7.06 DAROLUTAMIDE, Tablet 300 mg, Nubeqa®, Bayer Australia Ltd

1 Purpose

1.1 The early re-entry resubmission sought to list darolutamide as a General Schedule Authority Required (telephone/online PBS authorities system) listing for the treatment of patients with castration resistant prostate cancer (CRPC).

1.2 This resubmission sought to address the issues raised by the PBAC in March 2021 (Table 1).

Table 1: Summary of key matters to be addressed

Matter of concern	Response	Addressed?
Present a CMA between darolutamide and enzalutamide	The resubmission presented a CEA, with a 12% price reduction on the effective AEMP considered by the PBAC in the March 2021 meeting.	No
Provide patient estimates and the associated financial impact for listing darolutamide with a restriction that does not require the absence of distant metastases.	Utilisation and financial estimates were updated to omit the clinical criteria that a 'Patient must not have distant metastases on conventional imaging' from the restriction. In addition, the estimates accounted for an expected increase in the use of PSMA PET imaging and higher rates of cabazitaxel utilisation post darolutamide.	Yes

Source: paragraph 7.16, p38 of the March 2021 PSD
CEA = cost effectiveness analysis; CMA = cost minimisation analysis; PSMA = prostate-specific membrane antigen; SPA = special pricing arrangement

1.3 The revised base case incremental cost-effectiveness ratio (ICER) was $35,000 to < $45,000 per quality adjusted life year (QALY).

1.4 The early re-entry submission estimated a net cost to the PBS of $10 million to < $20 million in Year 6 of listing, with a total net cost to the PBS of $90 million to < $100 million over the first 6 years of listing (Table 2).

Table 2: Estimated use and financial implications

	2022	2023	2024	2025	2026	2027
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][5]	[redacted][5]	[redacted][5]
Estimated financial implications						
Cost to PBS/RPBS	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][10]
Cost offsets due to substituted therapies	-$[redacted][11]	-$[redacted][6]	-$[redacted][12]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Cost offsets due to prevention of downstream therapy	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]
Net cost to PBS/RPBS	**$**[redacted][11]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]
March 2021 pre-PBAC revised estimates						
Net cost to PBS/RPBS	$[redacted][6]	$[redacted][12]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]

Source: Table 8, p11 of the early re-entry submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Assuming 11.35 prescriptions per patient per year as estimated by the early re-entry submission and a mean of 25.72 prescriptions per patient

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] 40,000 to < 50,000
[6] $10 million to < $20 million
[7] $30 million to < $40 million
[8] $40 million to < $50 million
[9] $50 million to < $60 million
[10] $60 million to < $70 million
[11] $0 to < $10 million

2 Background

2.1 Darolutamide was TGA registered on 26 February 2020 for the treatment of patients with non-metastatic castration resistant prostate cancer (m0CRPC).

2.2 This was the third PBAC consideration for darolutamide.

2.3 In July 2020, the PBAC rejected a major submission. While the PBAC considered that darolutamide provided a substantial benefit for some patients compared with standard of care (SOC) in terms of delaying disease progression in the m0CRPC setting, it considered that the magnitude of the overall survival (OS) benefit was modest, and uncertain given the immaturity of the data. The PBAC considered that the modelled survival benefit was likely overestimated, the ICER was high and underestimated, and that a substantial price reduction would be required for darolutamide to be considered suitably cost-effective. Further, the PBAC considered that the estimated financial impact of listing darolutamide on the PBS was uncertain.

2.4 In March 2021, the PBAC rejected a major resubmission. The submission nominated SOC 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 ICER, in the m0CRPC setting, 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.

2.5 The updated key components of the early re-entry submission are presented below.

Table 3: Key components of the clinical issue addressed by the early re-entry

Component	Description
Population	Patients with CRPC and a PSADT of ≤ 10 months
Intervention	Darolutamide 600 mg (2 × 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 The PBAC considered in July 2020 that (i) darolutamide resulted in superior efficacy and inferior safety compared to SOC; (ii) the efficacy of darolutamide would likely be non-inferior compared to apalutamide and enzalutamide; and (iii) darolutamide may be better tolerated compared to apalutamide and enzalutamide due to its reduced penetration of the blood-brain barrier which could potentially result in less central nervous system toxicity (Item 5.05, paragraphs 6.29 & 6.30, darolutamide PSD, July 2020).

