

7.05 TALAZOPARIB

**Capsule 0.1 mg, Capsule 0.25 mg, Capsule 0.35 mg,
Capsule 0.5 mg**

Talzenna®

PFIZER AUSTRALIA PTY LTD

1 Purpose

- 1.1 The early re-entry resubmission requested a Section 85 General Schedule, Authority Required (telephone/online) listing for talazoparib + enzalutamide for the first line treatment of metastatic castration-resistant prostate cancer (mCRPC) patients with breast cancer gene (*BRCA*)1/2 pathogenic variants who have not received prior treatment with a novel hormonal agent (NHA).
- 1.2 The resubmission was based on the PBAC decision to not recommend talazoparib for this indication at the March 2024 PBAC meeting. This resubmission partially addressed the issues raised by PBAC as shown in the table below.

Public Summary Document – July 2024 PBAC Meeting

Table 1: Summary of key matters to be addressed

Matter of concern	Response	Addressed?
Noting that the final analyses were expected in July 2024, present any additional rPFS and OS data (paragraph 7.16, March 2024 PSD).	The early re-entry resubmission stated that no additional rPFS or OS data were available at the time of resubmission.	NA
Revise the economic model as per the March 2024 pre-PBAC response so that: - the time horizon is reduced from 10 to 7.5 years; - TTD for the enzalutamide component of the combination therapy was assumed to equal rPFS; - apply the overall, rather than the treatment specific, utility value to the progression free health state; - incorporate disutilities associated with adverse events (paragraph 7.11, March 2024 PSD).	The early re-entry resubmission made the revisions requested by the PBAC. The resubmission also made additional changes to the inputs of the economic model to align with the financial estimates. The additional changes reduced the ICER by \$ ¹ per QALY.	Partially.
Reduce the price of talazoparib so that the revised model results in an ICER of no more than \$ ² per QALY (paragraph 7.16, March 2024 PSD).	The price of talazoparib was reduced so that the model presented resulted in an ICER of \$ ² per QALY. A further % price reduction would be required if only the requested changes were made to the model.	Partially
Revise the financial estimates so that: - the eligible patient population decreased over the forward estimates; - reduce the assumed uptake rates of talazoparib + enzalutamide to no higher than %; - include the costs of enzalutamide, both in combination with talazoparib and as monotherapy; - apply any cost offsets consistently with the economic model (paragraphs 7.13 and 7.16, March 2024 PSD).	The early re-entry resubmission made a number of changes to the financial estimates (see Table 7): - decreased the eligible patient population compared to the March 2024 submission (the changes aligned with the March 2024 pre-PBAC response); - reduced the assumed uptake rates of talazoparib + enzalutamide to no higher than %; - included the incremental costs of enzalutamide (i.e. the additional costs of enzalutamide when used as combination therapy over when used as monotherapy due to increased duration of therapy); - applied cost offsets consistently with the economic model The early resubmission also: - applied a consistent BRCA1/2 prevalence (as per the March 2024 pre-PBAC response); - updated the MBS services to align with the economic evaluation.	Partially
Present a proposal to join the current olaparib RSA (paragraph 7.16, March 2024 PSD)	The early re-entry resubmission agreed in principle to join the current olaparib monotherapy RSA.	Yes

Source: March 2024 talazoparib PSD.

BRCA=breast cancer gene; ICER = incremental cost effectiveness ratio; NA = not applicable; OS = overall survival; QALY = quality adjusted life year; rPFS = radiographic progression free survival; RSA = risk sharing arrangement; TTD = time to treatment discontinuation, PSD = Public Summary Document

The redacted values correspond to the following ranges:

1 \$0 to < \$5,000

2 \$55,000 to < \$75,000

2 Background

2.1 The TGA delegate overview, which was received on 4 March 2024, supported the approval for registration of talazoparib for the following indication:

Public Summary Document – July 2024 PBAC Meeting

‘For use in combination with enzalutamide for the treatment of adult patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC)’.

2.2 Talazoparib was considered by the ACM on 5 April 2024.

2.3 The PICO from the March 2024 submission is presented below. It was unchanged in the resubmission.

Table 2: Key components of the clinical issue addressed by the March 2024 submission

Component	Description
Population	Adult patients diagnosed with mCRPC with evidence of <i>BRCA1/2</i> pathogenic variants who have not been previously treated with a novel hormonal agent
Intervention	TALA (0.5 mg) in combination with ENZA (160 mg)
Comparator	Main comparator: enzalutamide (monotherapy) Supplementary comparators: olaparib + abiraterone, abiraterone monotherapy
Outcomes	Primary: rPFS Secondary: OS, OR, time to second progression, safety, QoL
Clinical claim	Efficacy: A clinical claim of superior efficacy is made for TAL + ENZ versus PBO + ENZ. Safety: TAL + ENZ has an inferior safety profile to PBO + ENZ, with this being regarded as tolerable and manageable, as evidenced by no detriment to QoL.

