

**7.12 OLAPARIB,
Capsule 50 mg, Tablet 100 mg, Tablet 150 mg,
Lynparza[®],
AstraZeneca Pty Ltd**

1 Purpose of Application

- 1.1 The minor submission requested a change to the current General Schedule, Authority Required, listing for the treatment of platinum-sensitive relapsed ovarian, fallopian tube and primary peritoneal cancer in patients with germline BRCA1/2 (BRCA1/2 gene) mutations to also include patients with somatic BRCA1/2 mutations.

2 Requested listing

- 2.1 The submission requested the current initial treatment restriction prescribing instructions for olaparib tablet formulations (items 11522K and 11528R) be amended as follows:

Concept ID: Edit 20143	Prescribing Instructions: Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing a test of blood or tumour tissue.
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For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Olaparib was approved by the TGA on 23 December 2015 with the following indication:

“maintenance treatment of women with BRCAm (BRCA mutation) 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.”

- 3.2 The TGA subsequently removed the requirement for BRCAm testing in second-line maintenance therapy and the current second-line maintenance indication is:

“maintenance treatment of adult patients with platinum-sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.”

- 3.3 Olaparib was approved by the TGA effective 21 June 2019 for the following additional indication:

“Maintenance treatment of adult patients with advanced BRCAm (germline or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. BRCAm status should be determined by an experienced laboratory using a validated test method.”

- 3.4 Despite the key trial in the first-line maintenance setting (SOLO1) including only 2 patients with sBRCAm (somatic BRCA mutation), the TGA, US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved registration of olaparib for the proposed indication for both germline and somatic BRCAm. The TGA delegate’s summary noted the deficiency of patients with somatic mutations in SOLO1 and reasoned that:

“...based on the similar disease process in germline and somatic BRCA-mutated ovarian cancer, the scientific rationale for similar responsiveness to PARPi and evidence from clinical studies[...] showing similar responsiveness to PARPi in patients with germline and somatic mutations in other lines of therapy, it is considered acceptable for the indication to include patients with germline or somatic BRCA mutations.”

Previous PBAC and MSAC considerations

- 3.5 In March 2016, the PBAC and Medical Services Advisory Committee (MSAC) considered an integrated co-dependent application requesting:

- Medicare Benefits Schedule (MBS) listing for BRCA mutation testing to determine

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eligibility for maintenance therapy with olaparib after response to second line platinum-based chemotherapy; and

- PBS listing of olaparib after response to second line platinum-based chemotherapy in patients with high-grade epithelial ovarian cancer with a somatic or germline BRCA mutation.
- 3.6 At its March 2016 meeting, MSAC noted that the PBAC had deferred its decision on whether olaparib would be listed in the PBS. However, MSAC foreshadowed that, if the PBAC subsequently recommended olaparib for listing in the PBS, it would support the MBS funding of germline BRCA mutation testing to determine eligibility for olaparib second-line maintenance treatment for women with platinum-sensitive relapsed ovarian cancer. In November 2016, following advice from the PBAC that it had recommended to the Minister that olaparib be listed on the PBS, MSAC supported the MBS funding of germline BRCA mutation testing.
- 3.7 In November 2019, the PBAC and MSAC considered an integrated co-dependent application requesting:
- MBS listing of germline BRCA testing (Scenario 1) or tumour BRCA testing (Scenario 2) for the evaluation of BRCA pathological or likely pathological variants to determine eligibility for maintenance therapy with olaparib; and
 - PBS listing of olaparib following response to first-line platinum-based chemotherapy for the treatment of advanced, high-grade epithelial ovarian cancer with a somatic or germline BRCA.
- 3.8 In November 2019, the PBAC did not recommend olaparib for first-line maintenance treatment of ovarian, fallopian tube or primary peritoneal cancer. At its December 2019 meeting, the PBAC noted that in November 2019, MSAC did not provide advice regarding a first-line listing given that the PBAC rejected the submission, however MSAC did support changes to the related MBS items by adding somatic BRCA mutation testing to determine eligibility for the existing second-line PBS listing.
- 3.9 In its consideration of the March 2016 submission for olaparib following response to second-line platinum-based chemotherapy, the PBAC noted that, compared with germline BRCA testing, BRCA testing of tumour tissue is not standardised in current practice (paragraph 7.6, olaparib Public Summary Document (PSD), March 2016). In its consideration of the November 2019 submission MSAC considered that its previous concerns about somatic BRCA testing compared to germline BRCA testing were adequately addressed and supported funding of somatic BRCA testing to help identify additional patients who may be suitable for treatment with olaparib. The pre-PBAC response noted that the recommended modification to the MBS item descriptors is agnostic to line of therapy and thus enables somatic BRCA testing to occur at diagnosis or in the second-line setting.