Source: Compiled in preparation of submission overview
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

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The early re-entry submission proposed amendments to the previously considered PBS restriction, omitting the clinical criterion requiring patients to not have distant metastases on conventional imaging and adding that a patient must have a prostate-specific antigen (PSA) level of at least 2 ng/mL.

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~~ *Patient must have a PSA level of at least 2 ng/mL* 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	

3.2 The PBAC recalled that in March 2021 it advised, based on the increasing use of more sensitive prostate-specific membrane antigen (PSMA) PET scanning for staging of CRPC, the clinical criterion requiring patients to not have distant metastases on conventional imaging could be removed from the restriction. However, on review, the PBAC considered that it would be appropriate for the PBS indication to align with the TGA indication and recommended that darolutamide be listed on the PBS for m0CRPC only.

3.3 The PBAC noted that it had also previously recommended that a criterion be included in the restriction which restricted treatment to patients with a PSA level of at least 2 ng/mL, as this would identify patients who had a higher risk of developing metastases, which in turn would limit subsidy to more cost-effective circumstances. On review, the PBAC considered that the higher risk population would be adequately captured by the criterion requiring a short prostate-specific antigen (PSA) doubling time (i.e. doubling within 10 months). The clinical criteria for darolutamide should essentially reflect that proposed in the March 2021 resubmission.

3.4 The PBAC reiterated that treatment with a novel hormonal agent (NHA, i.e. darolutamide, enzalutamide or abiraterone) should cease upon disease progression

and that subsidy of enzalutamide or abiraterone following disease progression on darolutamide should not be available because the sequential use of these drugs in this manner had not been evaluated.

3.5 The early re-entry submission estimated that there would be 250 patients who would require transitioning arrangements from the non-PBS subsidised early access program to PBS-subsidised supply ('grandfathered' arrangements).

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (7) and organisations (9) via the Consumer Comments facility on the PBS website. The individual comments were strongly supportive of the proposed PBS listing and described the unmet clinical need for patients with m0CRPC.

4.3 The PBAC noted the advice received from the Prostate Cancer Foundation of Australia, the Prostate Cancer Support Group - Hastings, the Bathurst District Prostate Cancer Support Group, the South Eastern Prostate Cancer Support Group - Melbourne, the Tamworth and District Prostate Cancer Support Group, the Geelong Prostate Support Group, the Kalamunda (WA) Prostate Cancer Support Group and the Nepean and Blue Mountains Prostate Cancer Support Group. The PBAC noted that the organisations supported the proposed PBS listing and described the benefits of darolutamide treatment.

4.4 The Medical Oncology Group of Australia (MOGA) also 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. The PBAC noted that 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)[1], based on a comparison with placebo + ADT.

Economic analysis

4.5 The sponsor provided an updated cost effectiveness analysis comparing darolutamide with SOC that proposed an effective approved ex-manufacturer price (AEMP) of $[redacted], which was a 12% reduction from the March 2021 proposed AEMP of $[redacted].

4.6 The early-re-entry submission used the multivariate sensitivity analysis proposed in the pre-PBAC response to the March 2021 PBAC meeting as the base case. This applied a metastatic CRPC (mCRPC) utility of 0.635, Kaplan Meier data until approximately 20% of patients remained at risk and a 10-year time horizon that resulted in an ICER of $45,000 to < $55,000 per QALY. Reduction of the proposed effective AEMP from $[redacted] to $[redacted] resulted in an ICER of $35,000 to < $45,000 per QALY.

4.7 The model presented in the early re-entry submission again applied a utility value to the mCRPC health state (0.635) which was considerably lower than that applied in the apalutamide model (0.721). The estimated QALY gains for darolutamide (0.76) remained substantially higher that estimated for apalutamide (0.49). In March 2021, the PBAC considered that the QALY gains obtained from the darolutamide model were overestimated (paragraph 7.10, darolutamide Public Summary Document (PSD), March 2021).