Source: Table 1 of the March 2024 talazoparib PSD

BRCA = breast cancer gene; *ENZA* = enzalutamide; *mCRPC* = metastatic castration-resistant prostate cancer; *NHA* = novel hormonal agent; *OR* = overall response; *OS* = overall survival; *PBO* = placebo; *QoL* = quality of life; *rPFS* = radiographic progression-free survival; *TALA* = talazoparib

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

3 Requested listing

3.1 The resubmission proposed a revised restriction which was phase agnostic (i.e. the initial, continuing and grandfather restrictions were combined). In March 2024, the PBAC considered that the phase agnostic restriction, as suggested by the Secretariat, was reasonable (paragraph 7.15, talazoparib Public Summary Document (PSD), March 2024).

3.2 Secretariat additions are in italics and deletions in strikethrough.

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TALAZOPARIB					
talazoparib 0.5 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
talazoparib 0.35 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
talazoparib 0.25 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
talazoparib 0.1 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
Safety Net Rule Penalty Applies? Yes					
Insert Restriction Summary [New 1] / Treatment of Concept: [New 1.1]: Authority Required					

Public Summary Document – July 2024 PBAC Meeting

Prescriber type: Medical practitioners
Restriction level: Authority required (telephone/online)
Episodicity: [blank]
Severity: Castration resistant metastatic
Condition: Carcinoma of the prostate
Indication: Castration resistant metastatic carcinoma of the prostate
Clinical criteria:
The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation
AND
Clinical criteria
Patient must not have received prior PBS-subsidised novel hormonal drug for prostate cancer prior to commencing treatment with this drug for this condition
AND
Clinical criteria:
Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance score no higher than 1 prior to treatment initiation
AND
Treatment criteria:
The treatment must be undergoing concurrent treatment with enzalutamide, unless an intolerance to enzalutamide requires either a: (i) temporary cessation, (ii) permanent discontinuation
AND
Treatment criteria:
The treatment must not be a PBS-subsidised benefit beyond disease progression
Note: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

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

4 Consideration of the evidence

Sponsor hearing

- 4.1 The sponsor requested a hearing for this item. The clinician discussed the poor response rates for mCRPC patients with *BRCA1/2* pathogenic variants and highlighted the high clinical need for effective treatments for these patients. The clinician described the clinical benefits of talazoparib + enzalutamide in terms of radiographic progression free survival (rPFS) and quality of life in *BRCA1/2* variant positive patients.

The clinician also discussed the results of the BRCAAway trial¹ which demonstrated that combination therapy with a NHA and a poly(adenosine diphosphate)-ribose polymerase (PARP) inhibitor resulted in a longer PFS compared to either agent alone or sequentially.

Consumer comments

- 4.2 The PBAC noted that the Medical Oncology Group of Australia (MOGA) again expressed its support for the talazoparib submission. The PBAC noted that the MOGA stated that an ESMO-MCBS score for the *BRCA1/2* subgroup could not be determined as the subgroup did not meet the ESMO-MCBS requirements.²
- 4.3 The PBAC recalled that in March 2024 Rare Cancers Australia also supported the submission, describing the need for earlier and more effective treatments for patients with *BRCA1/2* variants.

Clinical evidence and claim

- 4.4 No new evidence was presented in the resubmission. In March 2024, the submission presented data from a subgroup of patients from the TALAPRO-2 trial, which compared talazoparib + enzalutamide to placebo + enzalutamide, with *BRCA1/2* pathogenetic variants.
- 4.5 Talazoparib + enzalutamide was associated with a benefit over enzalutamide monotherapy in terms of both rPFS (HR = 0.20, 95% CI: 0.11, 0.36) and overall survival (OS; HR = 0.47; 95% CI: 0.26, 0.85).
- 4.6 Overall, in March 2024 the PBAC considered that although the claim that talazoparib + enzalutamide was superior compared to enzalutamide monotherapy in terms of efficacy, the magnitude of the benefit was uncertain as the *BRCA1/2* subgroup was *post hoc*, small and the outcomes were informed by immature data (paragraph 7.9, talazoparib PSD, March 2024).
- 4.7 In terms of safety, in March 2024 the PBAC considered that the claim that talazoparib + enzalutamide was inferior compared to enzalutamide monotherapy was reasonable, particularly as the combination therapy was associated with more Grade 3 and 4 adverse events and more serious adverse events, including anaemia (paragraph 7.10, talazoparib PSD, March 2024).
- 4.8 The PBACs consideration of the comparative clinical effectiveness and safety of talazoparib + enzalutamide remained unchanged from March 2024.

¹ Hussain MHA, et al, BRCAAway: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) bearing homologous recombination-repair mutations (HRRm). *Journal of Clinical Oncology*. 2024;42(4).