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

4 Population and disease

- 4.1 The pivotal evidence leading to PBS reimbursement of olaparib in the platinum-sensitive relapsed ovarian cancer setting (second-line maintenance) was from Study 19 (Ledermann 2012, 2014, 2016, Dougherty 2017). The minor submission stated that in the most recent molecular analysis from Study 19, 114/209 (55%) platinum-sensitive relapsed (PSR) ovarian cancer patients carried a tumour BRCA mutation, 20 (9.6%) of which were somatic BRCA only (Dougherty et al. 2017). No mutations identified by blood-based germline testing in this study were identified by tumour testing as somatic.
- 4.2 The minor submission concluded that it is reasonable to estimate an additional 10% of patients could become eligible for olaparib treatment if this was extended to include patients with somatic BRCA1/2 mutations identified from a test of tumour tissue.
- 4.3 The increase in patients identified by somatic BRCA testing and eligible for olaparib treatment in the minor submission was based on the prevalence of somatic BRCA from Study 19, in which 20/114 (17.5%) of BRCA were somatic. A number of other sources for this estimate were identified in the evaluation of the November 2019 olaparib submission. Eight of the diagnostic accuracy studies included in the November 2019 submission reported data that enabled the proportion of germline and somatic BRCA to be determined. Across these studies, a median of 24.6% (range 14.3%–45.5%) of all BRCA identified were somatic. In six studies, somatic BRCA were identified in a median of 7.9% (range 4.0–10.9) of women diagnosed with epithelial ovarian cancer (EOC), serous ovarian cancer (SOC) or high grade serous ovarian cancer (HGSOC). For the two studies reporting on women with HGSOC, the median prevalence of somatic pathogenic variants was also 7.9% (range 6.4–9.3) (Olaparib November 2019 Commentary). This compares with 20/209 (9.6%) platinum-sensitive HGSOC patients in Study 19.
- 4.4 MSAC considered that the number of extra women eligible for testing by including somatic BRCA testing would be small and noted that somatic BRCA testing is likely to detect about 5% more women with BRCA pathogenic variants than detected by germline BRCA testing alone (page 3, 1554 – BRCA1/2 PSD, November 2019 MSAC meeting).
- 4.5 The pre-PBAC response argued that Study 19 provides the most relevant data for the patient group who would access somatic BRCA testing in the second-line setting.
- 4.6 The PBAC noted that the prevalence of sBRCA varies in the literature. The PBAC identified four large studies, in which the prevalence of sBRCA ranged from 3% to

7%^{1,2,3,4}. The PBAC considered that 5% was the reasonable estimate of additional patients who would be identified through somatic BRCAm testing based on the available literature and consistent with MSAC's advice.

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

5 Comparator

- 5.1 The previous major submission for olaparib in second-line maintenance, considered by the PBAC in November 2016, nominated standard follow-up care as the comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (1) via the Consumer Comments facility on the PBS website.
- 6.3 The consumer comments noted that somatic testing is offered to women diagnosed with ovarian cancer in the UK and urged that somatic testing of BRCA1/2 be made available for Australian women to identify patients who may benefit from certain treatments or clinical trials.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the olaparib submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the SOLO1 trial. It was not clear from MOGA's advice whether support was for the proposed listing in second line treatment of patients with sBRCAm ovarian cancer as the SOLO1 trial was as first line treatment.

¹ The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609-15. Epub 2011/07/02.

² Hahnen et al. Prevalence of somatic mutations in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1 study). Journal of Clinical Oncology 34, no 15_suppl (May 20, 2016) 5544-5544.

³ Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res. 2014;20(3):764-75.

⁴ Coleman et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med 2019 Dec 19;381(25):2403-2415. Epub 2019 Sep 28.

Clinical trials

- 6.5 The minor submission stated that the available evidence presented in the olaparib SOLO1 co-dependent submission indicates that patients with somatic BRCA and germline BRCA mutations respond similarly to PARP inhibitor treatment.
- 6.6 The minor submission did not re-present the clinical evidence supporting this claim. Details of the trials presented in the November 2019 submission to support this claim are provided in the table below.
- 6.7 The pivotal evidence presented in the November 2019 submission for first-line maintenance olaparib was from SOLO1 (Moore et al 2018). This study included only two patients (2/391) with somatic BRCA. Therefore, in order to demonstrate that patients with somatic BRCA and germline BRCA respond similarly to PARP inhibitors, the submission presented an indirect comparison of the treatment effect for PARP inhibitors in patients with germline vs somatic BRCA, with placebo as a common reference arm. This analysis included four RCTs comparing PARP inhibitor maintenance therapy with placebo: Study 19 and SOLO2 (olaparib), NOVA (niraparib), and ARIEL3 (rucaparib). All studies in this analysis were in the second-line maintenance setting. For SOLO2 only the germline BRCA subgroup was included in the meta-analysis as no patients with somatic BRCA were included in the study.

Table 1: Trials and associated reports presented in the re-submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
Study 19	<p>Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens.</p> <p>Ledermann J, Harter P, Gourley C, <i>et al.</i> Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.</p> <p>Ledermann J, Harter P, Gourley C, <i>et al.</i> Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCAm status in a randomised phase 2 trial.</p> <p><i>Dougherty, B. A., et al. (2017). "Biological and clinical evidence for somatic mutations in BRCA1 and BRCA2 as predictive markers for olaparib response in high-grade serous ovarian cancers in the maintenance setting."</i></p>	<p>Clinical study report (CSR). 31 July 2013</p> <p>NEJM. 2012; 366(15):1382-1392.</p> <p>The Lancet Oncol. 2014; 15(8):852-861.</p> <p><i>Oncotarget 8(27): 43653-43661</i></p>
SOLO2	<p>Pujade-Lauraine, E., <i>et al.</i> (2017). "Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a <i>BRCA1/2</i> mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial."</p>	<p>Lancet Oncol 18(9): 1274-1284.</p>
NOVA	<p>Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, <i>et al.</i> Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer..</p>	<p>N Engl J Med. 2016;375(22):2154-64</p>
ARIEL3	<p>Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, <i>et al.</i> Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.</p>	<p>Lancet. 2017;390(10106):1949-61.</p>

Comparative effectiveness

- 6.8 The outcomes from the four studies that reported on the PFS (and OS in one study) for patients receiving olaparib maintenance therapy compared to placebo in HGSOC patents with either a germline or a somatic BRCAm are summarised in Table 2.

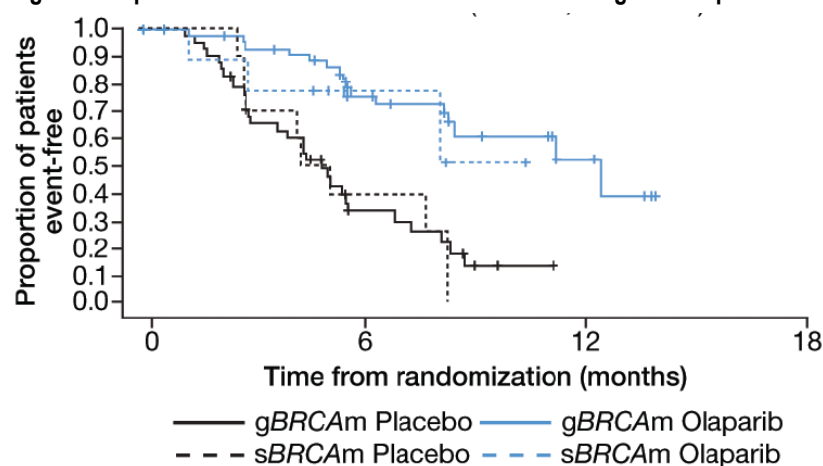
Table 2: The clinical utility of the NGS *BRCAM* test to triage patients with somatic vs germline *BRCAM* for olaparib