Table 4: Results of the economic evaluation

	Incremental cost	Incremental QALYs	ICER
July 2021: AEMP = $[redacted]	$[redacted]	0.76	$[redacted] *,1
March 2021, pre-PBAC response: AEMP = $[redacted]	$[redacted]	0.76	$[redacted] 2

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life year

* The DPMQs of enzalutamide and abiraterone were also updated to reflect changes to fees applied

The redacted values correspond to the following ranges:

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

[2] *$45,000 to < $55,000*

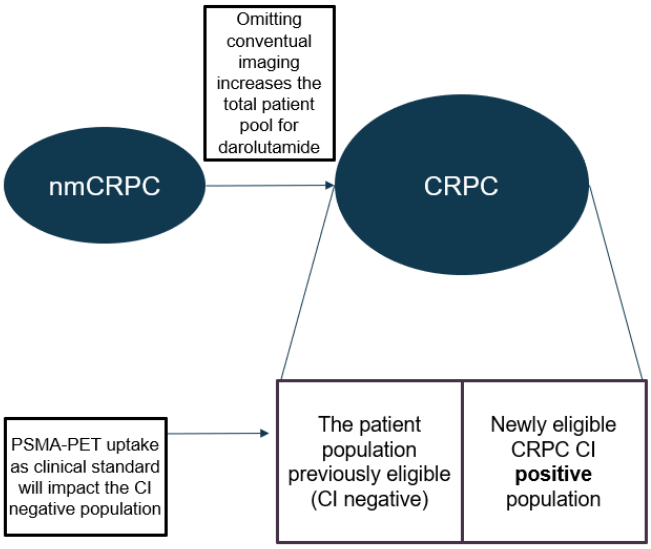
Estimated PBS usage & financial implications

4.8 Updated utilisation and financial estimates were provided which omitted the clinical criteria from the proposed restriction that 'Patient must not have distant metastases on conventional imaging'. The early re-entry submission presented estimates that also accounted for an expected increase in PSMA PET imaging. The early re-entry submission stated that these changes had two distinct consequences for the financial estimates:

1. The patient population previously defined m0CRPC on the basis of no distant metastases on conventional imaging was re-classified based on uptake of PSMA-PET and the proportion of patients that have metastases detected on PSMA-PET but not on conventional imaging (i.e. the 'CRPC; conventional imaging negative' cohort). The increased uptake of PSMA-PET in m0CRPC patients on conventional imaging did not change epidemiological estimates of the number of eligible patients but did impact the utilisation and financial impact of darolutamide due to the overlapping restriction with abiraterone and enzalutamide.
2. A population with distant metastases on conventional imaging, not previously considered eligible for darolutamide, was now eligible (i.e. the 'CRPC; conventional imaging positive' cohort). The PBAC previously stated, "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" (paragraph 7.15, darolutamide PSD, March 2021). Therefore, newly eligible patients with distant metastases detected on conventional imaging had almost no net financial impact to the PBAC.

Figure 1: Patient population considered eligible for darolutamide



Source: Figure 1, p4 of the early re-entry submission
CI = conventional imaging; CRPC = castrate resistant prostate cancer; nmCRPC = non-metastatic castration resistant prostate cancer; PSMA = prostate-specific membrane antigen

4.9 The table below summarises the revised approach to calculating the utilisation and financial estimates.

Table 5: Summary of approach to revised budget impact analysis

Eligible patient population	Impact of new restriction on eligibility	Estimation of patient numbers and utilisation	Relevant calculation if applicable	Treatments on the PBS associated with cost-offsets	Net financial impact
CRPC; CI negative; No PSMA-PET	Previously eligible, i.e. m0CRPC population	Derived from validated patient flow model (March 2021 resubmission) and accounting for uptake of PSMA-PET	m0CRPC[a] population x (1 – uptake of PSMA-PET)	Downstream docetaxel and cabazitaxel treatment in mCRPC setting.	Derived from validated approach to financial estimates in (March 2021 resubmission) and accounting for increased cabazitaxel use relative to docetaxel in the mCRPC.
CRPC; CI negative; PSMA-PET negative		Derived from validated patient flow model (March 2021 re-submission) and accounting for uptake of PSMA-PET and proportion of patients that are CI negative/PSMA-PET negative (Fendler 2019 as considered by the PBAC (paragraph 5.6, darolutamide PSD, March 2021))	m0CRPC[a] population x uptake of PSMA-PET x 45%		
CRPC; CI negative; PSMA-PET positive			m0CRPC[a] population x uptake of PSMA-PET x 55%	Overlapping restriction with abiraterone and enzalutamide	Cost neutral given the identical price to enzalutamide and abiraterone
CRPC; CI positive	<u>Newly</u> eligible	Based on DUSC estimates provided to Bayer in March 2021 resubmission	-		

Source: Table 4, p5 of the early-re-entry submission

CI = conventional imaging; CRPC = castration resistant prostate cancer; DUSC = Drug Utilisation Sub-Committee; mCRPC = metastatic castration resistant prostate cancer; m0CRPC = non-metastatic castration resistant prostate cancer; PBAC = Pharmaceutical Benefits Advisory Committee; PSMA = prostate-specific membrane antigen

[a] These calculations seem to imply PSMA-PET is used sequentially from CI. However, it is accepted PSMA-PET will likely replace CI in a proportion/majority of patients. The calculations are presented in this manner because the underlying epidemiological estimates of the size of the "CRPC negative for distant metastases on CI" population will not change with the uptake of PSMA-PET. In other words, this population can be interpreted as the population that 'would have otherwise been CI negative were they to have received CI'.