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

Economic analysis

4.9 At the March 2024 PBAC meeting, the PBAC advised that the economic model should be revised as per the pre-PBAC response so that:

- The time horizon was reduced from 10 to 7.5 years;
- Time to treatment discontinuation in the enzalutamide component of the combination therapy was assumed to equal rPFS;
- The overall, rather than treatment specific, utility value should be applied to the progression free health state; and
- Disutilities associated with adverse events were incorporated.

4.10 In addition, the PBAC advised that the price of talazoparib should be reduced so that the revised model resulted in an incremental cost effectiveness ratio (ICER) of no more than \$55,000 to < \$75,000 per quality adjusted life year (QALY).

4.11 The resubmission revised the model as per paragraph 4.9. However, the resubmission also made a number of other changes to align the economic model with the financial estimates as outlined in the table below.

Table 3: Changes to inputs to the economic model

Input	March 2024 submission	July 2024 early re-entry resubmission	Comment
Time horizon	10 years	7.5 years	Changed as per PBAC's advice.
TTD for ENZA component of TALA + ENZA	Modelled according to KM data from TALAPRO-2.	Set to equal rPFS.	Changed as per PBAC's advice.
Utility values for progression-free state	Treatment-specific utility values: TALA + ENZA = 0.811 ENZA monotherapy = 0.777	Overall utility value: TALA + ENZA and ENZA monotherapy = 0.793	Changed as per PBAC's advice.
Disutilities for AEs	Incorporated	Incorporated	Incorporated.
% of progressed patients receiving subsequent therapies	68.4% (George 2020)	71.4% (ePAD registry 2023)	The resubmission stated that this was adjusted to align with the financial estimates. The financial estimates assumed 71.3% of patients would receive subsequent therapy.
% of patients in the ENZA monotherapy arm receive OLA as subsequent therapy	100%	OLA = 80% DTX = 14% CBZ = 6%	The resubmission stated that this was adjusted to align with the revised financial estimates. The March 2024 financial estimates assumed that all patients from the ENZA monotherapy arm who received subsequent therapy would receive OLA. The PBAC considered that this was overestimated.
Duration of subsequent therapies	Medians OLA: 7.4 months (De Bono 2020)	Means (and median for DTX) OLA: 10.9 months (OLA PSD 11-21)	The resubmission stated as mean time on treatment was preferred in the financial estimates, that the durations of OLA and CBZ were

Public Summary Document – July 2024 PBAC Meeting

Input	March 2024 submission	July 2024 early re-entry resubmission	Comment
	DTX: 5.9 months (Tannock 2004) CBZ: 5.1 months (de Wit 2019)	DTX: 5.9 months (Tannock 2004) CBZ: 5.2 months (OLA PSD 11-21)	adjusted to align with the revised financial estimates. The mean time of treatment for DTX was not available.
Estimation of average duration of subsequent therapies	The proportion of patients receiving 2 nd line treatment in any given cycle is determined by splitting the progressed disease state according to the difference in median rPFS and OS.	The proportion of patients receiving 2 nd line treatment in any given cycle is determined by splitting the progressed disease state such that the mean time on 2 nd line treatment matches the weighted average duration of subsequent therapies.	The resubmission stated that to align more closely with the financial estimates the proportion of time spent in the 2 nd line treatment substate of the progressed disease health state has been adjusted for each arm such that the calculated mean time in 2 nd line treatment now matches the estimated duration of treatment, rather than using the difference in median rPFS and OS.
EMP of talazoparib	\$█	\$█	The proposed EMP of talazoparib was reduced to \$█ in the pre-PBAC response.

Source: Table 3 of the early re-entry resubmission

AE = adverse event; CBZ = cabazitaxel; DTX = docetaxel; EMP = ex-manufacturer price; ENZA = enzalutamide; KM = Kaplan Meier; OLA = olaparib; OS = overall survival; rPFS = radiographic progression free survival; TALA = talazoparib; TTD = time to treatment discontinuation,

4.12 The resubmission also stated that other PBS and MBS items were updated according to the published Schedules. The resubmission applied assumed effective ex-manufacturer prices (EMPs) for enzalutamide and olaparib.