Study	Population	Outcome			
			olaparib	placebo	HR (95%CI)
Dougherty et al 2017 Study 19	N=113 patients with platinum-sensitive HGSOC (second-line maintenance)	PFS			
		s <i>BRCAM</i>	3/10 (30%)	8/10 (80%)	0.23 (0.04, 1.12)
		g <i>BRCAM</i>	16/49 (33%)	30/44 (68%)	0.17 (0.09, 0.34)
		OS			
		s <i>BRCAM</i>	3/10 (30%)	7/10 (70%)	0.15 (0.02, 0.88)
		g <i>BRCAM</i>	24/49 (49%)	22/44 (50%)	0.62 (0.34, 1.12)
Pujade-Lauraine et al 2017 SOLO2	N=286 patients with platinum-sensitive HGEOC (second-line maintenance)	PFS	olaparib n=190	placebo n=96	HR (95%CI) 0.33 (0.24, 0.44)
Mirza et al 2016 NOVA	N=553 patients with platinum-sensitive HGEOC (second-line maintenance)	PFS	niraparib	placebo	HR (95%CI)
		s <i>BRCAM</i>	n=35	n=12	0.27 (0.08, 0.90)
		g <i>BRCAM</i>	n=138	n=65	0.27 (0.17, 0.41)
Coleman et al 2017 ARIEL3	N=186 patients with platinum-sensitive HGEOC (second-line maintenance)	PFS	rucaparib	placebo	HR (95%CI)
		s <i>BRCAM</i>	18/40 (45%)	12/16 (75%)	0.23 (0.10, 0.54)
		g <i>BRCAM</i>	47/82 (57%)	42/48 (88%)	0.25 (0.16, 0.39)
Study 19, NOVA, ARIEL3, SOLO2	Meta-analysis (no heterogeneity between studies)	PFS	PARPi	placebo	HR (95%CI)
		s <i>BRCAM</i>	n=85	n=38	0.24 (0.13, 0.46)
		g <i>BRCAM</i>	n=459	n=253	0.27 (0.09, 0.33)

BRCA = breast cancer gene 1 and 2; g*BRCAM* = germline *BRCA* pathological or likely pathological variant; HGSOC = high-grade serous ovarian, fallopian tube or primary peritoneal cancer; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; RR = relative risk; s*BRCAM* = somatic *BRCA* pathological or likely pathological variant
Source: Section 2.2.D.11.4 of the November 2019 submission

6.9 Study 19 found that although both the germline and somatic *BRCAM* groups had improved PFS, the difference between olaparib and placebo in the somatic mutation group did not reach statistical significance. Kaplan–Meier curves for PFS by somatic or germline *BRCAM* are shown in Figure 1.

Figure 1: Kaplan-Meier curves for PFS of s*BRCAM* versus g*BRCAM* patients

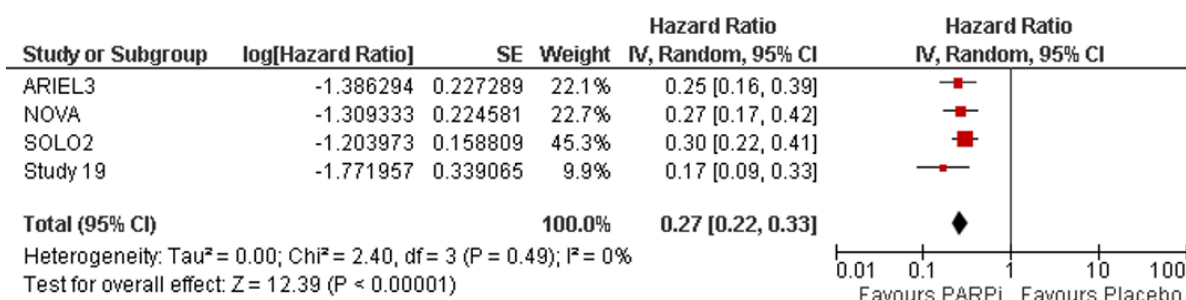


Source: Dougherty et al (2017)

