDE, Tablet 300 mg, Nubeqa[®], Bayer Australia Ltd.

1 Purpose of submission

- 1.1 The resubmission requested a General Schedule Authority Required (Telephone) listing for darolutamide for treatment of patients with non-metastatic castration resistant prostate cancer (m0CRPC) at high risk of distant metastases.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus standard of care (SOC). The key components of the clinical issue addressed by the submission are presented in Table 1. The only difference compared to the July 2020 submission was that the resubmission claimed that darolutamide was non-inferior in terms of safety compared to apalutamide and enzalutamide (the July 2020 submission claimed that darolutamide was superior).

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

Component	Description
Population	Patients with non-metastatic CRPC who are at high risk of developing distant metastases; with high risk defined as a PSADT of ≤ 10 months
Intervention	Darolutamide 600 mg (2 $\times$ 300 mg) twice daily (total dose 1,200 mg/day) with background ADT
Comparator	Main comparator: watchful waiting (SOC) with ongoing ADT Near-market comparators: apalutamide 240 mg/day; enzalutamide 160 mg/day
Outcomes	MFS, OS, time to pain progression, time to initiation of first cytotoxic chemotherapy, time to first symptomatic skeletal event, patient-reported outcomes, safety
Clinical claim	Superior efficacy and inferior safety vs. watchful waiting (SOC) Non-inferior efficacy and non-inferior safety vs. apalutamide and vs. enzalutamide It was noted that darolutamide appeared to have a more favourable safety profile in some outcomes of interest compared to apalutamide and enzalutamide, with the PBAC considering that darolutamide may be better tolerated compared to apalutamide and enzalutamide [para 7.11, darolutamide PSD, July 2020].

Source: Table 1-1, p4 of the resubmission.

ADT = androgen deprivation therapy; CRPC = castration resistant prostate cancer; MFS = metastasis free survival; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PSADT = prostate-specific antigen doubling time; PSD = Public Summary Document; SOC = standard of care

2 Background

Registration status

- 2.1 Darolutamide was evaluated by the TGA under a work-sharing initiative with Health Canada and TGA registered on 26 February 2020 for the treatment of patients with m0CRPC.

Previous PBAC consideration

- 2.2 Darolutamide was previously considered by the PBAC for this indication in July 2020.
- 2.3 The table below summarises the key matters from the July 2020 PBAC consideration and how the resubmission has addressed those concerns.

Public Summary Document– March 2021 PBAC Meeting

Table 2: Summary of key matters of concern from the July 2020 submission and how they have been addressed in the resubmission

Component	Matter of concern, July 2020 submission	How the resubmission addresses it
Restriction		
Price of darolutamide	A substantial price reduction would be required for darolutamide to be considered suitably cost-effective [para 7.1, July 2020 PSD].	The resubmission proposed a 25% price reduction, reducing the effective AEMP from \$[REDACTED] in July 2020 to \$[REDACTED].
PSA level	The PBAC considered that treatment should be restricted to patients with a PSA level of at least 2 ng/mL, which was a criterion of the ARAMIS trial [para 3.2, July 2020 PSD].	The resubmission stated that this clinical criteria was not included in the proposed restriction as it was removed by the PBAC from the proposed restriction for apalutamide in July 2019.
Clinical evidence		
Magnitude of OS benefit	The PBAC considered the magnitude of the OS benefit to be uncertain because of the immaturity of the data. [para 7.8, July 2020 PSD]	No new data presented.
Economic analysis		
OS curves	The PBAC noted that the modelled OS curves did not converge within the 10 year time horizon, and that the difference in survival at 10 years (20%) was substantially larger than that observed in the ARAMIS trial at 3 years (5.7%) [para 7.13, July 2020 PSD].	The darolutamide OS curve was no longer extrapolated using an independently fitted parametric curve, instead the resubmission applied the trial-based HR (0.685) to the SOC OS curve. The difference in survival at 10 years was 11%.
mCRPC utility value	The PBAC noted that ICER was sensitive to the utility value for the mCRPC health state, with the value being substantially lower than the values applied in the m0CRPC health state. The PBAC considered that the value (0.530) was too low given that metastatic disease may initially be asymptomatic [para 7.14, July 2020 PSD].	A value of 0.560 was applied to the mCRPC health state. This was based on a study by Sullivan, 2007.
m0CRPC utility values	The PBAC considered that the same utility value should be applied to all patients in the m0CRPC health state [para 7.14, July 2020 PSD].	The same utility value was applied to both arms in the m0CRPC health state (0.813).
ICER	The PBAC considered that the ICER was high and underestimated and that an ICER in the range of \$40,000 to \$45,000 per QALY would be required [para 7.15, July 2020 PSD].	The updated ICER was \$[REDACTED] ¹ .
Financial estimates		
Financial impact	The PBAC considered that the estimated financial impact of more than \$100 million over 6 years to be high and uncertain. The PBAC considered that the number of incident and prevalent patients was highly uncertain [para 7.16, July 2020 PSD].	The method to derive incident and prevalent patients is unchanged. Uncertainty remains in the size of the eligible and treated populations. Based on the July 2020 DUSC advice: treatment uptake assumptions have been increased in the initial years of listing; the treatment compliance assumption has been reduced from 98.88% to 92%; and additional costs of ADT and MBS item costs are excluded.
RSA	The PBAC considered that the uncertainty with the financial estimates could be addressed with an RSA [para 7.16, July 2020 PSD].	A risk-sharing arrangement is proposed in the form of an expenditure cap with a [REDACTED]% rebate for expenditure above the amounts estimated for annual net cost to the PBS and RPBS.

Source: Compiled during evaluation

ADT = androgen deprivation therapy; AEMP = approved ex-manufacturer price; DUSC = Drug Utilisation Sub-Committee; HR = hazard ratio; ICER = incremental cost effectiveness ratio; MBS = Medicare Benefits Schedule; m0CRPC = non-metastatic castration resistant

Public Summary Document– March 2021 PBAC Meeting

prostate cancer; mCRPC = metastatic castration resistant prostate cancer; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSA = prostate-specific antigen; PSD = public summary document; RPBS = Repatriation Pharmaceutical Benefits Scheme; QALY = quality adjusted life year; RSA = risk sharing arrangement; SOC = standard of care
The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

2.4 The PBAC considered a submission for apalutamide for this indication in November 2020. The PBAC did not recommend the listing of apalutamide and considered that:

- while apalutamide provides a substantial benefit to some patients in delaying metastases, the magnitude of the survival benefit was modest;
- not all of the requested changes to the economic model were implemented in the resubmission;
- the incremental cost-effectiveness ratio (ICER) remained high and uncertain, and a price reduction would be required to bring the ICER into an acceptable range; and
- the estimated financial impact of listing apalutamide on the PBS remained high (November 2020 PBAC Outcomes – Subsequent decisions not to recommend, pbs.gov.au).

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

3 Requested listing

Name, restriction, manner of administration, form	Max. Qty. (packs)	Max. Qty. (units)	No. of repeats	Dispensed price for Max. Qty.	Proprietary name and manufacturer
DAROLUTAMIDE Tablet, 300 mg	1	112	5	Published: AEMP: \$4,123.90 DPMQ: \$4,285.06 Effective: AEMP: \$ DPMQ: \$	Nubeqa, Bayer

Public Summary Document– March 2021 PBAC Meeting

Prescriber type:	☒ Medical Practitioners
PBS indication:	Castration resistant carcinoma of the prostate
Restriction type:	☒ Authority Required (immediate/real-time assessment by Services Australia)
Treatment phase:	Initial
Clinical criteria: Patient must not have distant metastasis on conventional imaging AND Treatment must be used in combination with androgen deprivation therapy AND Patient must have a PSA doubling time of 10 months or less AND Patient must have a WHO performance score of 0 or 1 AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug	
Prescriber Instructions: The PSA doubling time must have been calculated using at least three PSA values obtained during androgen deprivation therapy	
Treatment phase:	Continuing
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Treatment must be used in combination with androgen deprivation therapy AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug	
Administrative Advice: Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised	

- 3.1 The resubmission proposed an effective approved ex-manufacturer price (AEMP) of \$ [REDACTED], which was a 25% reduction from the July 2020 proposed AEMP of \$ [REDACTED]. The pre-PBAC response offered a further 14% price reduction, resulting in an AEMP of \$ [REDACTED].
- 3.2 The proposed initial and continuing restrictions were unchanged from July 2020.
- 3.3 The PBAC noted that the proposed restriction included the criterion 'Patient must not have distant metastases on conventional imaging', and that this was consistent with its recommendation for apalutamide for the same indication at the November 2020 meeting on the basis that it aligned the PBS population with the trial population (paragraph 3.5, apalutamide Public Summary Document (PSD, November 2020). However, noting the increasing use of more sensitive prostate-specific membrane antigen (PSMA) PET scanning for staging CRPC, and hence the broader population classified as having distant metastases, including a substantial proportion of patients classified as mOCRPC on conventional imaging, the PBAC reconsidered that the clinical criterion requiring patients to not have distant metastases be omitted. Further support for removal of this criterion is that the majority of patients with a PSA

doubling time of 10 months or less are likely be diagnosed with, or would soon progress to, metastatic castration resistant prostate cancer (mCRPC) especially with the use of the more sensitive PSMA PET scans.

- 3.4 The PBAC reiterated that treatment with a novel hormonal agent (NHA, i.e. darolutamide, enzalutamide or abiraterone) should be limited to one treatment course per lifetime.
- 3.5 In July 2020 the PBAC stated that the restriction should limit darolutamide use to patients with a prostate-specific antigen (PSA) level of at least 2 ng/mL, noting that PSA doubling time was not always an indicator of risk, and as a PSA level of at least 2 ng/mL was an inclusion criteria of the ARAMIS trial. The PBAC previously considered that restricting treatment to patients with a PSA level of at least 2 ng/mL would help limit darolutamide use to higher risk patients who were more likely to benefit from treatment (paragraph 3.2, darolutamide PSD, July 2020). The resubmission stated that this clinical criterion was not included in the proposed restriction as it was removed by the PBAC from the proposed restriction for apalutamide in July 2019. The PBAC considered that omission of this criterion would not be consistent with the intent to limit subsidy to high risk patients.
- 3.6 The resubmission estimated that < 500 patients would receive therapy in the patient access program and would require transitioning arrangements. The July 2020 submission estimated there would be < 500 grandfathered patients.

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

4 Population and disease

- 4.1 mOCRPC is a disease stage of prostate cancer where patients have rising levels of PSA but no radiographic evidence of distant metastatic disease. Patients with mOCRPC are classified into two groups based on PSA doubling time (PSADT) – patients with PSADT > 10 months are at low risk while patients with a PSADT ≤ 10 months are classified as high risk.
- 4.2 Patients with mOCRPC are currently managed with androgen deprivation therapy (ADT) with possible use of secondary hormonal therapies. It is expected that approximately one-third of all patients with mOCRPC will develop metastases within two years, with more than half becoming metastatic within three years. Once metastases occur, the disease becomes incurable and median survival has been estimated to be 16 to 30 months. The submission noted that many patients will require the initiation of cytotoxic chemotherapy to delay the occurrence of further metastases, which can result in highly undesirable adverse events that further add to the treatment burden. The PBS listing of darolutamide was requested for treatment of patients at high risk of distant metastases with mOCRPC to delay the onset of metastatic disease, avoid the need for cytotoxic therapy and preserve patients' quality of life (QoL), as well as improving patient overall survival (OS).