4.13 The results of the revised economic analysis are presented in the table below.

Table 4: Results of the revised economic analysis

	Talazoparib + enzalutamide	Enzalutamide monotherapy	Increment
Costs	\$█	\$█	\$█
QALYs	2.4263	1.6701	0.756
Incremental cost/extra QALY gained			\$¹
March 2024 submission			
Costs (all costs, discounted)	\$█	\$█	\$█
QALY	2.50	1.65	0.85
Incremental discounted cost/extra QALY gained			\$¹
March 2024 pre-PBAC response			
Costs (all costs, discounted)	\$█	\$█	\$█
QALY	2.4366	1.6616	0.75
Incremental discounted cost/extra QALY gained			\$²

Source: Table 7 of the early re-entry resubmission, Table 12 of the talazoparib PSD, March 2024 and Talazoparib economic model workbook

QALY = quality adjusted life year

The redacted values correspond to the following ranges:

1 \$55,000 to < \$75,000

2 \$75,000 to < \$95,000

4.14 The effects of the changes made in the resubmission on the ICER are presented below.

Table 5: Effects of input changes on the ICER

Model assumption/parameter	Inc costs	Inc QALYs	ICER
March 2024 submission - base case	\$█	0.85	█ ¹
+ EMP of talazoparib = \$█	\$█	0.850	█ ²
+ PBAC requested changes: • Time horizon = 7.5 years • TTD for ENZA = rPFS • Overall utility value applied to progression free health state • Disutilities for AEs incorporated	\$█	0.775	█ ¹
Additional changes to align with the financial estimates:			
+ % of progressed patients receiving subsequent therapy = 71.4%	\$█	0.775	█ ¹
+ % of progress patients in the ENZA monotherapy arm receiving OLA = 80%	\$█	0.778	█ ¹
+ changes to duration of subsequent therapies	\$█	0.761	█ ¹
+ changes to estimation of average duration of subsequent therapies	\$█	0.756	█ ¹
+ changes to PBS and MBS items	\$█	0.756	█ ¹

Source: Talazoparib economic model workbook

AE = adverse event; EMP = ex-manufacturer price; ENZA = enzalutamide; ICER = incremental cost effectiveness ratio; OLA = olaparib; QALY = quality adjusted life year; rPFS = radiographic progression free survival; TTD = time to treatment discontinuation

The redacted values correspond to the following ranges:

1 \$55,000 to < \$75,000

2 \$45,000 to < \$55,000

4.15 The resubmission proposed an effective EMP for talazoparib of \$█. When this was applied in conjunction with the changes requested by PBAC in March 2024, it resulted in an ICER of \$55,000 to < \$75,000 per QALY. To achieve an ICER of \$55,000 to < \$75,000 per QALY when applying the changes requested by the PBAC in March 2024 only, the EMP of talazoparib would have to be reduced by █% to \$█. Although the pre-PBAC response stated that the additional amendments made to align the economic model and financial estimates were reasonable, the pre-PBAC response reduced the proposed EMP for talazoparib to \$█. As noted, this resulted in an ICER of \$55,000 to < \$75,000 per QALY when only the changes requested by PBAC in March 2024 were made. The ICER was \$55,000 to < \$75,000 per QALY when the reduced price was applied in conjunction with the resubmissions additional changes to align the economic model and financial estimates.

Estimated PBS usage & financial implications

4.16 In March 2024, the PBAC advised that the financial estimates be revised so that:

- The eligible patient population decreased over the forward estimates;
- The uptake rate of talazoparib + enzalutamide was reduced to no more than █%;
- The costs of enzalutamide were included, both in combination with talazoparib and as monotherapy; and
- Any cost offsets were applied consistently with the economic model.

4.17 The table below provides a summary of the key assumptions informing the utilisation and financial impact estimates in the March 2024 submission and the July 2024 early re-entry resubmission.

