4.04 OLAPARIB Capsule, 50 mg, Lynparza®, AstraZeneca Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission sought to address the PBAC's reasons for not recommending olaparib at the July 2016 meeting.

2 Requested listing

2.1 The proposed PBS restriction for olaparib as presented in the July 2016 PBAC Public Summary Document (PSD), was accepted by the sponsor in the November 2016 minor submission (with amendments by the PBAC Secretariat made in italics to reflect the Special Pricing Arrangement requested).

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
OLAPARIB Capsule 50 mg, 448	1	2	$[redacted]*	Lynparza ™	AstraZeneca Pty Ltd

** This is the proposed effective price, the submission requests a special pricing arrangement.*

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	High grade serous
Condition:	Ovarian cancer, fallopian tube cancer, primary peritoneal cancer
PBS Indication:	High grade serous ovarian cancer, High grade serous fallopian tube cancer, High grade serous primary peritoneal cancer
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined

Clinical criteria:	The condition must be platinum sensitive AND Patient must have received at least two previous platinum-containing regimens AND Patient must have relapsed following a previous platinum-containing regimen AND Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen AND The treatment must be as monotherapy AND The treatment must be maintenance therapy AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition.
Population criteria:	Patient must have evidence of a germline class 4 or 5 BRCA1 or BRCA2 gene mutation.
Administrative Advice:	Platinum sensitivity is defined as disease progression greater than 6 months after completion of the penultimate platinum regimen. A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing. *Special Pricing Arrangements apply.*

Name, Restriction, Manner of administration and form	**Max. Qty**	**№.of Rpts**	**Dispensed Price for Max. Qty**	**Proprietary Name and Manufacturer**	
OLAPARIB Capsule 50 mg, 448	1	5	$[redacted]	Lynparza ™	AstraZeneca Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	High grade serous
Condition:	Ovarian cancer
PBS Indication:	High grade serous ovarian cancer
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be as monotherapy AND The treatment must be maintenance therapy AND Patient must not have progressive disease.
Administrative Advice:	*Special Pricing Arrangements apply.*

3 Background

3.1 Olaparib was granted orphan drug designation by the TGA on 15 January 2015.

3.2 Olaparib was approved by the TGA on 23 December 2015 as monotherapy for the maintenance treatment of women with *BRCA*m platinum-sensitive relapsed ovarian cancer who are in response (complete or partial) after platinum-based chemotherapy. Prior treatments must have included at least two courses of platinum-based regimens.

3.3 Olaparib was considered by the PBAC previously in March 2016 and in July 2016.

3.4 This minor resubmission sought to address the remaining concerns raised by the PBAC in July 2016, by

- Proposing a new price, and
- Updating the financial estimates to reflect the new proposed price; and
- Proposing a risk-sharing arrangement with capped PBS expenditure.

3.5 Table 1 summarises the issues raised in the previous submissions and the changes made for the current minor resubmission.

Table 1: Key differences between the November 2016 minor resubmission and the July 2016 minor resubmission and March 2016 submission

	March 2016 submission	**July 2016 minor resubmission**	**November 2016 minor resubmission**
Requested MBS listing	Detection of *BRCA1* or *BRCA2* mutations (*BRCA*m) in women with PSR ovarian cancer **MSAC comment:** MSAC foreshadowed alignment of any MBS listing of *BRCA* testing to germline mutations only.	Requested germline *BRCA* testing only.	Unchanged
Requested PBS listing	*BRCA*m PSR ovarian cancer **PBAC comment:** *BRCA* testing of tumour tissue is not standardised in current practice [Paragraph 7.6] The PBAC recommended that PBS-subsidised access to olaparib would be determined through germline *BRCA* testing only (not tumour). Further, the classification of presence of *BRCA* mutation would be restricted to class 4 or 5 mutations only [a] [Paragraph 7.10].	Unchanged. Requested germline *BRCA* testing only. The minor resubmission requested that the PBAC consider aligning the wording of the PBS restriction for olaparib with standard clinical practice (follow-up care). **PBAC comment:** Agreed with the requested germline *BRCA* testing only and agreed to include standard clinical practice wording in the administrative advice section of the restriction for monitoring disease progression.	Unchanged. Agreed with the July 2016 suggested wording.
DPMQ	$[redacted]	$[redacted], a [redacted]% price reduction. Pre-PBAC $[redacted] a [redacted]% reduction	$[redacted] a [redacted]% reduction
Main comparator	Standard follow-up care (placebo). **PBAC comment:** The PBAC agreed that this was the appropriate comparator [Paragraph 7.02].	Unchanged.	Unchanged