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

5 Comparator

- 5.1 Like the July 2020 submission, the resubmission nominated watchful waiting/placebo as the main comparator where 'watchful waiting' is in addition to ongoing ADT with or without the addition of secondary hormonal therapies. The wording 'standard of care (SOC)' is used herein instead of placebo. The main arguments provided in support of this nomination were that there are currently no other PBS-funded treatment options available for the proposed patient population, and that watchful waiting was accepted by the PBAC as the main comparator for apalutamide. In July 2020, the PBAC considered that watchful waiting/SOC was the appropriate comparator (paragraph 7.5, darolutamide PSD, July 2020).
- 5.2 The resubmission also again nominated two near-market comparators, apalutamide and enzalutamide. In July 2020, the PBAC considered that apalutamide and enzalutamide were appropriate near market comparators (paragraph 7.5, darolutamide PDS, July 2020).
- 5.3 The ESC had previously noted that PSMA PET screening is an increasingly common staging modality for CRPC and is standard of care in many centres in Australia. As PSMA PET is more sensitive compared with conventional imaging, its use could result in patients otherwise classified as mCRPC being classified as having occult metastatic disease. The ESC noted that, in clinical practice, a patient with metastatic disease detected with PSMA PET scanning, but not with conventional imaging, would be eligible for either (i) darolutamide; or (ii) PBS-subsidised treatment with enzalutamide or abiraterone following docetaxel or as a first line treatment for metastatic disease if the patient has a predicted intolerance to docetaxel.
- 5.4 The PBAC noted data provided by the DUSC Secretariat (Table 3) indicating that the majority of mCRPC patients are being treated with abiraterone and enzalutamide without prior treatment with docetaxel (72% and 69%, respectively, in 2019).

Public Summary Document– March 2021 PBAC Meeting

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

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

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

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

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

Source: DUSC Secretariat

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

5.5 The ESC noted a study by Fendler et al 2019¹ that retrospectively assessed the extent of disease detected by PSMA PET in a cohort (N = 200) of high-risk patients, selected to be similar to that included in ARAMIS (and SPARTAN and PROSPER), with CRPC defined as non-metastatic by conventional imaging. PSMA PET positive cancer was detected in 98% of all study patients and 55% of the study population had distant metastatic disease despite having no signs of distant metastases on conventional imaging.

5.6 The pre-PBAC response estimated that the overlapping population would be in the range of 7.7% to 19.3% (20% or 50% x 55% x 70%), assuming that:

- 20% to 50% of patients would receive a PSMA PET scan;
- 55% would not have signs of distant metastases on conventional imaging but would have signs using the PSMA PET scan (from Fendler et al 2019); and
- 70% of patients would be at risk of docetaxel toxicities and therefore able to receive abiraterone or enzalutamide.

5.7 The PBAC considered that given the use of abiraterone and enzalutamide prior to docetaxel, the increasing use of PSMA PET scanning, and the results of the study by

¹ Fendler et al, Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer; Clin Cancer Res December 2019 (25) (24) 7448-7454; Accessed at: <https://clincancerres.aacrjournals.org/content/25/24/7448>

Fendler et al 2019, the overlapping population would be substantial. As noted in paragraph 3.3, this supports a restriction for darolutamide that does not require staging as mOCRPC, and for this scenario the extent of overlap would be greater.

- 5.8 The PBAC therefore considered that, while SOC had previously been considered the relevant comparator, changing clinical practices supported current treatments for mCRPC (i.e. abiraterone and enzalutamide) also being relevant comparators.

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 health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the unmet clinical need for patients with mOCRPC and the benefits of treatment darolutamide including improved overall survival and a well tolerated safety profile.
- 6.3 The PBAC noted the advice received from the Prostate Cancer Foundation of Australia clarifying the likely use of darolutamide in clinical practice. The PBAC specifically noted the advice that the use of darolutamide may delay metastases and increase overall survival for patients with mOCRPC. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.4 The PBAC noted that there was no input from the Medical Oncology Group of Australia (MOGA), but that in July 2020 the MOGA expressed its strong support for the darolutamide submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the ARAMIS trial. In July 2020 the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for darolutamide, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)², based on a comparison with placebo + ADT.

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

Clinical trials

- 6.5 The resubmission was again based on the ARAMIS trial, a direct comparison of darolutamide and SOC in patients with mOCRPC at high risk of developing distant metastases. No updated data were presented from the ARAMIS trial.
- 6.6 Indirect treatment comparisons (ITCs) versus the near market comparators apalutamide (using the SPARTAN trial) and enzalutamide (using the PROSPER trial), with SOC as the common reference were also again presented. Final OS data were presented for both the SPARTAN and PROSPER trials.
- 6.7 The resubmission also presented data from two matching-adjusted indirect comparisons (MAICs) of MFS (Jiang 2020a) and safety (Jiang 2020b) as supplementary analyses to the ITCs.
- 6.8 Details of the trials presented in the submission are provided in Table 4.

Public Summary Document– March 2021 PBAC Meeting

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Darolutamide trial		
ARAMIS	A multi-national, randomised, double blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high risk non-metastatic-castration-resistant prostate cancer. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in non-metastatic castration-resistant prostate cancer. Shore N, Zurth C, Fricke R, et al. Evaluation of clinically relevant drug-drug-interactions and population pharmacokinetics of darolutamide in patients with non-metastatic castration-resistant prostate cancer: Results of pre-specified and post hoc analyses of the Phase III ARAMIS trial. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide.	February 2019 <i>NEJM</i> . 2019;380(13): 1235-1246 <i>Target Oncol</i> . 2019;14(5): 527-539 <i>NEJM</i> . 2020;383:1040-1049.
Apalutamide trial		
SPARTAN	Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. Uemura H, Satoh T, Tsumura H, et al. Efficacy and safety of apalutamide in Japanese patients with nonmetastatic castration-resistant prostate cancer: a subgroup analysis of a randomized, double-blind, placebo-controlled, Phase 3 study.	<i>NEJM</i> . 2018;378: 1408-1418 <i>Ann Oncol</i> . 2019;30(11): 1813-1820 <i>European Urology</i> . 2020; doi.org/10.1016/j.eururo.2020.08.011 <i>Prostate International</i> . 2020; doi.org/10.1016/j.pnrl.2020.05.002
Enzalutamide trial		
PROSPER	Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with non-metastatic, castration-resistant prostate cancer. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic castration-resistant prostate cancer.	<i>NEJM</i> . 2018;378(26): 2465-2474 <i>NEJM</i> . 2020;382(23): 2197-2206
Matching-adjusted indirect treatment comparisons		
Jiang 2020a	Jiang S, Terasawa E, Garcia-Horton v, et al. Darolutamide versus apalutamide and enzalutamide in non-metastatic castration-resistant prostate cancer (nmCRPC): matching-adjusted indirect comparisons	Poster presented at AMCP 2020 Annual Meeting, April 21-24, Houston, TX
Jiang 2020b	Jiang S, Terasawa E, Garcia-Horton V, et al. Safety outcomes of darolutamide vs, apalutamide and enzalutamide in non-metastatic castration-resistant prostate cancer (nmCRPC): matching-adjusted indirect comparisons.	Poster presented at ASCO 2020, May 29-31, Chicago, IL

Source: Table 2-6, p48 of the resubmission

6.9 The key features of the included evidence and the comparisons made are summarised in the table below.

Table 5: Summary of trials used in the direct and indirect comparisons

Trial	N	Design/ Duration	Risk of bias	Patient population	Outcomes	Comparisons	Use in modelled evaluation
ARAMIS	DARO: N = 955 SOC: N = 554 Total: N = 1,509	R, DB, MC DARO + ADT vs. SOC + ADT Median follow-up = 29.1 months	Moderate	m0CRPC with high risk of distant metastases (PSADT ≤ 10 months)	Primary: MFS Secondary: OS, PFS, time to: PSA progression, pain progression, first skeletal event, cytotoxic chemo, first use subsequent anti- neoplastic therapy	Direct comparison vs. SOC; ITC vs. APA and ENZA; MAIC vs. APA and ENZA	Yes
SPARTAN	APA: N = 806 SOC N = 402 Total: N = 1,208	R, DB, MC APA + ADT vs. SOC + ADT Median follow-up = 52.0 months	Moderate		Primary: MFS Secondary: PFS, OS, time to: PSA progression, symptomatic progression, cytotoxic chemo, metastasis	ITC vs. DARO; MAIC vs. DARO	No
PROSPER	ENZA: N = 933 SOC: N = 468 Total: N = 1,401	R, DB, MC ENZA + ADT vs. SOC + ADT Median follow-up = 48.0 months	Moderate		Primary: MFS Secondary: OS, time to: PSA progression, pain progression, first use subsequent anti- neoplastic therapy	ITC vs. DARO; MAIC vs. DARO	No

Source: Table 2-7, p51 of the resubmission.

ADT = androgen deprivation therapy; APA = apalutamide; chemo = chemotherapy; DARO = darolutamide; DB = double blind; ENZA = enzalutamide; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; m0CRPC = non-metastatic castration resistant prostate cancer; MC = multi-centre; MFS = metastasis-free survival; OS = overall survival; PSA = prostate specific antigen; R = randomised; PFS = progression-free survival; SOC = standard of care

6.10 The PBAC previously considered that the risk of bias across the three trials was likely to be moderate given occurrence of adverse events (AEs) in the active treatment arms such as rash and fatigue which would potentially result in unblinding (paragraphs 6.6 and 6.7, darolutamide PSD, July 2020).

6.11 The intention-to-treat (ITT) analysis of the key outcome, metastasis-free survival (MFS), in the ARAMIS trial included patients who had been misclassified at baseline as not having metastases (5.2% of patients in the darolutamide arm and 7.0% of patients in the SOC arm). Results for MFS, the primary outcome, were presented with and without correction for the misclassification.

Comparative effectiveness

6.12 A summary of the results for key time-to-event outcomes in ARAMIS are presented below.

Table 6: Summary of time-to-event outcomes in ARAMIS

Outcome	Interim analysis (17.9 months)		Updated analysis (29.1 months)	
	Darolutamide (N = 955)	SOC (N = 554)	Darolutamide (N = 955)	SOC (N = 554)
Metastasis-free survival (MFS)			Not reported	
Event n (%)	221 (23.1%)	206 (39.0%)		
Median months to metastasis (95% CI)	40.4 (34.3, NR)	18.4 (15.5, 22.3)		
HR (95% CI)	0.41 (0.34, 0.50)			
Metastasis-free survival (MFS) – censored (corrected for misclassification of patients)			Not reported	
Event n (%)	171 (17.9%)	177 (31.9%)		
Median months to metastasis (95% CI)	40.5 (35.8, NR)	22.1 (18.3, 25.8)		
HR (95% CI)	0.36 (0.29, 0.44)			
Overall survival (OS)				
Died n (%)	78 (8.2%)	58 (10.5%)	148 (15.5%)	106 (19.1%)
Median months to death (95% CI)	NE	NE	NE	NE
HR (95% CI)	0.71 (0.50, 0.99) ^a		0.69 (0.53, 0.88)	
Time to first symptomatic skeletal event (SSE)				
Event n (%)	16 (1.7%)	18 (3.2%)	29 (3.0%)	28 (5.1%)
Median months to SSE (95% CI)	NE	NE	NE	NE
HR (95% CI)	0.43 (0.22, 0.84) ^a		0.48 (0.29, 0.82) ^a	
Time to initiation of cytotoxic chemotherapy				
Event n (%)	73 (7.6%)	79 (14.3%)	127 (13.3%)	98 (17.7%)
Median months chemotherapy (95% CI)	NE	38.2 (22.4, 35.6)	NE	NE
HR (95% CI)	0.43 (0.31, 0.60) ^a		0.58 (0.44, 0.76) ^a	
Time to pain progression				
Event n (%)	251 (26.3%)	178 (32.1%)	Not reported	
Median months pain progression (95% CI)	40.3 (33.2, 41.2)	25.4 (19.1, 29.6)		
HR (95% CI)	0.65 (0.53, 0.79)			

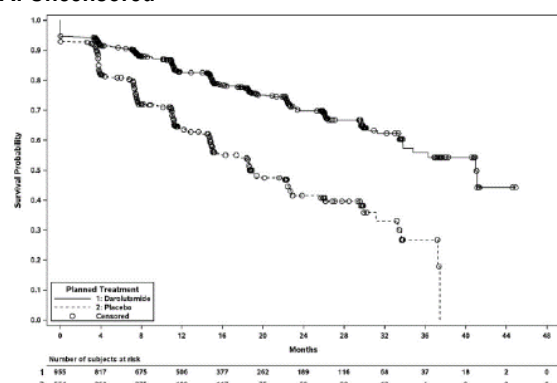
Source: Table 2-18, p74 of the resubmission.

CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; NE = not estimable; OS = overall survival; SOC = standard of care; **bold** = statistically significant^a Not statistically significant given the pre-specified alpha significance level for the analysis was 0.0005.

- 6.13 The censored analysis of MFS, corrected for misclassification, showed a statistically significant improvement for darolutamide compared to SOC, demonstrating a 64% reduction in the risk of developing distant metastasis or death (HR = 0.36; 95% CI: 0.29, 0.44). The median months to metastasis was approximately 18 months longer for darolutamide compared to SOC.
- 6.14 The Kaplan Meier plots for MFS, for both the uncensored and censored analyses (correcting for patient misclassification) are provided in Figure 1.

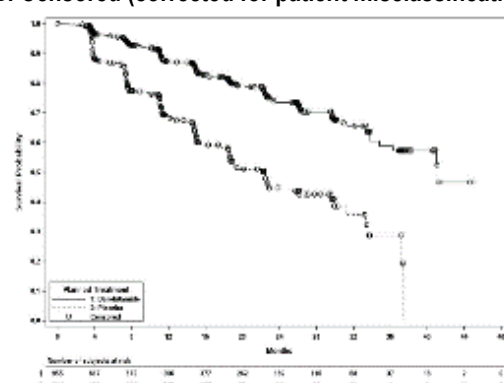
Figure 1: Kaplan Meier curves for MFS

A: Uncensored



Source: Figure 2.8, p79 of the resubmission.

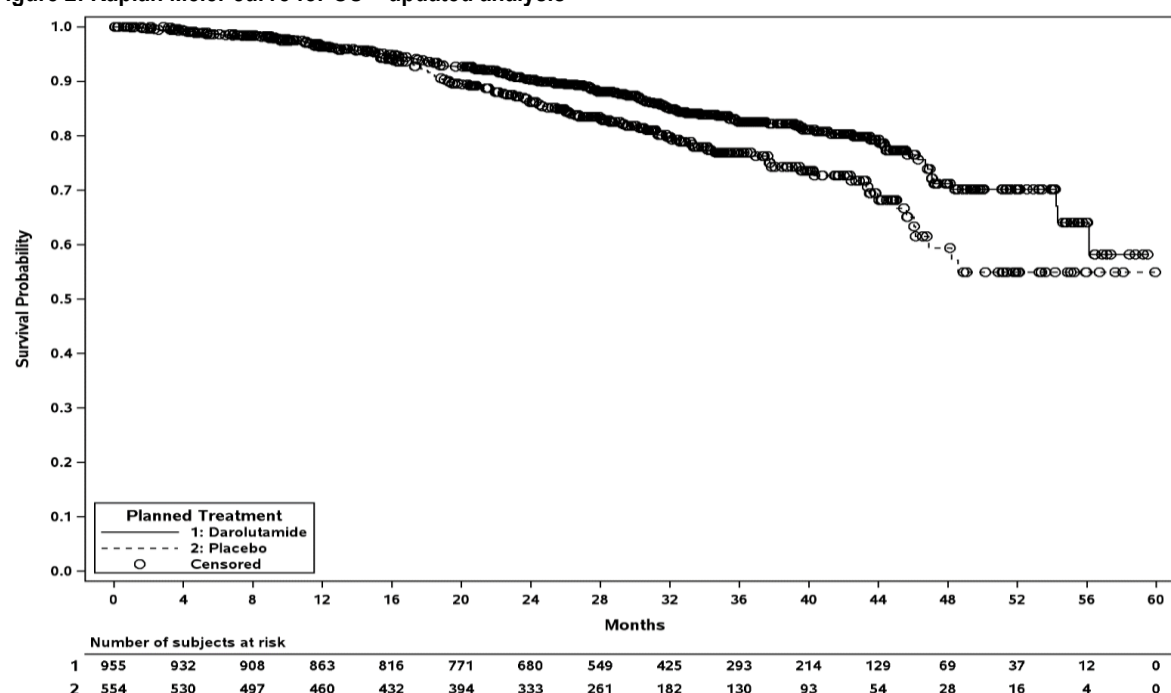
B: Censored (corrected for patient misclassification)



Source: Figure 2-9, p79 of the resubmission.

6.15 The ESC noted that the interim analysis for OS (median follow-up of 17.9 months) indicated no statistically significant advantage for darolutamide as the pre-specified alpha significance level of 0.0005 (to take into account alpha spent with multiple comparisons) was not met. In the updated analysis (median follow-up of 29.1 months) the planned number of events (240) was reached and the pre-specified significance level of 0.05 was met (HR = 0.69; 95% CI: 0.53, 0.88; p=0.003). The Kaplan Meier plot for the updated analysis is provided in Figure 2.

Figure 2: Kaplan Meier curve for OS – updated analysis



Source: Figure 2.11, p81 of the resubmission.

- 6.16 Darolutamide was associated with a significant delay in the time to a symptomatic skeletal event, initiation of cytotoxic chemotherapy and pain progression.
- 6.17 For patient-reported outcomes, while there were statistically significant differences reported for some scales (BPI-SF, EORTC), these differences were not clinically meaningful, as the differences did not reach the minimally important difference thresholds. There were no statistically significant, or clinically meaningful, differences between darolutamide and SOC observed for the EQ-5D. In July 2020, the PBAC noted that although there were statistically significant differences reported for some scales, there were no clinically meaningful differences across the darolutamide and SOC arms for any of the QoL measures (paragraphs 6.15 and 7.9, darolutamide PSD, July 2020).
- 6.18 Results of the ITCs for efficacy versus apalutamide and enzalutamide are presented below.

Table 7: Results of indirect comparisons for darolutamide vs. apalutamide and darolutamide vs. enzalutamide – MFS and OS

Trial/comparison	Outcome	Active treatment n/N (%)	SOC n/N (%)	HR (95% CI)
MFS (uncensored)				
ARAMIS: darolutamide (17.9 months median follow-up)	Events	221/955 (23.1%)	206/554 (39.0%)	-
	Median months MFS	40.4	18.4	0.41 (0.34, 0.50)
SPARTAN: apalutamide (20.3 months median follow-up)	Events	184/806 (22.8%)	228/401 (48.7%)	-
	Median months MFS	40.5	14.7	0.28 (0.23, 0.35)
PROSPER: enzalutamide (18.5 months ^a median follow-up)	Events	219/933 (23.5%)	228/468 (48.7%)	-
	Median months MFS	36.6	14.7	0.29 (0.24, 0.35)
indirect comparison darolutamide vs. apalutamide				1.48 (1.11, 1.96)
indirect comparison darolutamide vs. enzalutamide				1.42 (1.09, 1.86)
MFS (censored - corrected for misclassification of patients in ARAMIS)				
ARAMIS: darolutamide (29.1 months median follow-up)	Events	171 (17.9%)	177 (31.9%)	-
	Median months MFS	40.5	22.1	0.36 (0.29, 0.44)
SPARTAN: apalutamide (20.3 months median follow-up)	Events	184/806 (22.8%)	228/401 (48.7%)	-
	Median months MFS	40.5	14.7	0.28 (0.23, 0.35)
PROSPER: enzalutamide (18.5 months ^a median follow-up)	Events	219/933 (23.5%)	228/468 (48.7%)	-
	Median months MFS	36.6	14.7	0.29 (0.24, 0.35)
indirect comparison darolutamide vs. apalutamide				1.27 (0.94, 1.72)
indirect comparison darolutamide vs. enzalutamide				1.23 (0.92, 1.63)
OS (updated analyses)				
ARAMIS: darolutamide (29.1 months median follow-up)	Dead	148/955 (15.5%)	106/554 (19.1%)	-
	Median months OS	NE	NE	0.69 (0.53, 0.88)
SPARTAN: apalutamide (41.0 months median follow-up)	Dead	178/806 (22.1%)	107/401 (26.7%)	-
	Median months OS	NE	NE	0.75 (0.59, 0.96)
PROSPER: enzalutamide (NR median follow-up)	Dead	NR	NR	-
	Median months OS	NR	NR	0.83 (0.65, 1.06)
indirect comparison darolutamide vs. apalutamide (41.0 months follow-up)				0.91 (0.64, 1.30)
indirect comparison darolutamide vs. enzalutamide (NR follow-up)				0.83 (0.58, 1.17)
OS (final analyses of ARAMIS, SPARTAN and PROSPER)				
ARAMIS: darolutamide (29.1 months median follow-up)	Dead	148/955 (15.5%)	106/554 (19.1%)	-
	Median months OS	NE	NE	0.69 (0.53, 0.88)
SPARTAN: apalutamide (52.0 months median follow-up)	Dead	274/806 (34.0%)	154/401 (38.4%)	-
	Median months OS	73.9	59.9	0.78 (0.64, 0.96)
PROSPER: enzalutamide (48.0 months median follow-up)	Dead	288/933 (31.8%)	178/468 (38.0%)	-
	Median months OS	67.0	56.3	0.73 (0.61, 0.89)
indirect comparison darolutamide vs apalutamide (52.0 months follow-up)				0.88 (0.64, 1.21)
indirect comparison darolutamide vs. enzalutamide (48.0 months follow-up)				0.94 (0.69, 1.29)

Source: Table 2-18, p84; Table 2-20, p90; Table 2-21, p94; Table 2-34, p138; and Table 2-35, p141 of the resubmission.

CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; NE = not estimable; NR = not reported; OS = overall survival; SOC = standard of care; **bold** = statistically significant^a Median-follow-up for the SOC arm in PROSPER was 15.1 months

For the indirect comparisons, HR results <1 favour darolutamide

- 6.19 The ITCs of MFS (not corrected) resulted in a statistically significant advantage for both apalutamide and enzalutamide when compared to darolutamide. However, when the MFS comparisons were performed correcting for the misclassification of ARAMIS patients who had baseline metastases, the differences were not statistically

significant. The submission argued that the inclusion of patients with metastases at baseline resulted in an underestimation of the darolutamide treatment effect.

- 6.20 The ITCs of OS using the final analysis results from ARAMIS, SPARTAN and PROSPER resulted in no statistically significant differences between darolutamide and apalutamide or between darolutamide and enzalutamide. However, the trials differed in terms of length of follow-up and extent of cross-over.
- 6.21 Jiang 2020a presented MAIC results from comparisons of MFS between darolutamide and apalutamide, and between darolutamide and enzalutamide. Patients in both arms of the ARAMIS trial were reweighted so that the average baseline characteristics matched the respective active and SOC arms in the SPARTAN and PROSPER trials.
- 6.22 In terms of efficacy, Jiang 2020a observed no significant differences in MFS between darolutamide and apalutamide prior to matching (HR = 1.29; 95% CI: 0.95, 1.74) or after matching (HR = 1.14; 95% CI: 0.83, 1.58). Similarly, there were no significant differences between darolutamide and enzalutamide prior to matching (HR = 1.23; 95% CI: 0.93, 1.64) or after matching (HR = 1.20; 95% CI: 0.87, 1.65). The resubmission noted that the results from Jiang 2020a were similar to the results of the Bucher ITCs presented in Table 7 (when the censored results from ARAMIS corrected for misclassification of patients were used).