Public Summary Document – July 2024 PBAC Meeting

Table 6: Key assumptions in the March 2024 and July 2024 submissions

Parameter	March 2024 submission			July 2024 early re-entry resubmission			Comment		
Eligible population									
Incident patients	Year	Growth	Population	Year	Growth	Population	The population decline was increased compared to the March 2024 submission. The changes aligned with those proposed in the March 2024 PSCR.		
	Year 1: 2024	-0.5%	1	Year 1: 2024	-5.0%	1			
	Year 2: 2025	-0.5%	1	Year 2: 2025	-5.0%	1			
	Year 3: 2026	-1.0%	1	Year 3: 2026	-5.0%	1			
	Year 4: 2027	-1.5%	1	Year 4: 2027	-4.0%	1			
	Year 5: 2028	-2.0%	1	Year 5: 2028	-3.0%	1			
	Year 6: 2029	-2.0%	1	Year 6: 2029	-2.0%	1			
BRCA1/2 positive, mCRPC patients (eligible population)	Year	Prevalence	Population	Year	Prevalence	Population	The BRCA1/2 positive population was amended. This aligned with what was proposed in the March 2024 PSCR. This was appropriate as the incidence of BRCA1/2 is not expected to change.		
	Year 1: 2024	7.0%	2	Year 1: 2024	7.0%	2			
	Year 2: 2025	8.0%	2	Year 2: 2025	7.0%	2			
	Year 3: 2026	8.5%	2	Year 3: 2026	7.0%	2			
	Year 4: 2027	9.0%	2	Year 4: 2027	7.0%	2			
	Year 5: 2028	10.0%	2	Year 5: 2028	7.0%	2			
	Year 6: 2029	10.5%	2	Year 6: 2029	7.0%	2			
Treatment utilisation									
Uptake rate	Year	Prevalence	Population	Year	Prevalence	Population	Uptake rates were adjusted to be no more than █%. This did not align with the PBAC's request (not more than █%). The resubmission stated that it is consistent with the assumed █% of patients who would commence OLA post ENZA monotherapy. Higher uptake rates than in the March 2024 submission were proposed for Years 2 and 3.		
	Year 1: 2024	█%	2	Year 1: 2024	█%	2			
	Year 2: 2025	█%	2	Year 2: 2025	█%	2			
	Year 3: 2026	█%	2	Year 3: 2026	█%	2			
	Year 4: 2027	█%	2	Year 4: 2027	█%	2			
	Year 5: 2028	█%	2	Year 5: 2028	█%	2			
	Year 6: 2029	█%	2	Year 6: 2029	█%	2			
Total patient numbers	Year	Initiating	Persistent	Total	Year	Initiating	Persistent	Total	The methodology applied appeared to be unchanged from the March 2024 submission.
	Year 1: 2024	█ ²⁺ █ ^{2*}	█ ²	█ ²	Year 1: 2024	█ ²⁺ █ ^{2*}	█ ²	█ ²	
	Year 2: 2025	█ ²	█ ²⁺ █ ^{2*}	█ ²	Year 2: 2025	█ ²	█ ²⁺ █ ^{2*}	█ ²	
	Year 3: 2026	█ ²	█ ²⁺ █ ^{2*}	█ ²	Year 3: 2026	█ ²	█ ²⁺ █ ^{2*}	█ ²	
	Year 4: 2027	█ ²	█ ²	█ ²	Year 4: 2027	█ ²	█ ²	█ ²	
	Year 5: 2028	█ ²	█ ²	█ ²	Year 5: 2028	█ ²	█ ²	█ ²	
	Year 6: 2029	█ ²	█ ²	█ ²	Year 6: 2029	█ ²	█ ²	█ ²	
* Grandfather patients				* Grandfather patients					
Scripts dispensed	Talazoparib (all strengths):				Talazoparib (all strengths):				The mean TTD for TALA of 27.5 months was applied rather than the median TTD of 22 months. This aligned with what was proposed in the March 2024 pre-PBAC response.
	Year	Total			Year	Total			
	Year 1: 2024	█ ¹			Year 1: 2024	█ ¹			
	Year 2: 2025	█ ¹			Year 2: 2025	█ ¹			
	Year 3: 2026	█ ³			Year 3: 2026	█ ³			
	Year 4: 2027	█ ³			Year 4: 2027	█ ³			
	Year 5: 2028	█ ³			Year 5: 2028	█ ³			
Year 6: 2029	█ ³			Year 6: 2029	█ ³				

Public Summary Document – July 2024 PBAC Meeting

Parameter	March 2024 submission	July 2024 early re-entry resubmission	Comment																																																																															
	<p>* Assuming 12.2 prescriptions per year ** Median treatment duration of 22 months</p>	<p>* Assuming 12.2 prescriptions per year ** Mean treatment duration of 27.5 months</p> <p>Enzalutamide (incremental scripts):</p> <table border="1"> <thead> <tr> <th>Year</th> <th>Total</th> </tr> </thead> <tbody> <tr><td>Year 1: 2024</td><td>1</td></tr> <tr><td>Year 2: 2025</td><td>1</td></tr> <tr><td>Year 3: 2026</td><td>1</td></tr> <tr><td>Year 4: 2027</td><td>1</td></tr> <tr><td>Year 5: 2028</td><td>1</td></tr> <tr><td>Year 6: 2029</td><td>1</td></tr> </tbody> </table> <p>* Assuming 12.2 prescriptions per year ** Incremental treatment duration of 13.9 months.</p>	Year	Total	Year 1: 2024	1	Year 2: 2025	1	Year 3: 2026	1	Year 4: 2027	1	Year 5: 2028	1	Year 6: 2029	1	<p>To estimate the additional use of ENZA the difference between the mean TTD of ENZA used in combination with TALA and the mean TTD for ENZA monotherapy was calculated, equating to 13.9 months. This aligned with what was proposed in the March 2024 pre-PBAC response.</p>																																																																	
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Taxanes	Weighted DPMAAs: DTX: \$161.42, CBZ: \$293.21	Weighted DPMAAs: DTX: \$152.16, CBZ: \$177.02	DTX price amended due to correction of an error, CBZ price amended due to change in AEMP.																																																																															

Source: Table 8 of the early re-entry resubmission

AEMP = approved ex-manufacturer price; BRCA = breast cancer gene; CBZ = cabazitaxel; DTX = docetaxel; DPMA = dispensed quantity for maximum amount; DPMQ = dispensed price for maximum quantity; ENZA = enzalutamide; mCRPC = metastatic castration resistant prostate cancer; OLA = olaparib; PFS = progression free survival; TALA = talazoparib; TTD = time to treatment discontinuation, PSCR = Pre-Sub-Committee Response