4.10 Although the number of eligible patients in the 'CRPC; conventional imaging negative' cohort did not change from the m0CRPC population presented in the March 2021 resubmission (Row A), it was divided into three populations (Table 6). Uptake in the 'No PSMA-PET' and 'PSMA-PET negative' populations was unchanged from March 2021; uptake in the 'PSMA-PET positive' population was halved due to the March 2021 recommendation that allowed abiraterone and enzalutamide to be used prior to docetaxel in patients with mCRPC. The PBAC considered that the 'CRPC; conventional imaging negative' cohort would represent likely use of darolutamide in the m0CRPC setting.

Table 6: Total number of patients eligible for and uptake of darolutamide in 'CRPC; CI negative' population

Row	Parameter	2022	2023	2024	2025	2026	2027	Source/calculation
A	Overall eligible 'CRPC; CI negative' population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	March 2021 resubmission[a]
B	Uptake of PSMA-PET	80%	85%	90%	90%	90%	90%	Assumption
C	**CRPC; CI negative; No PSMA-PET**	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	A x (1-B)
D	Darolutamide uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	March 2021 resubmission
E	Patients treated with darolutamide	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	C x D
F	% of 'CRPC; CI negative' population that have no distant metastases on PSMA-PET	45%	45%	45%	45%	45%	45%	Fendler 2019
G	**CRPC; CI negative; PSMA-PET negative**	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	A x B x F
H	Darolutamide uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	March 2021 resubmission
I	Patients treated with darolutamide	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][1]	G x H
J	% of 'CRPC; CI negative' population that have distant metastases on PSMA-PET	55%	55%	55%	55%	55%	55%	Fendler 2019
K	**CRPC; CI negative; PSMA-PET positive**	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	A x B x J
L	Darolutamide uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	Assumed 50% uptake of March 2021 resubmission
M	Patients treated with darolutamide	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	K x L
N	Total number of 'CRPC; CI negative' patients treated with darolutamide	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	E + I + M

Source: Table 5, p6 of the early re-entry submission

CI = conventional imaging; CRPC = castration resistant prostate cancer; m0CRPC = non-metastatic castration resistant prostate cancer; PS = performance status; PSMA = prostate-specific membrane antigen; WHO = World Health Organisation

[a] Total high risk m0CRPC patients with WHO PS of 0-1

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] < 500

4.11 The PBAC noted that the estimated number of patients treated with darolutamide in the m0CRPC setting was 500 to < 5,000 in Year 1 and 500 to < 5,000 in Year 6 (i.e. Row N of Table 6).

4.12 The number of newly eligible CRPC patients with distant metastases on conventional imaging was based on data from the DUSC Secretariat of the prevalent mCRPC population treated on the PBS. The early re-entry submission assumed [redacted]% of patients would have already received treatment with darolutamide, abiraterone or enzalutamide and that uptake of darolutamide would be low as abiraterone and enzalutamide are established therapies (Table 7).

Table 7: Total number of eligible patients and market share of darolutamide in the 'CRPC; CI positive' population

Row	Parameter	2022	2023	2024	2025	2026	2027	Source/calculation
A	Number of prevalent patients treated with enza or abi on the PBS	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	DUSC Secretariat data; Assumed to increase by 3% per year
B	% of patients already treated with daro/enza/abi	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	Assumption
C	**CRPC; CI positive**	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	**A x B**
D	Darolutamide uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	Assumption
E	Patients treated with darolutamide	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	C x D

Source: Table 6, p7 of the early re-entry submission

abi = abiraterone; CI = conventional imaging; CRPC = castrate resistant prostate cancer; daro = darolutamide; DUSC = Drug Utilisation Sub-Committee; enza = enzalutamide

The redacted values correspond to the following ranges:

[1] 5,000 to < 10,000

[2] 10,000 to < 20,000

[3] < 500

[4] 500 to < 5,000

4.13 The total number of patients treated with darolutamide in this early re-entry submission is compared with the March 2021 resubmission in Table 8.