Comparative harms

- 6.23 The resubmission provided post-hoc analyses of a wide range of AEs associated with ADT treatment (e.g. fracture, falls) and those associated with the novel anti-androgens (e.g. seizure and rash). In July 2020, the PBAC noted that there was a statistically significantly greater occurrence of rash, fatigue and cardiovascular disorders associated with darolutamide treatment compared to SOC. The PBAC considered that fatigue/asthenia may have a considerable impact on cognitive function, given treatment is likely to be long-term and the majority of the patient population are elderly (paragraph 7.10, darolutamide PSD, July 2020).
- 6.24 In its consideration of the previous submission, the ESC noted the cardiovascular adverse event data and 'considered that post-market monitoring would be important to discern whether there are additional safety signals for cardiac events with darolutamide' (paragraph 6.23, darolutamide PSD, July 2020). The resubmission re-presented data from the July 2020 Pre-Sub-Committee Response (PSCR) demonstrating the incidence of cardiovascular disorders in the ARAMIS trial. The resubmission noted that the major contributors to the disproportion between the darolutamide (11.8%) and SOC (7.4%) arms in terms of cardiovascular events (OR = 3.32; 95% CI: 1.27, 8.65) were cardiac arrhythmias (particularly, cardiac conduction disorders, rate and rhythm disorders and supraventricular arrhythmias; however, there were no differences between the treatment arms in terms of ventricular arrhythmias or cardiac arrest), coronary artery disorders and heart failure.

Table 8: Incidence rates of cardiac disorder TEAEs in the ARAMIS trial (safety analysis set)

	Darolutamide (N = 954)		SOC (N = 554)		Incidence ratio for EAIR (95% CI)
	n (%)	EAIR per 100 PY	n (%)	EAIR per 100 PY	
Cardiac disorders, total	113 (11.8%)	NA	41 (7.4%)	NA	NA
Cardiac arrhythmias	64 (6.7%)	4.7	22 (4.0%)	3.8	1.24 (0.76, 2.01)
- cardiac conduction disorders	9 (0.9%)	0.7	2 (0.4%)	0.3	1.91 (0.41, 8.86)
- rate and rhythm disorders NEC	32 (3.4%)	2.4	6 (1.1%)	1	2.27 (0.95, 5.43)
- supraventricular arrhythmias	29 (3.0%)	2.1	9 (1.6%)	1.6	1.37 (0.65, 2.90)
- ventricular arrhythmias/cardiac arrest	6 (0.6%)	0.4	5 (0.9%)	0.9	0.51 (0.16, 1.67)
Coronary artery disorders	31 (3.3%)	2.3	14 (2.5%)	2.4	0.94 (0.50, 1.77)
- coronary artery disorders NEC	13 (1.4%)	1.0	3 (0.5%)	0.5	1.84 (0.53, 6.47)
- ischaemic coronary artery disorders	24 (2.5%)	1.8	11 (2.0%)	1.9	0.09 (0.45, 1.89)
Heart failures	18 (1.9%)	1.3	5 (0.9%)	0.9	1.53 (0.57, 4.12)

Source: Table 2-26, p110 of the resubmission

EAIR = exposure-adjusted incidence rate; NA = not available; NEC = not elsewhere classified; SOC = standard of care

- 6.25 The resubmission stated that, when interpreting the incidence of cardiac events in the ARAMIS trial, it should be noted that there were no significant differences between the darolutamide and SOC arms for any cardiac disorder related treatment emergent adverse event when the incident rate was adjusted for exposure, and patients in the darolutamide arms were more likely to have had a cardiac disorder at baseline (darolutamide arm = 46.1%; SOC arm = 40.3%).
- 6.26 The resubmission presented a post-hoc analysis, presented below, to demonstrate that patients with a medical history of cardiac disorders represented the majority of patients who experienced coronary artery disorders or heart failure in both treatment arms. As the post-hoc analysis did not include cardiac arrhythmias, the incidence of cardiac arrhythmias in patients with and without a medical history of cardiac disorders could not be assessed. In addition, it would be likely that a substantial proportion of darolutamide patients would have a medical history of cardiac disorders in clinical practice. Therefore, it would be expected that cardiovascular AEs would be observed in the Australian setting.

Table 9: Incidence of coronary artery disorders and heart failure by medical history of cardiac disorders in the ARAMIS trial

	With history of cardiac disorders		Without history of cardiac disorders		Total	
	DARO, n (%) N = 440	SOC, n (%) N = 223	DARO, n (%) N = 514	SOC, n (%) N = 331	DARO, n (%) N = 954	SOC, n (%) N = 554
Coronary artery disorders	23 (5.2%)	12 (5.4%)	8 (1.6%)	2 (0.6%)	31 (3.2%)	14 (2.5%)
- coronary artery disorders NEC	10 (2.3%)	2 (0.9%)	3 (0.6%)	1 (0.3%)	13 (1.4%)	3 (0.5%)
- ischaemic coronary artery disorders	17 (3.9%)	10 (4.5%)	7 (1.4%)	1 (0.3%)	24 (2.5%)	11 (2.0%)
Heart failures	13 (3.0%)	5 (2.2%)	5 (1.0%)	0	18 (1.9%)	5 (0.9%)

Source: Table 2-27, p110 of the resubmission

DARO = darolutamide; NEC = not elsewhere classified; SOC = standard of care

Benefits/harms

6.27 A summary of the comparative benefits and harms for darolutamide versus SOC is presented in Table 10.

Table 10: Summary of comparative benefits and harms for darolutamide and SOC

Table 16: Summary of comparative benefits and harms for darolutamide and SOC						
BENEFITS						
Metastasis-free survival (median follow-up 17.9 months); not censored/corrected for misclassification of patients with metastases at baseline						
ARAMIS	Darolutamide N = 955	SOC N = 554	Absolute difference	HR (95% CI)		
Event, n (%)	221 (23.1%)	206 (39.0%)	-	0.41 (0.34, 0.50)		
% metastasis-free (95% CI)	76.9% (NR)	61.0% (NR)	-			
Median months to metastasis (95% CI)	40.4 (34.3, NR)	18.4 (15.5, 22.3)	22.0			
% metastasis-free at 12 months (95% CI)	82.5% (79.9, 85.1)	63.5% (58.8, 68.1)	19.0			
% metastasis-free at 24 months (95% CI)	69.8% (65.8, 73.8)	41.5% (35.1, 48.0)	28.3			
% metastasis-free at 36 months (95% CI)	54.3% (46.6, 62.0)	26.8% (16.0, 37.5)	27.5			
Overall survival (median follow-up 29.1 months; not adjusted for crossover)						
Died, n (%)	148 (15.5%)	106 (19.1%)	-	0.69 (0.53, 0.88)		
% alive (95% CI)	84.5% (NR)	80.9% (NR)	-			
Median months to death (95% CI)	NE	NE	-			
% alive at 12 months (95% CI)	96.3% (95.1, 97.5)	96.4% (94.8, 98.1)	-0.1			
% alive at 24 months (95% CI)	90.3% (88.3, 92.3)	86.2% (83.0, 89.4)	4.1			
% alive at 36 months (95% CI)	82.6% (79.6, 85.5)	76.9% (72.4, 81.4)	5.7			
HARMS						
ARAMIS	Darolutamide N=955	SOC N=554	RR (95% CI)	Events/100 patients ^a		RD (95% CI)
				Darolutamide	SOC	
Cardiovascular disorders	113 (11.8%)	41 (7.4%)	1.60 (1.14, 2.25)	12	7	0.04 (0.01, 0.08)
Rash	28 (2.9%)	5 (0.9%)	3.25 (1.26, 8.37)	3	1	0.02 (0.01, 0.04)
Fatigue/ asthenia	151 (15.8%)	63 (11.4%)	1.39 (1.06, 1.83)	16	11	0.04 (0.01, 0.08)

Source: Table 2-18, p84; Table 2-25, pp107-108 of the resubmission; Table 9.2, p74 of the ARAMIS CSR; Table 14.2.2, p1 of the ARAMIS – final – efficacy-Table 14_ provided with the submission.

CI = confidence interval; HR = hazard ratio; NE = not estimable; NR = not reported; RD = risk difference; RR = relative risk; SOC = standard of care; **bold** = statistically significant

6.28 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with darolutamide in comparison with SOC:

- approximately 19 additional patients will remain metastasis-free after 12 months;
- approximately 28 additional patients will remain metastasis-free after 24 months and after 36 months;
- approximately 4 additional patients will remain alive after 24 months;
- approximately 6 additional patients will remain alive after 36 months; and
- after 18 months, approximately 4 additional patients would experience cardiovascular disorders, 2 additional patients would experience rash, and 4 additional patients would experience fatigue.

Clinical claim

- 6.29 The clinical claims for darolutamide, based on the direct comparison versus SOC, were unchanged from July 2020. The resubmission stated that darolutamide was superior in terms of effectiveness and inferior in terms of safety compared with placebo. In July 2020 the PBAC considered that the clinical claims that darolutamide resulted in superior efficacy and inferior safety compared to SOC were adequately supported by the evidence presented. The PBAC considered that due to the immaturity of the OS data, the magnitude of the survival benefit was uncertain (paragraph 6.29, darolutamide PSD, July 2020). Given no new OS data were provided, the magnitude of the survival benefit remained uncertain.
- 6.30 For the comparisons with the near market comparators, apalutamide and enzalutamide, the resubmission again claimed that darolutamide was non-inferior in terms of effectiveness. This claim remained reasonable. In July 2020 the PBAC noted the limitations of the indirect comparisons, but considered that overall, the efficacy of darolutamide would likely be non-inferior compared to apalutamide and enzalutamide (paragraph 6.30, darolutamide PSD, July 2020).
- 6.31 In July 2020, the submission claimed that darolutamide was superior in terms of safety compared to apalutamide and enzalutamide. Although the PBAC considered that darolutamide may be better tolerated compared to apalutamide and enzalutamide (paragraph 6.30, darolutamide PSD, July 2020), the resubmission has amended the safety claim to state that darolutamide is non-inferior in terms of safety compared to apalutamide and enzalutamide. The resubmission described this claim as conservative, noting that darolutamide appeared to have a more favourable safety profile in some outcomes of interest. This PBAC considered that the claim that darolutamide was non-inferior in terms of safety to apalutamide and enzalutamide was reasonable.

Economic analysis

- 6.32 The resubmission, like the July 2020 submission, presented a stepped economic evaluation based on the ARAMIS trial, comparing darolutamide to SOC. The modelled economic evaluation was a cost-utility analysis using a partitioned survival model with three health states.
- 6.33 The key components of the economic evaluation are summarised in the table below.

Table 11: Key components of the economic evaluation

Component	
Type of analysis	Cost-utility analysis.
Outcomes	QALYs; LYs
Time horizon	10 years <i>versus</i> median follow-up of 29.1 months for OS in the ARAMIS trial. Kaplan-Meier data were used for 54 months (4.5 years)
Methods used to generate results	Partitioned survival model
Health states	Three health states: • m0CRPC; metastatic free: Based on MFS data from ARAMIS • mCRPC; metastatic progressed: Based on OS data from ARAMIS • dead
Cycle length	28 days, half cycle correction applied
Transition probabilities	No specific transition probabilities were modelled; Health state allocation determined by MFS and OS curves, which were based on ARAMIS data with extrapolation. Darolutamide OS curve applied the trial-based hazard ratio to the SOC OS curve (which was extrapolated using the Weibull function between 55 and 120 months).
Discounting	5%
Software package	Excel 2016

Source: Table 3-2 of the resubmission.