	March 2016 submission	July 2016 minor resubmission	November 2016 minor resubmission
Clinical claim	The submission stated that olaparib: • was superior in terms of comparative effectiveness • had a 'consistent and well characterised' safety profile, *which was interpreted as slightly inferior but acceptable safety profile.* **PBAC comment:** The PBAC accepted the clinical claim of superior comparative effectiveness and inferior comparative safety [Paragraphs 6.34 & 6.35].	Unchanged.	Unchanged
Claim of co-dependence	The interaction test for *BRCA* status and PFS was statistically significant (p=0.03). **PBAC comment**: The PBAC accepted that any PBS-rebate of olaparib maintenance treatment would need to be confined to patients with *BRCA*m [Paragraph 7.08].	Unchanged.	Unchanged
Economic model	Cost-utility analysis, 10-year time horizon • ICER: $45,000 - $75,000 per QALY gained **PBAC comment:** The PBAC requested a 7.5-year time horizon with a corresponding price reduction to keep the ICER at $45,000 - $75,000 per QALY gained [Paragraph 7.20].	Cost-utility analysis, 8.75-year time horizon. ICER: $45,000 - $75,000 per QALY gained PrePBAC response: 7.5 year time horizon. ICER $45,000 - $75,000 per QALY gained.	Model unchanged. Cost-utility analysis, 7.5-year time horizon ICER: $45,000 - $75,000 per QALY gained
Drug cost/patient/course	$[redacted]	$[redacted]	$[redacted]
Number of patients treated with olaparib	• Submission: less than 10,000 in Yr 1 increasing to less than 10,000 in Yr 2, then decreasing to less than 10,000 in Yr 5 • PSCR: less than 10,000 in Yr 1 increasing to less than 10,000 in Yr 2, then decreasing to less than 10,000 in Yr 5 [b]	• less than 10,000 in Yr 1 increasing to less than 10,000 in Yr 2, then decreasing to less than 10,000 in Yr 5	• less than 10,000 in Yr 1 increasing to less than 10,00 in Yr 2, then decreasing to less than 10,000 in Yr 5

	March 2016 submission	July 2016 minor resubmission	November 2016 minor resubmission
Financial estimates Net cost over first 5 years	• more than $100 million (Submission). • more than $100 million (PSCR [b], also included a [redacted]% price reduction) **PBAC comment:** The PBAC recommended the financial estimates be revised to reflect the restricted patient population, i.e. patients must have evidence of a germline class 4 or 5 *BRCA*m [Paragraph 7.19].	• $60 - $90 million. **PBAC comment:** The PBAC did not comment on the revised net cost over first 5 years.	• $60 - $90 million
Risk sharing arrangement	Willing to enter RSA, none proposed. **PBAC comment:** To address the uncertainty surrounding the expected duration of use of olaparib, the PBAC recommended: • a [redacted]% rebate beyond olaparib treatment duration cap of two years [Paragraph 7.19].	The minor resubmission proposed an alternative RSA which was based on the: • application of a tiered percentage rebate on any PBS expenditure above agreed thresholds. **PBAC comment:** The PBAC did not comment on the proposed RSA	Revised risk-sharing arrangement, which capped the total PBS expenditure in any one year to $[redacted] after which the sponsor would rebate [redacted]% of the cost to the government.
PBAC decision	**Deferred**	**Rejected**	

Source: March 2016 PBAC minutes; and compiled during preparation of the overview

AIHW = Australian Institute of Health and Welfare; *BRCA*m = *BRCA1* or *BRCA2* mutation; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; PSCR = Pre-Sub-Committee Response; PSR = platinum-sensitive relapsed; QALY = quality-adjusted life year; RSA = risk-sharing arrangement; Yr = year

[a] Class 5 = definitely pathogenic (probability of being pathogenic > 0.99; Class 4 = likely pathogenic (probability of being pathogenic = 0.95-0.99) [Paragraph 7.6, March 2016 PSD]

[b] The previous Pre-Sub-Committee Response provided revised estimates of patients treated with olaparib (increased the AIHW incidence numbers by 16% to thereby include women with fallopian tube or primary peritoneal cancer (percentage from Study 19)).

4 Clinical place for the test and proposed therapy

4.1 The clinical place of *BRCA* testing for eligibility of olaparib maintenance treatment was unchanged in this minor resubmission.

5 Comparator

5.1 The submission considered by the PBAC in March 2016 nominated standard follow-up care (placebo) as the main comparator, and this was unchanged in the minor resubmission. The PBAC accepted this as the appropriate comparator [Paragraph 7.2, March 2016 PSD].