6.10 The NOVA and ARIEL3 studies, which used different PARP inhibitors, had similar findings to Study 19.

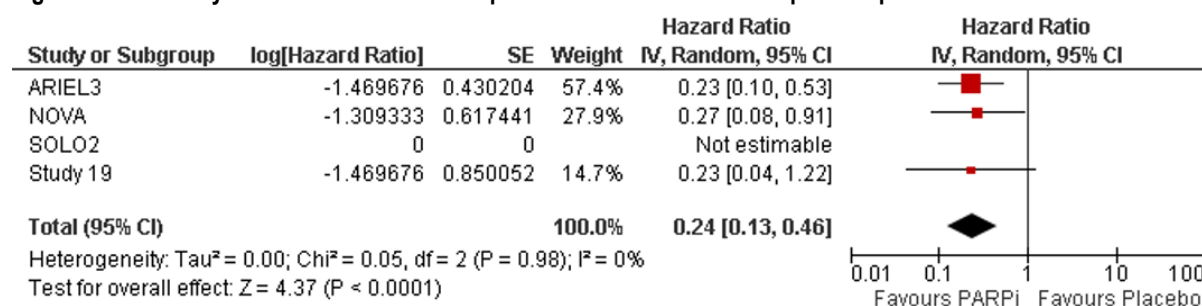
6.11 Meta-analyses of PFS in germline and somatic *BRCAM* are shown in Figure 2 and Figure 3, respectively.

Figure 2: Meta-analysis of PARP inhibitors vs placebo for PFS in gBRCAm-positive patients



Source: Figure 1, p13, Attachment 4.5 to the November 2019 submission.

Figure 3: Meta-analysis of PARP inhibitors vs placebo for PFS in sBRCAm-positive patients



Source: Figure 2, p14, Attachment 4.5 to the submission.

6.12 The pooled analysis of four studies (ARIEL3, NOVA, SOLO2 and Study 19) for PFS resulted in a hazard ratio of 0.27 (95% CI 0.22, 0.33) for PARP inhibitors versus placebo in patients with gBRCAm. In a second pooled analysis including 3 of the same studies (ARIEL3, NOVA and Study 19), the hazard ratio was 0.24 (95% CI 0.13, 0.46) for PARP inhibitors versus placebo in patients with sBRCAm. The indirect treatment comparison for gBRCAm vs sBRCAm (for PFS) gives a hazard ratio of 1.125 (95% CI 0.579, 2.184). While the central estimate slightly favours sBRCAm, there is no statistically significant difference between the gBRCAm and sBRCAm groups.

6.13 In consideration of the evidence presented in the November 2019 submission the PBAC “noted that the pooled analysis of studies in the second-line setting found similar hazard ratios for PARP inhibitors versus placebo in patients with gBRCAm and sBRCAm, which supported the efficacy of olaparib in the second-line setting for patients with sBRCAm in the absence of gBRCAm” (paragraph 7.9, olaparib PSD, November 2019).

Clinical claim

6.14 The minor submission did not make a clinical claim, however the requested change to the listing relies on the clinical claim of non-inferior comparative effectiveness and safety of second-line olaparib maintenance in patients with germline BRCAm compared with patients with somatic BRCAm.

- 6.15 The PBAC considered that it is reasonable to conclude sBRCA patients will derive similar benefit from olaparib as gBRCA patients, based on the pooled analysis of the trial data for PARP inhibitors in the second line setting.
- 6.16 The PBAC considered that it is reasonable to conclude that the safety profile of olaparib in patients with sBRCAm patients would be not be different from the safety profile in patients with gBRCAm.

Economic analysis

- 6.17 The minor submission did not present an economic analysis. The requested change assumes that the cost-effectiveness of treating patients with sBRCAm is similar to patients with gBRCAm.