LY = life year; m0CRPC = non-metastatic castration resistant prostate cancer; mCRPC = metastatic castration resistant prostate cancer; MFS = metastasis-free survival; OS = overall survival; QALY = quality adjusted life year

6.34 The major changes made to the economic model, as compared to July 2020, are outlined in the table below.

Public Summary Document– March 2021 PBAC Meeting

Table 12: Changes made to the economic model in the March 2021 resubmission

July 2020 submission	PBAC comments	March 2021 resubmission
Utilities – m0CRPC		
The values used in the m0CRPC state were 0.816 for darolutamide and 0.807 for SOC.	There were no clinically meaningful differences across the darolutamide and SOC arms for any of the QoL measures [para 7.9]. The same utility value should be applied to all patients in the m0CRPC health state [para 7.14].	The same utility value was applied to both arms in the m0CRPC health state (0.813). This was appropriate.
Utilities - mCRPC		
The values used in the mCRPC state were 0.530 for darolutamide and 0.530 for SOC. This was based on the average EQ-5D values reported in the placebo arm of the ALYSMPCA trial pre-symptomatic skeletal events.	The utility value applied for mCRPC was too low given that metastatic disease may initially be asymptomatic. The PBAC considered that 0.530 was more reflective of end stage palliation [para 7.14].	A utility value of 0.560 was applied to the mCRPC health state. This was the average utility value reported in mCRPC patients at 3, 6 and 9 months post-baseline in Sullivan, the study ESC (Wu being a secondary source) cited as being an appropriate source of mCRPC health state utilities. The value of 0.560 remained considerably lower than the value applied to the m0CRPC health state of 0.813.
Extrapolation		
Weibull parametric extrapolations were applied independently to the OS curves (ITT) for both the darolutamide and SOC arms. Updated OS results (29.1 months median follow-up), which were unadjusted for treatment switching were used. The number of QALYs gained in the: - trial period = 0.2494 (25%); - extrapolated period = 0.7406 (75%)	The OS parametric extrapolations were highly optimistic [para 7.13]. A revised economic model should incorporate more clinically appropriate methods of MFS and OS extrapolation [para 7.17].	Trial-based evidence was applied for 0-54 months for OS in the revised model (July 2020 model applied trial-based evidence for 0-44 months for OS). OS extrapolation in the SOC arm remained based on the Weibull parametric model. For the darolutamide arm, the trial-based HR (0.685) was applied to the SOC curve. Noting that the OS data from ARAMIS remained immature, the reliability of this approach was uncertain. MFS extrapolation remained unchanged with exponential parametric functions independently fitted to each arm.
	The difference in OS at 10 years (20%) was substantially larger than that observed in the ARAMIS trial (5.7% at 3 years) [para 7.13].	The difference in OS at 10 years is now 11%. Kaplan-Meier OS data were used until 54 months. The maximum survival benefit in the model occurs at 54 months.
	The model predicted 30% of patients treated with darolutamide would be alive at 10 years. This was unlikely given the prognosis of patients with mCRPC and the average age at entry to the model was 73.6 years [para 7.13].	The revised model predicted that approximately 20% of darolutamide patients would be alive at 10 years and, as was the case in the original submission, age matched general population mortality rates to account for impact of age on background mortality. The resubmission provided information to attempt to validate the clinical plausibility of the OS extrapolations.

Public Summary Document– March 2021 PBAC Meeting

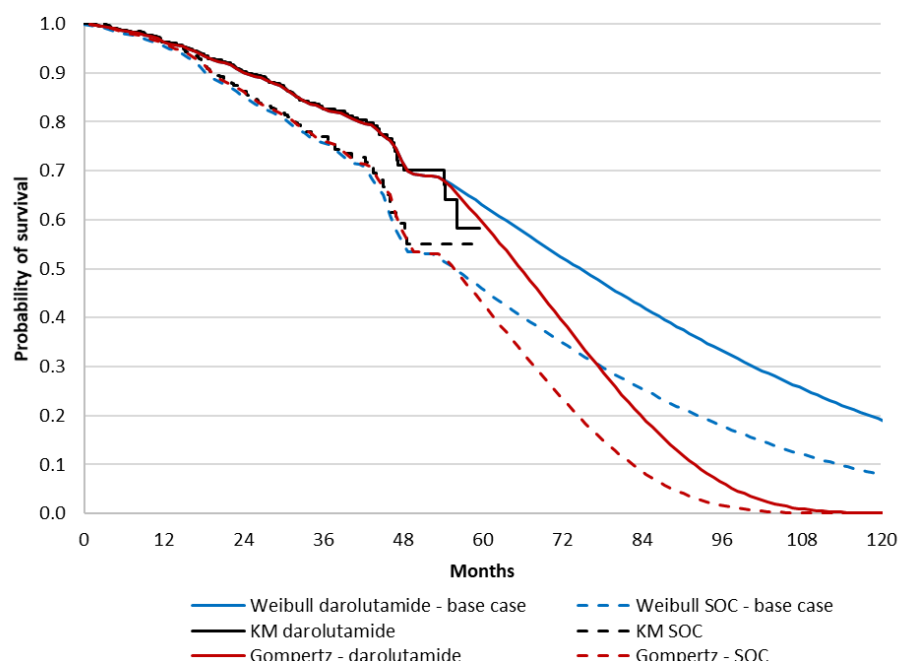
July 2020 submission	PBAC comments	March 2021 resubmission
	The majority of the life-years and QALYs were gained were in the extrapolated period of the model [para 6.42].	The number of QALYs gained in the: - trial period = 0.3566 (39%); - extrapolated period = 0.5551 (61%). However, some of the change in the QALYs gained in the trial versus the extrapolated period were due to the resubmission's use of Kaplan-Meier data for a longer period of time (when few patients remained at risk),

Source: Table 3-1, pp203-204 of the resubmission

ESC = Economic Sub-Committee; HR = hazard ratio; ITT = intention to treat; m0CRPC = non-metastatic castration resistant prostate cancer; mCRPC = metastatic castration resistant prostate cancer; OS = overall survival; QALY = quality adjusted life year; QoL = quality of life; SOC = standard of care

- 6.35 In the July 2020 submission, Weibull parametric extrapolations were applied independently to the OS curves for both the darolutamide and SOC arms. However, in July 2020, the ESC had noted that the Gompertz function had visibly good fit for the Kaplan-Meier OS data, and was more conservative than the Weibull model. The PBAC considered that given the uncertainty around the magnitude of survival benefit and immature trial data, a conservative approach to extrapolation may be appropriate (paragraph 6.46, darolutamide PSD, July 2020).
- 6.36 To address the PBAC's concerns, the resubmission presented a more conservative extrapolation of OS in the darolutamide arm by applying the trial-based hazard ratio of 0.685 (unadjusted for treatment switching) to the extrapolated SOC arm. The Weibull function continued to be applied to the SOC arm for OS. Noting that the model results were highly sensitive to the choice of parametric function (as shown in Figure 3 below) and the manner of extrapolation in the OS arms, indicating the high level of uncertainty in the extrapolated period, the ESC considered that the uncertainty could be reduced through the use of a shorter time horizon.

Figure 3: Comparison of extrapolations using the Weibull and Gompertz parametric functions in current model



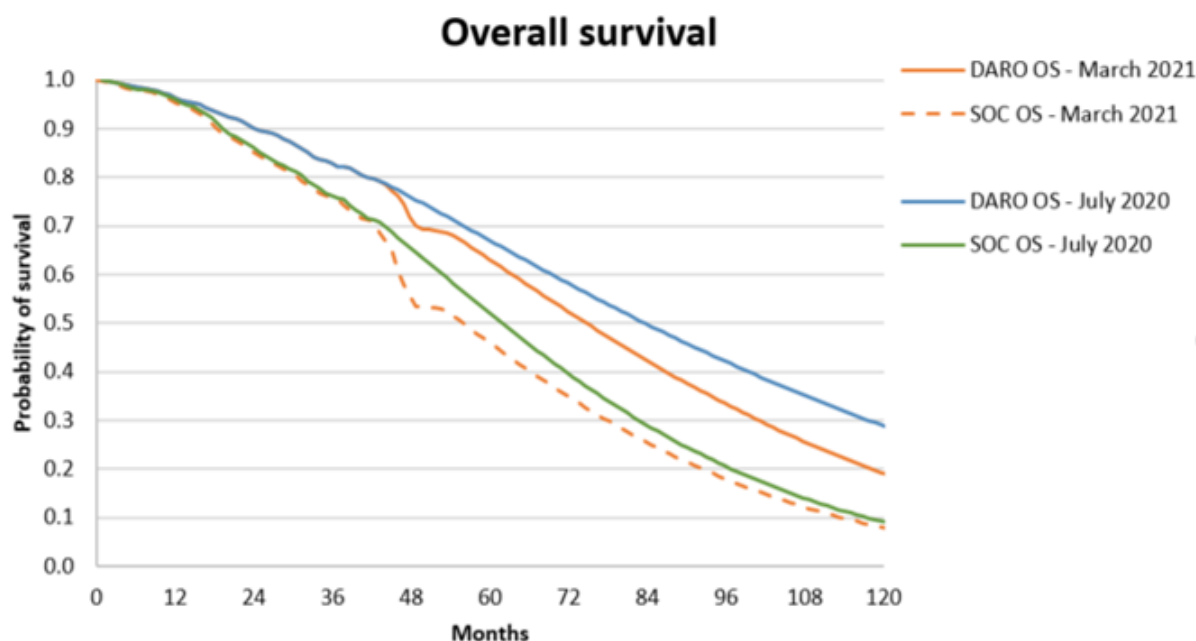
Source: Compiled during evaluation using Excel workbook 'DARO_Section3Model_November2020' and DARO_Section3Model_March2020_FINAL'

DARO = darolutamide; KM = Kaplan-Meier; SOC = standard of care

- 6.37 The other change to the OS extrapolations was that the Kaplan-Meier curves were applied until 54 months (rather than 44 months in the previous submission) which the resubmission stated was to reduce the length of the extrapolated period. However, at this time-point, fewer than 3.9% (37/955) of patients were at risk in the darolutamide arm and fewer than 2.9% of patients (16/554) were at risk in the SOC arm, and hence the Kaplan-Meier estimates are unlikely to be reliable at these later time-points. The ESC considered that it would be more reasonable to apply the Kaplan-Meier data until approximately 20% of patients remained at risk in each arm.
- 6.38 Figure 4 provides a comparison of the darolutamide and SOC OS curves from the July 2020 submission and this resubmission. The July 2020 model estimated that approximately 30% of patients treated with darolutamide and approximately 10% of patients treated with SOC patients were alive at 10 years (120 months), a difference of 20%. The resubmission's revised approach resulted in a similar proportion of patients alive at 10 years in the SOC arm; however, application of the trial-based hazard ratio from 55 months to the SOC OS curve resulted in approximately 19% of darolutamide patients being alive at 10 years, a difference of 11%. While the difference in the trial data at 54 months was 15.9% (which was the point at which the separation in the Kaplan-Meier curves was largest), the Kaplan-Meier data were unlikely to be reliable at this time-point.

- 6.39 Overall, 19% of patients remained alive in the darolutamide arm at 10 years. While lower than the 30% of patients estimated to remain alive in the previous submission, the ESC considered that this did not seem reasonable given the average age of patients was 73.6 years at the beginning of the model.

Figure 4: Comparison of darolutamide and SOC OS curves in the July 2020 submission and the March 2021 resubmission



Source: Compiled during evaluation using Excel workbook 'DARO_Section3Model_November2020' and DARO_Section3Model_March2020_FINAL'

DARO = darolutamide; OS = overall survival; SOC = standard of care

- 6.40 The resubmission sought to validate the clinical plausibility of the OS extrapolation in the SOC arm. However, the reliability and applicability of the data used for external validation was unclear e.g. it was unclear if the external validation based on the ePAD registry was applicable to the higher risk population proposed for PBS listing (which requires patients to have a PSA doubling time of 10 months or less); and while the submission claimed that the ePAD registry included follow-up OS data up to 100 months, it was unlikely that many patients were included beyond 50 months given the size of the steps in the ePAD Kaplan-Meier curve at these later time points. The submission and the PSCR also argued that the proportion of patients alive at 10 years in the darolutamide arm (19%) was clinically plausible and consistent with mortality data in an age-adjusted general Australian population which suggest that 70% of patients aged 74 years would be expected to survive to ten years. The applicability of these data to patients with CRPC was unclear.
- 6.41 In July 2020, the PBAC noted that the utility value for the mCRPC health state of 0.530 was substantially lower than the values applied in the mOCRPC health state (0.813 in

both arms in the resubmission). The PBAC considered that the value applied for mCRPC was too low given that metastatic disease may initially be asymptomatic. The PBAC considered that 0.530 was more reflective of end stage palliation (para 7.14, darolutamide PSD, July 2020). The resubmission identified three utility value studies in mCRPC and argued that all studies demonstrated a rapid, significant and sustained decline in quality of life outcomes from baseline which were indicative of the significant morbidity of symptomatic mCRPC disease.