Public Summary Document – July 2024 PBAC Meeting

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² < 500
- ³ 5,000 to < 10,000

4.18 The revised estimated use and financial impact of listing talazoparib + enzalutamide on the PBS is presented below.

Table 7: Estimated utilisation and financial impact estimates

	2024	2025	2026	2027	2028	2029
Estimated extent of use						
TALA + ENZA patients	1	1	1	1	1	1
TALA scripts	2	2	3	3	3	3
Incremental ENZA scripts	2	2	2	2	2	2
Estimated financial implications (less co-payments)						
Cost of TALA (less co-pay)	5	5	5	6	6	6
Incremental cost of ENZA	5	5	5	5	5	5
Total cost of TALA + ENZA	5	5	6	6	6	6
Estimated changes in use and financial impact of currently listed treatments (less co-payments)						
Change in OLA-2L (scripts)	-2	-2	-2	-2	-2	-2
Change in DTX-2L (scripts)	1	1	1	1	2	2
Change in CBZ-2L (scripts)	1	1	1	1	1	1
Total cost offsets	5	5	5	5	5	5
Net estimated financial implication (less co-payments)						
Net cost to PBS/RPBS	5	5	5	5	5	5
July 2024 pre-PBAC response: EMP of talazoparib = \$ (DPMQ = \$)						
Total cost of TALA + ENZA	5	5	6	6	6	6
Total cost offsets	5	5	5	5	5	5
Net cost to PBS/RPBS	5	5	5	5	5	5
March 2024 submission						
TALA patients	1	1	1	2	2	2
TALA scripts	2	2	2	3	3	3
Total cost of TALA	5	5	6	6	6	6
Total cost offsets	5	5	5	5	5	5
Net cost to PBS/RPBS	5	5	5	6	6	6
March 2024 pre-PBAC response						
TALA + ENZA patients	1	1	1	1	1	1
TALA + ENZA scripts	2	3	3	3	4	4
Total cost of TALA + ENZA	5	6	6	6	6	6
Total cost offsets	5	5	5	5	5	5
Net cost to PBS/RPBS	5	5	6	6	6	6

Source: Tables 11, 13, 14, 15, 16, 19 and 20, of the early re-entry resubmission

2L = second-line; CBZ = cabazitaxel; DPMQ = dispensed price, maximum quantity; DTX = docetaxel; EMP = ex-manufacturer price; ENZA = enzalutamide; NHA = novel hormonal agent; OLA = olaparib; TALA = talazoparib

The redacted values correspond to the following ranges:

- ¹ < 500
- ² 500 to < 5,000
- ³ 5,000 to < 10,000
- ⁴ 10,000 to < 20,000
- ⁵ \$0 to < \$10 million
- ⁶ \$10 million to < \$20 million

- 4.19 The resubmission estimated that listing talazoparib on the PBS/RPBS would cost \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6 and total \$40 million to < \$50 million over the first 6 years of listing. Using the reduced price for talazoparib, as proposed in the pre-PBAC response, resulted in an estimated cost of \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6 and a total of \$40 million to < \$50 million over the first 6 years of listing. This was reduced from \$50 million to < \$60 million over the first 6 years in the March 2024 submission and \$60 million to < \$70 million the in the March 2024 pre-PBAC response. The March 2024 submission did not include cost associated with enzalutamide. These were included in the March 2024 pre-PBAC response.
- 4.20 Although the total number of patients estimated to receive talazoparib was reduced in the revised estimates, the estimated number of talazoparib prescriptions increased due to the time on treatment increasing from 22 months to 27.5 months. Additionally, although the proportion of patients receiving subsequent olaparib following enzalutamide monotherapy decreased, the cost offsets were higher in Years 1 to 5 due to the correction of an error in the calculations used to derive the proportion of patients who transition out of the progression free health state. This resulted in more patients in the enzalutamide monotherapy arm receiving subsequent therapies compared to the March 2024 submission.
- 4.21 The resubmission estimated that the number of talazoparib prescriptions would be 500 to < 5,000 in Year 1 and 5,000 to < 10,000 in Year 6. Olaparib was listed as monotherapy for the treatment of *BRCA1/2* variant positive mCRPC following treatment with a novel hormonal agent in April 2022. In 2022, 396 olaparib prescriptions were dispensed; in 2023, 780 prescriptions were dispensed; and until April 2024, 247 prescriptions have been dispensed.³

Financial Management – Risk Sharing Arrangements

- 4.22 In March 2024, the noting the uncertainties related to the benefit of combination versus sequential treatment, the extent of use of combination treatment and the treatment duration of combination therapy, PBAC considered that it would be appropriate for talazoparib to join the existing olaparib monotherapy risk sharing arrangement (RSA).
- 4.23 The resubmission has agreed in principle to join the existing olaparib monotherapy RSA on the premise that the expenditure caps are revised to account for the use of talazoparib and that the rebates for use of talazoparib above the expenditure caps are the same as those for olaparib monotherapy.