Table 8: Total number of patients treated with darolutamide – July 2021 versus March 2021 submissions[a]

Parameter	2022	2023	2024	2025	2026	2027
July 2021 - total number of patients treated with darolutamide	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
July 2021 – total number of CI negative patients treated with darolutamide (i.e. m0CRPC)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
March 2021 - total number of patients treated with darolutamide	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]

Source: Compiled during preparation of the submission overview

a Does not include grandfather patients in Year 1

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

4.14 The estimated financial impact of darolutamide across the four eligible patient populations is presented below.

Table 9: Total number of patients eligible for and treated with darolutamide on the PBS/RPBS[a]

Parameter	2022	2023	2024	2025	2026	2027	Source/ calculation
CRPC; CI negative; No PSMA-PET							
Patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	Row E, Table 6
Cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	Attachment 4 of July 2021 submission
Cost offsets (substituted therapies)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	NA
Cost-offsets (prevention of downstream therapy)	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	Cost-offsets per patient as per the March 2021 submission
Total cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	-
CRPC; CI negative; PSMA-PET negative							
Patients treated	[redacted][3]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][3]	Row I, Table 6
Cost to PBS/RPBS	$[redacted][2]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	Attachment 4 of July 2021 submission
Cost offsets (substituted therapies)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	NA
Cost-offsets (prevention of downstream therapy)	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	Cost-offsets per patient as per the March 2021 submission
Total cost to PBS/RPBS	$[redacted][2]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	-
CRPC; CI negative; PSMA-PET positive							
Patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	Row M, Table 6
Cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	Attachment 4 of July 2021 submission
Cost offsets (substituted therapies)	-$[redacted][2]	-$[redacted][2]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	Cost neutral due to same price as abi/enza[b]
Cost-offsets (prevention of downstream therapy)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	NA
Total cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	-
CRPC; CI positive							

Parameter	2022	2023	2024	2025	2026	2027	Source/ calculation
Patients treated	[redacted][1]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	Row E, Table 7
Cost to PBS/RPBS	$[redacted][2]	$[redacted][4]	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	Attachment 4 of July 2021 submission
Cost offsets (substituted therapies)	-$[redacted][2]	-$[redacted][4]	-$[redacted][4]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	Cost neutral due to same price as abi/enza[b]
Cost-offsets (prevention of downstream therapy)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	NA
Total cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	-

Source: Table 7, pp9-10 of the early re-entry submission

abi = abiraterone; CI = conventional imaging; CRPC = castration resistant prostate cancer; daro = darolutamide; enza = enzalutamide; NA = not applicable; PBS = Pharmaceutical Benefits Scheme; PSMA = prostate-specific membrane antigen; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] These estimates do not account for few prescriptions in grandfather patients

[b] The offsets of abiraterone and enzalutamide are not exactly equal to the cost of darolutamide due to the different pack sizes (30, 28 and 28 respectively) and consequently, a slightly different cost per day at the dispensed price level

The redacted values correspond to the following ranges:

[1] < 500

[2] $0 to < $10 million

[3] 500 to < 5,000

[4] $10 million to < $20 million

[5] $20 million to < $30 million

4.15 The financial impact of the 'CRPC; conventional imaging negative; no PSMA-PET' and 'CRPC; conventional imaging negative; PSMA-PET negative' populations (i.e. those that do not have an overlapping restriction with abiraterone and enzalutamide) were as per the March 2021 resubmission, but with a higher subsequent utilisation of cabazitaxel relative to docetaxel applied (5% in March 2021; 20% in this early re-entry submission). The early re-entry submission stated that this was to address previous concerns that the cost-offsets from subsequent cabazitaxel utilisation were underestimated (paragraph 6.62, darolutamide PSD, March 2021). The PBAC considered that this change was reasonable.

4.16 The financial impact of the 'CRPC; conventional imaging negative; PSMA-PET positive' and 'CRPC; conventional imaging positive' patients (i.e. those that do have an overlapping restriction with abiraterone and enzalutamide) were approximately cost neutral give the equal price and place of darolutamide relative to these treatments on the PBS and due to the prior PBAC advice that treatment with a novel hormonal agent should be limited to one treatment course per lifetime.