- 6.42 The resubmission applied a utility value of 0.56 in the mCRPC health state, derived from Sullivan 2007, stating this was the upper estimate of the utility values in the three identified studies. The value of 0.56 was based on the average of the values observed in Sullivan 2007 at 3, 6 and 9 months (the baseline utility of 0.635 was not included in the calculation of the average utility). In Sullivan 2007, the mean time from diagnosis of (metastatic) hormone-refractory prostate cancer to study enrolment was 1.5 years. Thus, the utility value applied by the submission (0.560) would reflect patients who had been in the mCRPC health state for 1.75 to 2.25 years. In the economic model the mean time spent in this health state was 1.3 years in the darolutamide arm and 2.3 years in the SOC arm. Thus, the baseline utility of 0.635 may better reflect the entire duration of this health state. This is further supported by the fact that 30% of patients in Sullivan 2007 had died within 9 months of enrolment. This is also consistent with the ESC's previous advice that the baseline value of 0.635 (which was also reported in the secondary source, Wu et al 2007) may be more reflective of the total time spent in the mCRPC state (paragraph 6.45, darolutamide PSD, July 2020).
- 6.43 The PSCR stated that Sullivan 2007 reported a decline in utilities from 0.635 to 0.565 after 3 months which was indicative of the morbidity of symptomatic mCRPC. However, the ESC noted this decline occurred after patients had already had mCRPC for an average of 1.5 years. Overall, the ESC maintained that a utility value of 0.56 was too low for the mCRPC health state given that metastatic disease may initially be asymptomatic, and was not reflective of the total time spent in the mCRPC health state. The ESC re-iterated its previous advice that the baseline value of 0.635 may be more reflective of the total time spent in the mCRPC state.
- 6.44 A summary of the key drivers of the economic model is presented below.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Hazard ratio	The model was sensitive to the hazard ratio applied to the SOC OS curve to determine the OS curve for the darolutamide arm. Although darolutamide demonstrated a statistically significant advantage for darolutamide in OS (HR = 0.685; 95% CI: 0.53, 0.88), the magnitude of the benefit was still uncertain, as median OS had not yet been reached in either arm of the ARAMIS trial.	Moderate
Utilities	The value of 0.56 for patients in the mCRPC health state was considerably lower than the value applied to patients in the m0CRPC health state (0.813).	Moderate, favours darolutamide
Extrapolation approach	The overall approach to extrapolation resulted in a large proportion of patients remaining alive at 10 years (19% in the darolutamide arm) particularly given the average age of patients was 73.6 years at the beginning of the model.	Moderate, favours darolutamide

Source: Section 3.4.3, pp233-234 and Section 3.5.2, pp256-259 of the resubmission.

CI = confidence interval; HR = hazard ratio; m0CRPC = non-metastatic castration resistant prostate cancer; mCRPC = metastatic castration resistant prostate cancer; OS = overall survival; SOC = standard of care

- 6.45 The results of the economic evaluation are presented below. The resubmission noted that an effective price for enzalutamide and abiraterone have been assumed based on the effective price of enzalutamide provided to the sponsor as part of the listing of radium 223, while the price used for cabazitaxel was the published price.

Table 14: Results of the stepped economic evaluation

Step and component	Darolutamide	SOC	Increment
Step 1: trial-based time horizon (4.5 years)			
Costs	\$ [REDACTED]	\$38,234	\$ [REDACTED] ¹
LY	3.50	3.29	0.21
QALY	2.66	2.31	0.36
Incremental cost/extra LY gained			\$ [REDACTED] ²
Incremental cost/extra QALY gained			\$ [REDACTED] ³
Step 2: 10 year time horizon			
Costs	\$ [REDACTED]	\$56,683	\$ [REDACTED] ¹
LY	5.15	4.35	0.80
QALY	3.87	2.96	0.91
Incremental cost/extra LY gained (base case)			\$ [REDACTED] ⁴
Incremental cost/extra QALY gained (base case)			\$ [REDACTED] ⁴
March 2021 pre-PBAC response revised base case ICER (AEMP = \$ [REDACTED]; mCRCP utility = 0.635; KM data in OS arm used until 42 months)			
Costs	\$ [REDACTED]	\$57,155	\$ [REDACTED] ⁵
LY	5.17	4.49	0.68
QALY	3.98	3.22	0.76
Incremental cost/extra LY gained (base case)			\$ [REDACTED] ⁴
Incremental cost/extra QALY gained (base case)			\$ [REDACTED] ⁴
July 2020 submission results			
Costs	\$ [REDACTED]	\$57,236	\$ [REDACTED] ⁶
LY	5.45	4.51	0.94
QALY	4.00	2.96	1.05
Incremental cost/extra LY gained (base case)			\$ [REDACTED] ⁶
Incremental cost/extra QALY gained (base case)			\$ [REDACTED] ⁴

Source: Table 3-31, p281; Table 3-34, p283 of the resubmission and the 'Model Results' worksheet of the Excel workbook 'DARO_Section3Model_November2020' and p2 of the pre-PBAC response

AEMP = approved ex-manufacturer price; LY = life year; KM = Kaplan Meier; mCRPC = metastatic castration resistant prostate cancer; MFS = metastasis-free survival; OS = overall survival; QALY = quality adjusted life year; SOC = standard of care

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$155,000 to < \$255,000

³ \$95,000 to < \$115,000

⁴ \$45,000 to < \$55,000

⁵ \$25,000 to < \$35,000

⁶ \$55,000 to < \$75,000

6.46 The resubmission noted that changes to the economic model, including methods of OS extrapolation, health state utilities and a 25% reduction to the price of darolutamide have resulted in an ICER of \$45,000 to < \$55,000 per QALY (compared to an ICER of \$45,000 to < \$55,000 in July 2020). Although reduced, the ICER was not within the range of \$40,000 to \$45,000 per QALY which was what the PBAC considered would be cost-effective in July 2020 (paragraph 7.15, darolutamide PSD, July 2020). The pre-PBAC response applied Kaplan-Meier data until 42 months, increased the utility in the mCRPC health state to 0.635 and applied the revised AEMP of \$ [REDACTED], resulting in a revised base case ICER of \$45,000 to < \$55,000 per QALY (see paragraph 6.48). Applying the resubmission's proposed price to the July 2020 model resulted in an ICER of \$35,000 to < \$45,000 per QALY. The resubmission's model was more

Public Summary Document– March 2021 PBAC Meeting

conservative, and the key change that impacted the model results was the approach to extrapolation of OS in the darolutamide arm (by applying the trial-based HR to the OS SOC curve).

- 6.47 Sensitivity analyses indicated that the model was sensitive to the hazard ratio applied to the SOC OS curve, the utility value in the mCRPC health state and the extrapolation functions applied.

Table 15: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
Base case	\$ [REDACTED]	0.91	\$ [REDACTED] ¹	-
OS data (base case: not adjusted for treatment switching)				
Adjusted for treatment switching (IPE)	\$ [REDACTED]	0.94	\$ [REDACTED] ¹	-1.7%
OS hazard ratio in darolutamide arm (base case: 0.685)				
HR = 0.533 (lower 95% CI)	\$ [REDACTED]	1.00	\$ [REDACTED] ²	-11.1%
HR = 0.881 (upper 95% CI)	\$ [REDACTED]	0.81	\$ [REDACTED] ¹	+14.7%
OS extrapolation (base case: Weibull for SOC arms)				
Log-logistic	\$ [REDACTED]	0.94	\$ [REDACTED] ²	-5.3%
Gompertz	\$ [REDACTED]	0.71	\$ [REDACTED] ³	+35.6%
Use of KM data in OS arm (base case: until 54 months)				
Until ~20% of patients were at risk (42 months) ^a	\$ [REDACTED]	0.85	\$ [REDACTED] ¹	+6.5%
44 months, per previous submission ^b	\$ [REDACTED]	0.85	\$ [REDACTED] ¹	+6.1%
Darolutamide OS extrapolation (base case: application of trial-based HR (0.685) to the SOC curve)				
Independent extrapolation of SOC and darolutamide arms using the Weibull function	\$ [REDACTED]	1.02	\$ [REDACTED] ²	-13.5%
TTD extrapolation (base case: Gompertz)				
Weibull	\$ [REDACTED]	0.91	\$ [REDACTED] ¹	+9.2%
Time to initiation of subsequent therapy extrapolation (base case: log-normal)				
Weibull	\$ [REDACTED]	0.91	\$ [REDACTED] ¹	-5.1%
mCRPC health state utility (base case: 0.560)				
Decrease to 0.530 (July 2020 base case)	\$ [REDACTED]	0.94	\$ [REDACTED] ¹	-3.3%
Increase to 0.582 (average from Sullivan 2007 including the baseline value)	\$ [REDACTED]	0.89	\$ [REDACTED] ¹	+2.6%
0.635 – baseline utility in Sullivan 2007	\$ [REDACTED]	0.83	\$ [REDACTED] ¹	+9.4%
Time horizon (base case: 10 years)				
5 years	\$ [REDACTED]	0.43	\$ [REDACTED] ⁴	+98%
Multivariate analysis				
mCRPC utility and Use of KM data in OS arm (base case: 0.560 and until 54 months)				
0.635 and until 42 months	\$ [REDACTED]	0.76	\$ [REDACTED] ³	18.6%
mCRPC utility and SOC curve OS extrapolation (base case: 0.560 and Weibull)				
0.635 and Gompertz	\$ [REDACTED]	0.64	\$ [REDACTED] ³	+50.7%
mCRPC utility + Use of KM data in OS arm + curve OS extrapolation (base case: 0.560 and until 54 months and Weibull)				
0.635 + until 42 months + Gompertz	\$ [REDACTED]	0.59	\$ [REDACTED] ⁴	62.2%
mCRPC utility + Use of KM data in OS arm + time horizon (base case: 0.560 + until 54 months + 10 years)				
0.635 + until 42 months + 7.5 years	\$ [REDACTED]	0.58	\$ [REDACTED] ³	50.5%
Pre-PBAC revised base case – inclusion of AEMP of \$ [REDACTED]				
mCRPC utility and Use of KM data in OS arm (base case: 0.560 and until 54 months)				
0.635 and until 42 months	\$ [REDACTED]	0.76	\$ [REDACTED] ¹	-3.4%

Public Summary Document– March 2021 PBAC Meeting

Source: Table 3-35 of the resubmission and 'DARO_Section3Model_November2020'.

CI = confidence interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IPE = iterative parameter estimation; mCRPC = metastatic castration resistant prostate cancer; MFS = metastasis-free survival; OS = overall survival; QALY = quality adjusted life year; SOC = standard of care; TTD = time to treatment discontinuation

Italics indicate sensitivity analysis conducted during the evaluation.

^a The following cells were changed: 'Inputs' F62 was changed from 54 to 42; 'Inputs' F55 was changed to 3.5

^b The following cells were changed: 'Inputs' F62 was changed from 54 to 44; 'Inputs' F55 was changed to 3.667

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$35,000 to < \$45,000

³ \$55,000 to < \$75,000

⁴ \$75,000 to < \$95,000

- 6.48 The ESC noted a multivariate sensitivity analysis which applied a mCRPC utility of 0.635, Kaplan-Meier data until approximately 20% of patients remain at risk and a time horizon of 7.5 years and which resulted in an ICER of \$55,000 to < \$75,000 per QALY. The ESC considered this should be the revised base case. The ESC noted that a price reduction of approximately 31% would be required to achieve an ICER of around \$45,000 to < \$55,000 per QALY with this base case (using the effective prices assumed in the submission). The pre-PBAC accepted the changes to the mCRPC utility and the application of the Kaplan-Meier data and applied the revised AEMP \$ [REDACTED], resulting in a revised base case ICER of \$45,000 to < \$55,000 per QALY. The pre-PBAC response did not accept that the time horizon should be 7.5 years, noting that the 10 year time horizon had previously been accepted by the PBAC in the March 2017 consideration of enzalutamide in the mCRPC setting.
- 6.49 The ESC considered that darolutamide should cost no more (on a cost per day basis) than the existing price of enzalutamide in mCRPC, given the overlapping places in therapy and given that the PBAC has previously considered that darolutamide likely has non-inferior efficacy compared with enzalutamide. The pre-PBAC response acknowledged that there was likely to be some overlap between the places in therapy of darolutamide and enzalutamide, but considered that the extent of this overlap was overstated by ESC (see paragraphs 5.6 and 5.7).
- 6.50 The ESC noted the challenges of making comparisons across the darolutamide and apalutamide submissions. The ESC noted that the PBAC had previously considered that the available comparative evidence suggested that the two drugs are likely to be similarly clinically effective. Accordingly, the ESC considered that any difference in incremental QALYs gained between the models contradicted the clinical evidence and was an artefact of the different modelling approaches, including variability in the input parameters. The ESC considered that the only inputs that should result in a difference in the cost-effectiveness of darolutamide and apalutamide were the proposed drug costs and, potentially, any differences in costs or quality of life associated with differences in comparative safety.