³ Medicare statistics website. Pharmaceutical Benefits Schedule Item Reports – requested PBS & RPBS items processed from January 2022 to April 2024 for PBS item numbers 12921C, 12932P, 12913P, 12929L (accessed 7 June 2024).

Table 8: Estimated utilisation and financial impact estimates

	2024	2025	2026	2027	2028	2029
Estimated extent of use						
TALA + ENZA patients	1	1	1	1	1	1
TALA scripts	2	2	3	3	3	3
Estimated financial implications - early re-entry resubmission: EMP of talazoparib = \$ (DPMQ = \$)						
Cost of TALA	4	4	4	5	5	5
Estimated financial implications - pre-PBAC response: EMP of talazoparib = \$ (DPMQ = \$)						
Cost of TALA	4	4	4	4	4	4

Source: Table 23, of the early re-entry resubmission

DPMQ = dispensed price, maximum quantity; EMP = ex-manufacturer price; ENZA = enzalutamide; TALA = talazoparib

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ \$0 to < \$10 million

⁵ \$10 million to < \$20 million

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

5 PBAC Outcome

- 5.1 The PBAC recommended the listing of talazoparib, for use in combination with enzalutamide, for the first line treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients with breast cancer gene (*BRCA*)1/2 pathogenic variants who have not received prior treatment with a novel hormonal agent (NHA). The PBAC considered that the early re-entry resubmission appropriately addressed the outstanding economic and financial issues and that talazoparib was cost effective at the price proposed in the pre-PBAC response. The PBAC considered that talazoparib should join the risk sharing arrangement (RSA) that is in place for olaparib in the mCRPC setting.
- 5.2 The PBAC acknowledged that the Medical Oncology Group of Australia (MOGA) again expressed its support for the resubmission.
- 5.3 The PBAC recalled that in March 2024 it had considered that talazoparib + enzalutamide was superior compared to enzalutamide monotherapy in terms of both radiographic progression free survival (rPFS; HR = 0.20; 95% CI: 0.11, 0.36) and overall survival (OS; HR = 0.47; 95% CI: 0.26, 0.85) but had noted that the magnitude of the benefit was uncertain as the *BRCA*1/2 subgroup of the TALAPRO-2 trial was *post hoc*, small and the outcomes were informed by immature data.
- 5.4 The PBAC noted that the final analyses for rPFS and OS from the TALAPRO-2 trial were expected in July 2024. The PBAC requested that these data be presented to the Committee when they are available.
- 5.5 In terms of safety, the PBAC recalled that it had considered that talazoparib + enzalutamide was inferior compared to enzalutamide monotherapy.

- 5.6 The PBAC recalled that in March 2024 it had specified the following revisions to the economic model would be required to achieve an acceptable incremental cost-effectiveness ratio (ICER):
- Reducing the time horizon from 10 to 7.5 years;
 - Adjusting the time to treatment discontinuation (TTD) for the enzalutamide component of the combination therapy arm to be equal to rPFS;
 - Applying the overall, rather than treatment specific, utility value to the progression free health state;
 - Incorporating disutilities associated with adverse events; and
 - A price reduction so that the revised model resulted in an ICER of no more than \$55,000 to < \$75,000 per quality adjusted life year (QALY).
- 5.7 The PBAC noted that with the price proposed in the resubmission and the requested changes outlined above the ICER was \$55,000 to < \$75,000 per QALY.
- 5.8 The PBAC noted that the resubmission also made additional changes to the economic model to align the inputs with the financial estimates (see Table 3). The PBAC noted that when these changes were made, the revised base case ICER in the resubmission was \$55,000 to < \$75,000 per QALY (see Table 5).
- 5.9 The PBAC noted that the pre-PBAC response reduced the proposed EMP of talazoparib. The PBAC noted that when this reduction was applied, the ICER was \$55,000 to < \$75,000 per QALY when only the March 2024 PBAC requested changes were made to the model. The ICER was \$55,000 to < \$75,000 per QALY when the additional changes were made to align the inputs for the economic model with those for the financial estimates. The PBAC considered that, at the price proposed in the pre-PBAC response, talazoparib, for use in combination with enzalutamide, was likely to be cost-effective (including when using the true effective prices of olaparib and enzalutamide).
- 5.10 The PBAC recalled that it had previously advised that changes to the utilisation and financial impact estimates would be required as follows:
- The eligible patient population should be decreased over the forward estimates;
 - The uptake rate of talazoparib + enzalutamide should be reduced to no more than |%;
 - The costs of enzalutamide should be included, both in combination with talazoparib and as monotherapy; and
 - Any cost offsets should be applied consistently with the economic model.
- 5.11 The PBAC noted that the resubmission provided revised estimates which incorporated a decreased eligible population. The PBAC considered that the reduced number of patients estimated to receive talazoparib + enzalutamide was reasonable.