4.17 The net cost of darolutamide to the PBS/RPBS for the treatment of CRPC is presented below.

Table 10: Net cost to the PBS/RPBS of darolutamide[a]

	2022	2023	2024	2025	2026	2027
Net cost to the PBS/RPBS of darolutamide for CRPC[a]						
Total number of daro patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total cost to PBS/RPBS	$[redacted][2]	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][6]
Total cost offsets (substituted therapies)	-$[redacted][7]	-$[redacted][8]	-$[redacted][2]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Total cost-offsets (prevention of downstream therapy)	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost to PBS/RPBS	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]
Net cost to the PBS of darolutamide for m0CRPC[b]						
Total number of CI negative daro patients (i.e. m0CRPC)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total cost to PBS/RPBS	$[redacted][8]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Total cost offsets (substituted therapies)	-$[redacted][7]	-$[redacted][7]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]
Total cost-offsets (prevention of downstream therapy)	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost to PBS/RPBS of CI negative daro patients (i.e. m0CRPC)	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]

Source: Table 8, p11 of the early re-entry submission

[a] The above estimates do not account for fewer prescriptions in grandfather patients

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] $20 million to < $30 million

[3] $30 million to < $40 million

[4] $40 million to < $50 million

[5] $50 million to < $60 million

[6] $60 million to < $70 million

[7] $0 million to < $10 million

[8] $10 million to < $20 million

4.18 Despite treating a larger number of patients due to the proposed restriction change, the combined effect of a reduced price of darolutamide and higher cost offsets due to an overlapping place in therapy with abiraterone and enzalutamide, resulted in a lower net cost to the PBS/RPBS compared to the March 2021 submission (see Table 11).

Table 11: Difference in number of patients treated and net financial implications compared to the March 2021 re-submission for Years 1-6 of listing[a]

Parameter	March 2021 resubmission	July 2021 early re-entry submission	Difference	Explanatory Notes
As per the early re-entry submission				
Total number of darolutamide patients	[redacted][1]	[redacted][2]	[redacted][3]	Increase due to inclusion of CRPC; CI positive patients under new restriction
Total cost to PBS/RPBS	$[redacted][4]	$[redacted][5]	-$[redacted][6]	Lower price of darolutamide
Net cost to PBS/RPBS[a]	$[redacted][5]	$[redacted][7]	-$[redacted][8]	Cost-offsets in overlapping populations
For CI negative darolutamide patients (i.e. m0CRPC)				
Total number of darolutamide patients	[redacted][1]	[redacted][1]	-[redacted][1]	Decrease due to reduced uptake in CRPC; CI negative, PSMA-PET positive patients with the March 2021 recommended changes to the abiraterone and enzalutamide restrictions for mCRPC
Total cost to PBS/RPBS[b]	$[redacted][4]	$[redacted][8]	-$[redacted][8]	Decrease due to lower price of darolutamide and smaller patient population
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][7]	-$[redacted][8]	Cost-offsets in overlapping populations

Source: Updated Utilisation and Cost Model Workbook (attachment 3) and supplement workbook (attachment 4)

CI = conventional imaging; CRPC = castration resistant prostate cancer; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] These estimates do not account for fewer prescriptions in grandfather patients

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] 10,000 to < 20,000

[3] 500 to < 5,000

[4] $300 million to < $400 million

[5] $200 million to < $300 million

[6] $30 million to < $40 million

[7] $90 million to < $100 million

[8] $100 million to < $200 million

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the listing of darolutamide for the treatment of patients with non-metastatic castration resistant prostate cancer (m0CRPC). The PBAC was satisfied that darolutamide provides, for some patients, a moderate overall survival (OS) benefit compared to standard of care (SOC). The PBAC considered that at the updated proposed price, the revised economic model resulted in an incremental cost effectiveness ratio (ICER) for darolutamide versus SOC in the m0CRPC setting which was cost-effective. The PBAC also considered that the revised estimated utilisation and financial estimates for the m0CRPC population were reasonable.

5.2 The PBAC, noting that prostate cancer can be a life-threatening condition and that similar novel hormonal agents (NHAs) are currently only PBS funded in metastatic castration resistant prostate cancer (mCRPC), considered that there was a moderate need for darolutamide for the treatment of m0CRPC.

5.3 The PBAC noted the consumer comments which supported the listing of darolutamide on the PBS for the treatment of m0CRPC.