6 Consideration of the evidence

Consumer comments

6.1 The PBAC noted that no new consumer comments were received for this item.

Clinical trials

6.2 No new clinical trials were presented in the minor resubmission.

Comparative effectiveness

6.3 The trial results were unchanged from the March 2016 submission.

Comparative harms

6.4 The adverse events results remain unchanged from the March 2016 submission.

Clinical claim

6.5 The March 2016 submission claimed superior comparative effectiveness and a 'consistent and well characterised safety profile', which was interpreted as a slightly inferior but acceptable safety profile. The clinical claim remained unchanged from the previous submissions.

6.6 The PBAC previously considered that the claim of superior comparative effectiveness and inferior comparative safety was reasonable.

Economic analysis

6.7 Table 2 presents a summary of the base case economic model presented in the March 2016 submission, the amended version presented in the Pre-PBAC/MSAC response to the March PBAC meeting, the recommendations made by the PBAC in the March 2016, the model presented in the July 2016 minor resubmission and the changes made in the current minor resubmission. The redacted table below shows ICERs in the range of $45,000/QALY - $75,000/QALY.

Table 2: Economic model timeline

Base case approach	March-16			July-16	November 2016
	Major submission	Pre-PBAC/MSAC response	Recommended by PBAC	Minor resubmission	Minor resubmission
Time horizon	10 years	10 years	7.5 years	8.75 years (7.5 years in pre PBAC response)	7.5 years
Olaparib price (DPMQ)	$[redacted]	$[redacted]	To result in ICER of $[redacted]	$[redacted] ($[redacted] in pre-PBAC response)	$[redacted]
OS data for *BRCA*m subgroup	'PARPi sites-excluded'	'PARPi sites-excluded'	For minor: 'PARPi sites-excluded' For major: 'PARPi sites-excluded', using updated OS analyses from Study 19 (up to 66 m) [a]	'PARPi sites-excluded'	Unchanged
OS: from TPs of Study 19; extrapolation method	Log-logistic curve throughout entire model	1. KM up to 28.5 m 2. Extrapolated with log-logistic > 28.5 m	For minor: log-logistic curve throughout entire model not specified [b,c] For major: justify an appropriate method to extrapolate beyond updated OS analyses (after 66 m) [b]	Log-logistic curve throughout entire model	Unchanged
ICER [d]	$[redacted]	$[redacted] [e]	$[redacted]	$[redacted] ($[redacted] in pre-PBAC response)	$[redacted] [e]

Source: Compiled for the minor overview

DPMQ = dispensed price for maximum quantity; HR = hazard ratio; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; PARPi = polyadenosine 5' diphosphoribose polymerase inhibitor; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; TP = transition probability; m = months

[a] [Paragraph 7.20, March 2016 minutes]

[b] [Paragraph 7.20, March 2016 minutes]

[c] The PBAC noted that when the updated survival analyses (up to 66 months) was compared with the revised model (using KM OS data up to 28.5 months), the model clearly overestimated the observed incremental OS for olaparib over its comparator [Paragraph 7.13, March 2016 Minutes]

[d] per QALY gained

[e] Could not be verified

Drug cost/patient/course: $[redacted]

6.8 The drug cost per patient was updated from the previous minor resubmission to $[redacted] per patient per course (reduced from $[redacted]). The drug cost per patient per course was based on the mean duration of treatment among *BRCA*m patients in Study 19 of 16.3 months (17.75 scripts, with one script providing medication for 28 days), their corresponding dose intensity of 84.5%, and a revised effective DPMQ of $[redacted] ([redacted]% price reduction over the March 2016 submission price). The PBAC noted that the only change from the previous submission was the reduction in the effective DPMQ.

Estimated PBS usage & financial implications

6.9 The minor resubmission updated the financial estimates to align with the suggested

PBAC modification to the proposed PBS listing for olaparib. This further restricted access to olaparib for women with germline *BRCA* mutations (class 4 or 5 only). For the revised financial estimates, the resubmission used the prevalence of germline mutations observed in Study 19 (45.7%) rather than the prevalence of *BRCA* mutations (53.5%) (using both germline and tumour testing methods). The minor resubmission presented the financial estimates (i) including the [redacted]% reduction on the initially proposed DPMQ for olaparib (revised down to $[redacted]); and (ii) with a cap on total expenditure per year of $[redacted] (Table 3). The redacted table below shows that at year 5, the estimated number of olaparib patients was less than 10,000.