Drug cost/patient/course

6.51 The intervention costs per patient per month and per course of treatment are provided below.

Table 16: Intervention costs^a per patient across one month and model duration

	Darolutamide		
	Trial dose and duration	Model	Financial estimates
Mean dose	1,186.61 mg/day	1,186.56 mg/day ^a	1,200 mg/day ^c
Mean duration	16.79 months	2.32 years	NR ^b
Total mg administered	606,412 mg	1,005,467 mg	913,920 mg ^c
Cost/patient/month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost/patient/course	\$ [REDACTED]	\$ [REDACTED] ^b	\$ [REDACTED]

Source: ARAMIS CSR Feb 2019; Excel workbook 'DARO_Section3Model_November2020' and DARO_Section4model_November 2020_Supplementary.

^a The economic model applied a dose intensity of 98.88% to darolutamide; cost for one month was assumed to match cycle cost of 28 days.

^b Discounting rate of 5% applied

^c A dose intensity of 92% was applied to darolutamide for the financial estimates and it was assumed 10.63 packs would be used in Year 1, 7.84 packs in Year 2, 4.97 packs in Year 3, 2.54 packs in Year 4, 0.98 packs in Year 5 and 0.24 packs in Year 6.

Estimated PBS usage & financial implications

6.52 The resubmission was not considered by DUSC. There are no specific PBS listings for the treatment of m0CRPC. As such, the resubmission applied an epidemiological approach to estimate the number of patients eligible for treatment with darolutamide.

6.53 The following revisions were made in the resubmission compared to the July 2020 submission: the forward estimates period was extended from 2022 to 2027; the proportion of high risk m0CRPC patients with WHO status 0-1 was reduced from [REDACTED]% to [REDACTED]%; the estimate of grandfathered patients in Year 1 of listing was increased from < 500 to < 500; treatment uptake assumptions were increased in the initial years of listing; the treatment compliance assumption was reduced from 98.88% to 92%; additional costs of ADT were excluded; and, based on the July 2020 DUSC advice, MBS item costs were excluded.

6.54 Table 17 summarises the inputs used for the financial estimates.

Public Summary Document– March 2021 PBAC Meeting

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible incident and prevalent patients	Incidence data: AIHW ACIM books (for 1982 to 2015) and Cancer in Australia 2019 - Supplementary data tables (for 2016 to 2019 estimates); Cancer incidence projection, Australia 2011 to 2020 AIHW (2012), pg. 85-90; 96% incident patients assumed to be non-metastatic, based on Cancer Australia; PCBaSe registry, Sweden.; and 'electronic CRPC Australian Database' (ePAD registry). Prevalent patients: Based on estimate derived from incident patients with a look back period of 12 years. Annual proportions derived from the MFS data from the placebo arm of the ARAMIS trial was applied to yearly cohorts of incident patients with high risk m0CRPC over the period 2011 to 2022.	Likely overestimated. Assumes a high proportion (86%) of eligible patients will use darolutamide and forgo the use of enzalutamide or abiraterone if patients progress to metastatic disease. In its consideration of the July 2020 submission, DUSC noted that the size of the treated population and estimates of the prevalent m0CRPC populations were unknown.
Uptake rate	Year 1: █%; Year 2: █%; Year 3: █%; Year 4: █%; Year 5: █%; Year 6: █%	In the July 2020 submission, uptake was assumed to be █% in Year 1 increasing to █% in Year 6. DUSC agreed with the evaluation that the uptake was likely to be underestimated in early years of listing as there is currently no other PBS listed agent for m0CRPC. The resubmission has increased the uptake rates in the initial years of listing.
Compliance rate	92%. A retrospective study by Behl 2017 conducted using the Truven Health MarketScan research databases (October 2012 to December 2014), reported medical possession ratios at 12 months in mCRPC patients administered abiraterone or enzalutamide of 0.95 and 0.92 respectively. The re-submission applies compliance rates reported in patients treated with enzalutamide equal to 92%.	The July 2020 submission assumed compliance with darolutamide of 98.88% based on the ARAMIS trial. DUSC considered that compliance was substantially overestimated as patients in practice were likely to be older and frailer than the trial population. The resubmission applied a revised assumption of 92% compliance with darolutamide. This may also be an overestimate. This was updated to █% in the pre-PBAC response.
Grandfathered patients	N = █¹	Estimated as █¹ patients in the July 2020 submission.
Dose	600 mg bid	The cost of background ADT is included in the economic model but not included in the financial estimates.
Offsets – subsequent therapy	Cost offsets for subsequent therapy (docetaxel, cabazitaxel only for darolutamide) were estimated.	Drugs affected are consistent between the economic model and financial estimates. The resubmission assumes higher use of docetaxel than cabazitaxel post darolutamide. Cost offsets could be higher if more patients are supplied cabazitaxel than estimated.
MBS items	Not included.	Based on July 2020 DUSC advice that the cost of MBS services for darolutamide would be similar to SOC in the m0CRPC setting.

Source: 'Darolutamide_Section4_model_November 2020_Workbook.xls'.

Public Summary Document– March 2021 PBAC Meeting

ACIM = Australian Cancer Incidence and Mortality; ADT = androgen deprivation therapy; AIHW = Australian Institute of Health and Welfare; CRPC = castration-resistant prostate cancer; DUSC = Drug Utilisation Sub-Committee; MBS = Medicare Benefits Scheme; m0CRPC = metastatic-free castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; MFS = metastatic-free survival; PBS = Pharmaceutical Benefits Scheme; SOC = standard of care

The redacted values correspond to the following ranges:

¹ < 500

6.55 The estimated utilisation and costs for the PBS listing of darolutamide are provided in Table 18. Updated financial impact estimates provided in the pre-PBAC response are provided below. These estimates applied the revised AEMP of \$[REDACTED], a compliance rate of [REDACTED]% and complied with ESCs advice that prescriptions for grandfathered patients be modelled separately to account for the duration of treatment already received.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹
Number of scripts dispensed ^a	[REDACTED] ²	[REDACTED] ³	[REDACTED] ⁴	[REDACTED] ⁴	[REDACTED] ⁴	[REDACTED] ⁴
Estimated financial implications of darolutamide						
Cost to PBS/RPBS less copayments	\$[REDACTED] ⁵	\$[REDACTED] ⁶	\$[REDACTED] ⁷	\$[REDACTED] ⁷	\$[REDACTED] ⁸	\$[REDACTED] ⁸
Estimated financial implications for subsequent mCRPC PBS listings (abiraterone, cabazitaxel, docetaxel and enzalutamide)						
Cost to PBS/RPBS less copayments	-\$[REDACTED] ⁹	-\$[REDACTED] ⁹	-\$[REDACTED] ⁹	-\$[REDACTED] ⁹	-\$[REDACTED] ⁹	-\$[REDACTED] ⁹
Net financial implications						
Net cost to PBS/RPBS	\$[REDACTED] ¹⁰	\$[REDACTED] ⁶	\$[REDACTED] ⁷	\$[REDACTED] ⁷	\$[REDACTED] ⁷	\$[REDACTED] ⁷
Net cost to MBS	No change	No change	No change	No change	No change	No change
Pre-PBAC revised financial implications						
Cost to PBS/RPBS	\$[REDACTED] ¹¹	\$[REDACTED] ¹⁰	\$[REDACTED] ⁵	\$[REDACTED] ⁵	\$[REDACTED] ⁵	\$[REDACTED] ⁵
Previous submission July 2020						
Net cost to PBS/RPBS	\$[REDACTED] ¹⁰	\$[REDACTED] ⁷	\$[REDACTED] ⁸	\$[REDACTED] ¹²	\$[REDACTED] ¹²	\$[REDACTED] ¹³

Source: Table 4-35 of the resubmission.

MBS = Medicare Benefits Schedule; mCRPC = metastatic castration-resistant prostate cancer; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming < 500 scripts per year as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 10,000 to < 20,000

³ 20,000 to < 30,000

⁴ 30,000 to < 40,000

⁵ \$30 million to < \$40 million

⁶ \$40 million to < \$50 million

⁷ \$50 million to < \$60 million

⁸ \$60 million to < \$70 million

⁹ \$0 to < \$10 million

¹⁰ \$20 million to < \$30 million

¹¹ \$10 million to < \$20 million

¹² \$80 million to < \$90 million

¹³ \$90 million to < \$100 million

6.56 The total cost to the PBS/RPBS of listing darolutamide was estimated in the submission to be \$60 million to < \$70 million in Year 6, and a total of \$300 million to < \$400 million

in the first six years of listing. The total cost to the PBS/RPBS, as estimated in the pre-PBAC response, was \$30 million to < \$40 million in Year 6 and a total of \$100 million to < \$200 million over the first six years.

- 6.57 There are a lack of Australian epidemiological data to inform the estimates of high risk mOCRPC patients who would be eligible for darolutamide. Further, the willingness to treat patients with darolutamide, which would make them ineligible for subsidised abiraterone or enzalutamide if they progress to metastatic disease, was also uncertain. The resubmission assumed that a maximum of 86% of high risk mOCRPC (WHO 0-1) patients in a given year would be considered for treatment with a second generation androgen receptor antagonist (such as darolutamide) and forgo the opportunity to use enzalutamide or abiraterone for mCRPC. This was applied as a separate uptake rate and was informed by the opinion of an unknown number of international panel experts from the 2019 Advanced Prostate Cancer Consensus Conference. The resubmission acknowledged that as the panel consisted of international clinicians, its responses may not be indicative of an Australian treatment setting. Overall, the number of initiating patients was likely to be overestimated.
- 6.58 The resubmission assumed an uptake rate of ■%, in Year 1 gradually increasing to ■% in Year 6. The rates in Years 1 to 4 were increased compared to the previous submission in response to DUSC's advice that the previous treatment uptake assumptions were underestimated in at least the first two years of darolutamide listing (previously ■% and ■% in Years 1 and 2, respectively increased to ■% and ■% in the resubmission). It was unclear if these revised uptake rates were appropriate, and were likely overestimated given the overlapping place in therapy with the existing use of enzalutamide and abiraterone.
- 6.59 Compliance to darolutamide was assumed to be 92% (based on real-world compliance data for enzalutamide) which may overestimate the utilisation of darolutamide. The July 2020 submission assumed a compliance to darolutamide of 98.88% based on the ARAMIS trial, which DUSC considered was substantially overestimated as patients in practice were likely to be older and frailer than the trial population. The revised assumption of 92% is of similar magnitude to the original estimate. This was revised to ■% in the pre-PBAC response.
- 6.60 The resubmission attempted to validate the epidemiological estimates using PBS utilisation data for mCRPC listings provided by the DUSC Secretariat. These data indicated that there are approximately 500 to < 5000 patients initiating mCRPC treatment each year. The resubmission's epidemiological model estimated that 500 to < 5000 high risk mOCRPC patients will initiate mCRPC treatment each year, which indicated that approximately 35% (500 to < 5000/500 to < 5000) of mCRPC treated patients came via the mOCRPC disease pathway. The resubmission presented data from the ePAD registry which indicated that 45% (323/712) of mCRPC patients in the registry were metastatic at diagnosis before developing CRPC. Based on this, the resubmission estimated that the remaining 55% of ePAD patients were from the

mOCRPC disease pathway which is higher than the 35% estimated in the resubmission. As such, the resubmission considered that its estimated number of high risk mOCRPC patients was likely to be conservative. However, the representativeness of the ePAD registry for all Australian patients is unclear as the sample size of the registry mOCRPC cohort is small relative to the number of patients estimated to be eligible for darolutamide.