5.4 The PBAC recalled that in March 2021 it advised, based on the increasing use of more sensitive prostate-specific membrane antigen (PSMA) PET scanning for staging of castration resistant prostate cancer (CRPC), that the clinical criterion requiring patients to not have distant metastases on conventional imaging could be removed from the restriction. However, on review, the PBAC considered that it would be appropriate for the PBS indication to align with the TGA indication and recommended that darolutamide be listed on the PBS for m0CRPC only.

5.5 The PBAC considered that separate treatment phases for initial and continuing treatment proposed in the March 2021 resubmission were appropriate for the use of darolutamide in m0CRPC, but that they could be merged into a single listing for practicality reasons. The PBAC noted that there were an estimated < 500 patients currently receiving darolutamide via an early access program, but considered that a separate 'grandfathered' listing was not required if the sole restriction was worded in such a way as to not inadvertently preclude them. The intent would be that such patients be no different to non-'grandfathered' patients in terms of PBS eligibility.

5.6 The PBAC noted that it had previously recommended that a criterion be included in the restriction which restricted treatment to patients with a PSA level of at least 2 ng/mL as this would identify patients with a higher risk of developing metastases, which in turn would confine subsidy to more cost-effective circumstances. On review, the PBAC considered that the higher risk population would be adequately captured by the criterion requiring a short prostate-specific antigen (PSA) doubling time (i.e. doubling within 10 months).

5.7 The PBAC reiterated that treatment with a novel hormonal agent (NHA, i.e. darolutamide, enzalutamide or abiraterone) should cease upon disease progression and that subsidy of enzalutamide or abiraterone following disease progression on darolutamide should not be available because the sequential use of these drugs in this manner had not been studied.

5.8 The PBAC recalled that it had previously considered that the clinical claims that darolutamide resulted in superior efficacy and inferior safety compared to SOC in the treatment of m0CRPC were adequately supported. The PBAC considered that darolutamide offered a moderate benefit in terms of OS, symptom improvement and health related quality of life, noting that darolutamide treatment in the ARAMIS trial resulted in an additional 6% of patients alive at 3 years, a delay in the development of metastases (median time to metastases of 40.5 months in darolutamide patients versus 22.1 months for SOC patients), a delay in time to pain progression (median of 40.3 months for darolutamide patients versus 25.4 months SOC patients), a reduction in the initiation of chemotherapy (13.3% of darolutamide patients versus 17.7% of SOC patients had initiated chemotherapy at a median follow up of 29.1 months) and a

reduction in symptomatic skeletal events (3.0% of darolutamide versus 5.1% of SOC patients had an event at a median follow up of 29.1 months). The PBAC considered that darolutamide offered less benefit in terms of adverse events compared to SOC, noting that for every 100 patients treated, four additional patients would experience cardiovascular events, four additional patients would experience fatigue and two additional patients would experience rash with a median duration of treatment of 14.8 months for darolutamide and 11.04 months for SOC.

5.9 The PBAC was confident in the efficacy estimates observed in the ARAMIS trial. The PBAC considered that the revised model, which applied (i) a mCRPC utility of 0.635; (ii) Kaplan Meier data until approximately 20% of patients remained at risk; (iii) a 10 year time horizon; and (iv) the proposed 12% price reduction for darolutamide was reasonable. The PBAC noted that although the quality adjusted life year (QALY) gains remained overestimated, the model provided moderate certainty in terms of modelled benefits and costs. Overall, the PBAC considered that the resulting ICER of $35,000 to < $45,000 per QALY provided a high level of certainty regarding the cost effectiveness of darolutamide.

5.10 In terms of the estimated utilisation and financial impact, the PBAC noted that the early re-entry submission presented, as requested, updated estimates that omitted the clinical criteria that a 'Patient must not have distant metastases on conventional imaging' from the restriction. The PBAC considered that the 'CRPC; conventional imaging negative' cohort was representative of use in the m0CRPC setting and that the cost offsets due to substituted therapies and prevention of downstream therapy were appropriate. The PBAC considered that the utilisation (500 to < 5,000 patients in Year 1 and 500 to < 5,000 in Year 6) and the net PBS financial impact ($10 million to < $20 million in Year 1 and $10 million to < $20 million in Year 6) estimates provided a reasonable indication of the likely use and expenditure of darolutamide in the m0CRPC setting.

5.11 The PBAC advised that darolutamide is not suitable for prescribing by nurse practitioners.

5.12 The PBAC advised that darolutamide should not be exempt from the Early Supply Rule.

5.13 The PBAC advised that, under Section 101(3BA) of the *National Health Act 1953*, darolutamide should not be treated as interchangeable on an individual patient basis with any other drug.