Public Summary Document – July 2024 PBAC Meeting

- 5.12 The PBAC noted that the uptake rate of talazoparib + enzalutamide was reduced from a maximum of █% in the March 2024 submission to a maximum of █%, rather than █% as advised. The resubmission stated that this was to align with the assumed uptake of olaparib post enzalutamide monotherapy applied in the economic analysis and financial estimates. The PBAC considered that this was reasonable.
- 5.13 The PBAC noted that the costs of enzalutamide were included and that cost offsets were applied consistently with the economic model.
- 5.14 Overall, the PBAC considered that the revised utilisation and financial impact estimates were reasonable.
- 5.15 The PBAC considered that talazoparib should join the existing RSA for olaparib monotherapy. The PBAC noted that the existing RSA may need to be revised to account for the use of talazoparib and the modelled reduction in the use of olaparib.
- 5.16 In terms of the restriction, to allow for delays in *BRCA1/2* testing, the PBAC considered that it would be reasonable to allow treatment of talazoparib + enzalutamide to be initiated after commencing treatment with a NHA in the mCRPC setting. The PBAC noted flow on changes would be required to the enzalutamide restriction in this setting as the current restriction would not allow a patient who had commenced with abiraterone in the metastatic setting to switch to enzalutamide (in combination with talazoparib) once *BRCA1/2* status was confirmed.
- 5.17 The PBAC advised that talazoparib should not be treated as interchangeable on an individual patient bases with any other drugs, according to s101(3BA) of the *National Health Act 1953*.
- 5.18 The PBAC advised that talazoparib is not suitable for prescribing by nurse practitioners.
- 5.19 The PBAC advised that talazoparib should not be exempt from the Early Supply Rule.
- 5.20 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for talazoparib:
- a) The treatment may be expected to provide a clinically relevant improvement in efficacy, over alternative therapies, but the magnitude of benefit is uncertain;
 - b) The treatment is not expected to address a high and urgent unmet clinical need because there are alternative treatment options for *BRCA1/2* variant positive mCRPC;
 - 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.

Public Summary Document – July 2024 PBAC Meeting

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

Outcome:

Recommended

6 Recommended listing

6.1 Add new item:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TALAZOPARIB					
talazoparib 0.5 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
talazoparib 0.35 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
talazoparib 0.25 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
talazoparib 0.1 mg capsule, 30	NEW (TBD) MP	1	30	5	Talzenna
Safety Net Rule Penalty Applies? Yes					
Insert Restriction Summary [New 1] / Treatment of Concept: [New 1.1]: Authority Required					
Prescriber type: Medical practitioners					
Restriction level: Authority required (telephone/online)					
Episodicity: [blank]					
Severity: Castration resistant metastatic					
Condition: Carcinoma of the prostate					
Indication: Castration resistant metastatic carcinoma of the prostate					
Clinical criteria:					
The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation					
AND					
Clinical criteria					
Patient must not have received prior PBS-subsidised novel hormonal drug <i>in any non-metastatic setting of prostate cancer</i> prior to commencing treatment with this drug for this condition					
AND					
Clinical criteria:					
Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance score no higher than 1 prior to treatment initiation					
AND					
Treatment criteria:					
The treatment must be undergoing concurrent treatment with enzalutamide, unless an intolerance to enzalutamide requires either a: (i) temporary cessation, (ii) permanent discontinuation					
AND					
Treatment criteria:					
The treatment must not be a PBS-subsidised benefit beyond disease progression					

Public Summary Document – July 2024 PBAC Meeting

Note: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

6.2 [REDACTED] Amend existing listing as follows:

Flow-on changes:

Amend current enzalutamide listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ENZALUTAMIDE					
enzalutamide 40 mg capsule, 112	10174L MP	1	112	2	Xtandi
Safety Net Rule Penal Applies? Yes					
Edit Restriction Summary 12894 / ToC: 12937: Authority Required					
Prescriber type: Medical practitioners					
Restriction level: Authority required (telephone/online)					
Severity: Castration resistant metastatic					
Condition: Carcinoma of the prostate					
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 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 only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or					
Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation; or					
<i>Patient must have been receiving treatment with abiraterone or abiraterone plus methylprednisolone in this setting prior to being associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation</i>					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone and methylprednisolone, (iii) apalutamide, (iv) darolutamide, (v) enzalutamide.					

	Administrative Advice: No increase in the maximum quantity or number of units may be authorised
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Poly ADP-ribose polymerase inhibitors applicable to this listing are: olaparib

These restrictions 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

The sponsor had no comment.