6.61 In terms of flow-on impacts, the resubmission assumed that listing darolutamide would:

- reduce the number of patients initiating mCRPC treatments (docetaxel, cabazitaxel, abiraterone and enzalutamide) each year due to superior MFS compared to SOC. The proportion of high risk metastatic-free patients progressing to metastatic disease and initiating a mCRPC listing was based on the time to initiating subsequent treatment (chemotherapy or anti-neoplastic treatment) Kaplan-Meier data from the ARAMIS trial. The number of patients who would progress to mCRPC treatment after darolutamide listing was assumed to be the difference in patients receiving subsequent treatment in the watchful waiting arm versus the darolutamide arm of ARAMIS.
- impact treatment selection in mCRPC given the PBAC previously advised that the restriction should preclude the use of abiraterone or enzalutamide after darolutamide. The resubmission estimated the reduction in use of abiraterone and enzalutamide in mCRPC (and the impact on use of cabazitaxel and docetaxel) using data provided by the DUSC Secretariat. This included informing assumptions on the distribution of metastatic patients on each mCRPC agent, the number of packs per course of treatment and net impact on the use of abiraterone, cabazitaxel, docetaxel and enzalutamide after the listing of darolutamide. Compared with the current scenario with patients managed by 'watchful waiting', the resubmission estimated that the availability of darolutamide would reduce the number of mOCRPC patients accessing mCRPC treatment by < 500 in Year 1 to < 500 in Year 6.

6.62 The resubmission assumed that, of those patients who initiate cytotoxic chemotherapy for mCRPC after darolutamide, 95% would be initiated on docetaxel and 5% on cabazitaxel based on initiation data provided by the DUSC Secretariat. This may underestimate the impact on cabazitaxel utilisation given use of abiraterone and enzalutamide would be precluded after darolutamide.

6.63 The ESC considered that given the increased use of PSMA PET, darolutamide will have the same place in therapy as enzalutamide and abiraterone in some patients (i.e. those patients with metastases detected on PSMA PET but with no signs of distant metastases on conventional imaging, who have predicted intolerance to docetaxel). Enzalutamide and abiraterone, which are already established therapies in the treatment of mCRPC, may be used in preference to darolutamide in these patients,

which would substantially decrease the utilisation of darolutamide. Overall, the ESC considered that the size of the incremental population relative to the existing market for abiraterone and enzalutamide, and thus the net financial impact of listing darolutamide, was substantially overestimated. The extent will depending on uptake of PSMA PET, the proportion of the population who have metastasis detected on PSMA PET but not on conventional imaging, and the extent of use of abiraterone and enzalutamide prior to docetaxel (these were further discussed in the ‘requested listing’ and ‘comparator’ sections).

- 6.64 The requested restriction included a grandfather provision. The resubmission estimated there would be an additional < 500 patients in the patient access program who will continue to receive PBS subsidised darolutamide. The ESC considered that grandfather patients were likely to have been double-counted, as they would likely already be included in the overall prevalent estimate. The ESC considered that, while including grandfather patients as additional patients was likely inappropriate, scripts for these patients should be modelled separately to account for the duration of treatment already received in this cohort. The pre-PBAC response provided revised estimates which accounted for the duration of treatment already received by grandfathered patients.

Quality Use of Medicines

- 6.65 The resubmission did not address quality use of medicines issues. In its consideration of the July 2020 submission, DUSC noted that there was a likelihood of cross-resistance between apalutamide (a near market comparator) and abiraterone or enzalutamide in sequential use. DUSC advised that it was essential that the restrictions prevent use of abiraterone and enzalutamide following darolutamide.

Financial Management – Risk Sharing Arrangements

- 6.66 The sponsor proposed to address any remaining uncertainty with a risk-sharing arrangement in the form of an expenditure cap with a [REDACTED] % rebate for expenditure above the amounts estimated for annual net cost to PBS and RPBS (Table 18). The estimated caps were highly sensitive to the increasing use of more accurate diagnostic methods (PSMA PET), the forecasted number of eligible mOCRPC patients, willingness to use darolutamide over enzalutamide or abiraterone should a patient progress to metastatic disease or should a patient have micro metastases, and the assumptions regarding compliance to treatment. Each of these modelling parameters were likely to be overestimated, and as such, the overall caps were likely to be substantially overestimated.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of darolutamide for the treatment of patients

with non-metastatic castration resistant prostate cancer (m0CRPC) who are at high risk of distant metastases. The submission nominated best supportive care as the comparator, consistent with previous PBAC advice; however, the PBAC considered that based on changing clinical practice, abiraterone and enzalutamide were also relevant comparators. The PBAC noted that the resubmission provided revisions to the economic model, but considered that the resultant incremental cost effectiveness ratio (ICER) remained underestimated and high at the proposed price. Further, the PBAC considered that the size of the incremental population relative to the existing market for abiraterone and enzalutamide, and thus the net financial impact of listing darolutamide, was substantially overestimated.

- 7.2 The PBAC noted consumer comments which generally supported the listing of darolutamide on the PBS for the treatment of m0CRPC.
- 7.3 The PBAC noted that the proposed restriction included the criterion 'Patient must not have distant metastases on conventional imaging', and that this was consistent with its recommendation for apalutamide for the same indication at the November 2020 meeting on the basis that it aligned the PBS population with the trial population (paragraph 3.5, apalutamide PSD, November 2020). However, noting the increasing use of more sensitive prostate-specific membrane antigen (PSMA) PET scanning for staging CRPC, and hence the broader population classified as having distant metastases, including a substantial proportion of patients classified as m0CRPC on conventional imaging, the PBAC reconsidered that the clinical criterion requiring patients to not have distant metastases could be omitted. Further support for removal of this criterion is that the majority of patients with a PSA doubling time of 10 months or less are likely be diagnosed with, or would soon progress to, metastatic castration resistant prostate cancer (mCRPC), especially with the use of the more sensitive PSMA PET scans.
- 7.4 The PBAC reiterated that treatment with a novel hormonal agent (NHA, i.e. darolutamide, enzalutamide or abiraterone) should be limited to one treatment course per lifetime.
- 7.5 The PBAC noted that, in clinical practice, a patient with metastatic disease detected with PSMA PET scanning, but not with conventional imaging, would receive either (i) darolutamide; or, noting data provided by the DUSC secretariat indicated that the majority of mCRPC patients are being treated with abiraterone and enzalutamide without prior treatment with docetaxel, (ii) abiraterone or enzalutamide. The PBAC further noted that if the PBS restriction for darolutamide does not require staging as m0CRPC using conventional imaging, the overlap in the darolutamide and abiraterone/enzalutamide populations would be substantial.
- 7.6 The PBAC therefore considered that, while standard of care had previously been considered the relevant comparator, the changing clinical practices outlined above supported the current treatments for mCRPC (i.e. abiraterone and enzalutamide) also

being relevant comparators.

- 7.7 The PBAC recalled that it had previously considered that the clinical claims that darolutamide resulted in superior efficacy and inferior safety compared to standard of care (SOC) were adequately supported by the evidence presented. The PBAC recalled that it considered that the efficacy of darolutamide would likely be non-inferior compared to apalutamide and enzalutamide. The PBAC noted that the resubmission amended the safety claim to state that darolutamide was non-inferior in terms of safety compared to apalutamide and enzalutamide and considered this appropriate.
- 7.8 The PBAC noted that the resubmission made a number of revisions to the economic model, including to the methods of overall survival extrapolation and to the health state utilities. These revisions, plus the inclusion of the 25% reduction to the price of darolutamide, resulted in a difference in overall survival (OS) at 10 years of 11% (19% of darolutamide patients and 8% of SOC patients were estimated to be alive at 10 years) and an ICER of \$45,000 to < \$55,000 per quality adjusted life year (QALY), compared to a 20% difference in OS and an ICER of \$45,000 to < \$55,000 per QALY in July 2020.
- 7.9 The PBAC noted that the ESC proposed an alternate base case which applied a mCRPC utility of 0.635, Kaplan-Meier data until approximately 20% of patients remain at risk and a time horizon of 7.5 years which resulted in an ICER of \$55,000 to < \$75,000 per QALY. The PBAC noted that the pre-PBAC response presented a revised base case which accepted the ESC proposed changes, with the exception of the 7.5 year time horizon. The PBAC considered that the application of a 10 year time horizon was reasonable and was consistent with what was considered acceptable in the apalutamide submission (Table 12, apalutamide PSD, November 2020).
- 7.10 In further comparisons with the apalutamide model, the PBAC noted the utility value applied to the mCRPC health state in the darolutamide model (0.635) was considerably lower than that applied in the apalutamide model (0.721), and that the estimated incremental QALY gains for darolutamide (0.76) were substantially higher than for apalutamide (0.49) (Tables 12 and 14, apalutamide PSD, November 2020). Considering that the available comparative evidence suggested that darolutamide and apalutamide were likely to be non-inferior in terms of efficacy and safety, the PBAC considered that any differences in QALYs gained were artefacts of the different modelling approaches. The PBAC considered that this suggested the QALY gains for darolutamide remained overestimated.
- 7.11 Alternatively, noting that abiraterone and enzalutamide are relevant comparators, the PBAC considered that darolutamide could be cost-minimised to abiraterone or enzalutamide.
- 7.12 The PBAC noted that when darolutamide was cost minimised to abiraterone or enzalutamide, application of this price in a model scenario more consistent with that

presented for apalutamide in November 2020 would result in an ICER which was in the range previously considered cost-effective (\$40,000 to \$45,000 per QALY).

- 7.13 The PBAC agreed with ESC that the size of the incremental population relative to the existing market for abiraterone and enzalutamide, and thus the net financial impact of listing darolutamide, was substantially overestimated (paragraph 6.63). The PBAC noted that the pre-PBAC response estimated, under the current restrictions, that 2.3% to 5.7% of the darolutamide population would overlap with the enzalutamide and abiraterone population. The PBAC considered that the overlapping population would be more substantial, noting that for patients with a rapidly rising prostate specific antigen (PSA), PSMA PET imaging was likely common clinical practice.
- 7.14 Noting that the use of a NHA would remain limited to one treatment course per lifetime, the PBAC considered that any use of darolutamide in the overlapping population would, in the majority of cases, replace the use of abiraterone or enzalutamide.
- 7.15 The PBAC noted that removal of the requirement for no distant metastases for access to darolutamide would increase the number of eligible patients; however, the increase in use would be offset by reduced use of abiraterone or enzalutamide.
- 7.16 The PBAC considered the outstanding issues may be addressed in a simple resubmission for darolutamide if the following changes were made, without any additional amendments, to the -
- 1) economic evaluation:
 - Perform a cost minimisation analysis between darolutamide and enzalutamide;
 - 2) utilisation and financial impact estimates:
 - Provide patient estimates and the associated financial impact for listing darolutamide with a restriction that does not require the absence of distant metastases.
- 7.17 The PBAC considered an Early Re-Entry pathway would be acceptable if the resubmission accepted either of the options stated above with no further adjustment. The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If any of these terms are not acceptable to the sponsor, a Standard Re-Entry pathway is available.
- 7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

Bayer is disappointed by the PBAC's decision not to recommend darolutamide for the treatment of castration resistant carcinoma of the prostate. Bayer remains committed to working with the PBAC to find a pathway forward to ensure darolutamide is made available to Australian patients through the PBS.