Table 3: Updated financial estimates *and estimated use*

	Year 1	Year 2	Year 3	Year 4	Year 5
ESTIMATED USE					
Estimated extent of use *BRCA* test					
Number of BRCA *tests ([redacted]% uptake)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated extent of use, olaparib					
Eligible population [a,b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of olaparib	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number treated [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Script (1 per pack) [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESTIMATED COST					
(1) Costs: PBS listing for patients with germline *BRCA*m (class 4 or 5), with [redacted]% rebate on the DPMQ					
NET cost to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
NET cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
NET cost to Government	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table 2, p2 of the minor re-submission, *and extracted from Excel spreadsheet*

AIHW = Australian Institute of Health and Welfare; *BRCA*m = *BRCA1* or *BRCA2* mutation; DPMQ = Dispensed Price for Maximum Quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule; PSCR = pre-Sub-Committee Response PSR = platinum-sensitive relapsed; Yr = year

[a] *BRCA*m PSR ovarian, fallopian tube or primary peritoneal cancer, using germline testing

[b] The previous Pre-Sub-Committee Response provided revised estimates of patients treated with olaparib (increased the AIHW incidence numbers by 16% to thereby include women with fallopian tube or primary peritoneal cancer (from Study 19)).

[c] 15 packs/patient (one script per pack), which was based on average number of scripts/year for olaparib, assuming equal monthly proportions.

6.10 The resubmission estimated that:

- the net cost to the MBS would be less than $10 million over the first five years;
- the net cost to the PBS would be $60 - $100 million over the first five years; and
- the net cost to the Government would be $60 - $100 million over the first five years.

6.11 The revised financial estimates presented in the minor resubmission, did not attempt to estimate the impact of including grandfathered patients.

6.12 As this was a minor submission the validity of the ICER and Financial estimates was not confirmed.

Financial Management – Risk Sharing Arrangements

6.13 To address the uncertainty surrounding the expected duration of use of olaparib the PBAC recommended "a 100% rebate beyond an olaparib treatment duration cap of two years" [Paragraph 7.19, March 2016 PSD]. In response, the minor resubmission proposed an alternative risk-sharing arrangement, which capped the total PBS expenditure in any one year to $[redacted] after which the sponsor would rebate [redacted]% of the cost to the government.

6.14 The minor resubmission stated that the sponsor would be willing to work with the Department of Health to finalise this matter.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of olaparib for the treatment of high grade serous ovarian cancer, high grade serous fallopian tube cancer, and high grade serous primary peritoneal cancer. The PBAC was satisfied that olaparib provides, for some patients, a significant improvement in efficacy over best supportive care.

7.2 The PBAC agreed with the proposed restriction.

7.3 The PBAC recalled that at its July 2016 meeting it had not recommend olaparib because it considered that the evidence provided showed that the incremental health outcomes (driven by the incremental gain in overall survival) were insufficient to justify the incremental cost of treatment at the price proposed at the time. The PBAC additionally considered that the time horizon in the model should be 7.5 years consistent with the approach taken in the sponsor's pre-PBAC response.

7.4 The PBAC considered that with the current submission's use of the 7.5 year time horizon in the economic model and lower price offer, the incremental cost of treatment was now acceptable, despite the PBAC noting that there was outstanding uncertainty inherent in the model.

7.5 The PBAC agreed that the Risk Share Agreement proposed by the sponsor which caps total PBS expenditure in any one year to $[redacted] after which the sponsor would rebate [redacted]% of the cost to the government, would allay some of the risk arising from the uncertainty in the extent of the overall survival benefit.

7.6 The PBAC recommended that olaparib should not be treated as interchangeable on an individual patient basis with any other drugs.

7.7 The PBAC advised that olaparib is not suitable for prescribing by nurse practitioners.

7.8 The PBAC recommended that the Early Supply Rule should apply to olaparib.

7.9 The PBAC noted that there were no flow-on restriction changes associated with this listing.

7.10 The PBAC noted that this submission is not eligible for an Independent Review as olaparib has been recommended for listing.

Outcome:
Recommended

8 Recommended listing

8.1 Add item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
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Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	High grade serous
Condition:	High grade serous
PBS Indication:	Ovarian cancer, fallopian tube cancer, primary peritoneal cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	The condition must be platinum sensitive AND Patient must have received at least two previous platinum-containing regimens AND Patient must have relapsed following a previous platinum-containing regimen AND Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen AND The treatment must be as monotherapy AND The treatment must be maintenance therapy AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition.
Population criteria:	Patient must have evidence of a germline class 4 or 5 BRCA1 or BRCA2 gene mutation.

Prescriber Instructions:	Platinum sensitivity is defined as disease progression greater than 6 months after completion of the penultimate platinum regimen. A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing.
Administrative Advice:	Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
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Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be as monotherapy AND The treatment must be maintenance therapy AND Patient must not have progressive disease.
Administrative Advice:	Special Pricing Arrangements apply.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.