5.14 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for darolutamide:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over standard of care. The PBAC considered the improvement in efficacy with darolutamide over standard of care to be moderate;

b) The treatment is not expected to address a high and urgent unmet clinical need. The PBAC considered there was a moderate clinical need noting that similar novel androgen deprivation therapy is PBS listed although only for CRPC patients with metastases;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

Outcome:
Recommended

6 Recommended listing

6.1 Add new medicinal product as follows:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. Qty (units)**	**Max. Qty (packs)**	**No. of Rpts**	**Available brands**
DAROLUTAMIDE					
darolutamide 300 mg tablet, 112	New	112	1	5	Nubeqa
Restriction Summary / Treatment of Concept: [NEW]					
	Category/Program: GENERAL – General Schedule (GE)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required – immediate/real-time assessment (online/telephone)				
	Episodicity: [blank]				
	Severity: Castration resistant non-metastatic				
	Condition: carcinoma of the prostate				
	PBS indication: Castration resistant non-metastatic carcinoma of the prostate				
	Treatment phase: [blank]				
	Clinical criteria:				
	The condition must have evidence of an absence of distant metastases on the most recently performed conventional medical imaging used to evaluate the condition.				
	AND				
	Clinical criteria:				
	The condition must be associated with a prostate-specific antigen level that has observed to have at least doubled in value in a time period of within 10 months prior to first commencing treatment with this drug.				
	AND				
	Clinical criteria:				
	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 1 prior to treatment initiation.				
	AND				
	Clinical criteria:				

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Available brands
	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.				
	Treatment criteria:				
	Patient must be undergoing concurrent treatment with androgen deprivation therapy.				
	Prescribing instructions: Prescribing instructions: Retain the results of all investigative imaging and prostate-specific antigen (PSA) level measurements on the patient's medical records - do not submit copies of these with this authority application. The PSA level doubling time must be based on at least three PSA levels obtained within 10 months prior to first commencing treatment with this drug. The third reading is to demonstrate that the doubling was durable and must be at least 1 week apart from the second reading.				
	Administrative advice: Special Pricing Arrangements apply				

6.2 Flow on changes to abiraterone and enzalutamide PBS restrictions to prevent their use subsequent to darolutamide use (the March 2021 PBAC recommendation to remove the requirement to trial docetaxel in the first instance, is repeated below) are as follows:

Abiraterone [PBS item codes 2698B (250 mg tablet) & 11206T (500 mg tablet)]:

Restriction Summary / Treatment of Concept: 6944 (current as at 1 July 2021)) - Authority Required	
	Indication: Castration resistant metastatic carcinoma of the prostate
	Clinical criteria:
	The treatment must be used in combination with a corticosteroid
	AND
	Clinical criteria:
	The treatment must not be used in combination with chemotherapy
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must have failed treatment with docetaxel due to resistance or intolerance; or~~
	~~Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel~~
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less
	AND
	Clinical criteria:
	~~Patient must not receive PBS-subsidised abiraterone if progressive disease develops while on abiraterone~~
	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
	AND
	Clinical criteria:
	~~Patient must not have received prior treatment with enzalutamide; or~~
	Patient must not be undergoing treatment with this drug following treatment with any of: (i) darolutamide, (ii) enzalutamide; or
	Patient must have developed intolerance to enzalutamide of a severity necessitating permanent treatment withdrawal
	Administrative Advice: Special Pricing Arrangements apply.

Enzalutamide (PBS item code: 10174L):

Restriction Summary / Treatment of Concept: 4670 (current as at 1 July 2021) - Authority Required	
	Indication: Castration resistant metastatic carcinoma of the prostate
	Clinical criteria:

	The treatment must not be used in combination with chemotherapy
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must have failed treatment with docetaxel due to resistance or intolerance; or~~
	~~Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel~~
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less
	AND
	Clinical criteria:
	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
	AND
	Clinical criteria:
	~~Patient must not have received prior treatment with abiraterone; or~~
	Patient must not be undergoing treatment with this drug following treatment with any of: (i) darolutamide, (ii) abiraterone; or
	Patient must have developed intolerance to abiraterone of a severity necessitating permanent treatment withdrawal
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.

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

7 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.

8 Sponsor's Comment

Bayer welcomes the PBAC decision to recommend the PBS listing of darolutamide (Nubeqa®) for men with non-metastatic castration resistant prostate cancer.