Estimated PBS usage & financial implications

- 6.18 The minor submission estimated a net cost to the PBS of less than \$10 million in Year 6 of listing (2023, the final year included in the current Deed for olaparib), with a total net cost to the PBS of less than \$10 million over the remaining four years of the deed. This is summarised in Table 4.
- 6.19 The financial estimates assumed 100% use of tablet formation rather than capsule use. This is consistent with the initial use item for the capsule formulation having been discontinued as of July 2019.
- 6.20 The estimated number of eligible, treated patients for 2020 to 2023 (years 3 to 6 of the financial estimates presented in the previous minor submission), as presented in the minor submission, are shown in Table 3. The financial estimate calculations are based on estimates from the March 2018 submission for listing of the olaparib tablet formation, with the updated DPMQ (\$ [REDACTED] effective price) and updated patient co-payment amounts (\$40.30 General, \$6.50 Concessional, current as at December 2019).
- 6.21 The minor submission estimated the financial impact of the requested extension of the listing by increasing the current olaparib eligible population by 10%. Referring to worksheet '2a. Patients – epi' in the Section 4 estimates model, this was based on the proportions derived by dividing the number of germline BRCA patients sensitive to platinum (row 74) by the total number of incident patients with either ovarian, primary peritoneal and fallopian tube cancer (row 61). This approach underestimates the number of additional patients who would be identified as it does not include somatic patients. Including patients with both germline and somatic tumours (i.e. row 73, the total number of patients tested for BRCA) would identify an additional 10% of the total platinum-sensitive relapsed ovarian cancer patient population as having BRCA mutations. As such, it would increase the current eligible population (gBRCAm) by 21.3% (i.e. from less than 10,000 to less than 10,000 patients), rather than 10%. Corrected estimates, assuming less than 10,000 out of less than 10,000 (54.5%) platinum-sensitive relapsed ovarian cancer patients carried a somatic or germline

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BRCA mutation, consistent with the evidence from Study 19 are shown in italics in Table 3 and Table 4. In the pre-PBAC response the sponsor agreed with this correction to calculation of additional patient numbers.

6.22 Revised estimates shown in Table 4 below indicate the net cost to the PBS in year 6 (2023) is less than \$10 million, with a total net cost to the PBS of less than \$10 million over the remaining four years of the deed.

Table 3: Estimated number of eligible, treated patients

	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023
PSR HGS ovarian cancer patients (germline BRCA1/2) eligible, treated	■	■	■	■
Additional PSR HGS ovarian cancer (somatic BRCA1/2) eligible, treated	■	■	■	■
Revised total eligible, treated patients	■	■	■	■

Source: Lynparza Section 4 estimates revised, worksheet '2a Patients epi' row 15 and worksheet "Annual pack utilisation" row B5-B8

The redacted table shows that at Year 6, the estimated number of eligible patients was less than 10,000.

Table 4: Estimated financial impact of change to listing to include somatic BRCAm patients

	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 [#] 2023
Cost to the R/PBS at the effective price (corrected)				
Total	\$ ■	\$ ■	\$ ■	\$ ■
Overall cost to the R/PBS at the effective price less co-payments	\$ ■	\$ ■	\$ ■	\$ ■
Net additional cost to the R/PBS for including patients with somatic BRCAm (corrected)				
Total net cost prior to change*	\$ ■	\$ ■	\$ ■	\$ ■
RSA caps	\$ ■	\$ ■	\$ ■	\$ ■
Overall cost to the R/PBS at the effective price less co-payments	\$ ■	\$ ■	\$ ■	\$ ■

Source: Table 2.2.3 Olaparib minor submission, 'Lynparza Section 4 estimates revised' excel workbook

* Values in the submission could not be verified against values in the Section 4 estimates worksheet. Net cost prior to change was calculated by changing worksheet '2a. Patients – epi' cells E14 to J14 AND worksheet 'Annual pack utilisation' by removing the additional 10% and rounding patient numbers to whole numbers and adding PBS and RPBS costs on worksheet '3c. Impact –EFF' and using the corrected patient numbers shown in Table 4.

Rounding the number of new patients per month in cells C2 to C9 worksheet 'Annual pack utilisation' resulted in the same cost for years 5 and 6 despite different total patient numbers. In the revised estimates the number of new patients per month has not been rounded.

6.23 As a minor submission, the financial estimates have not been independently evaluated.

6.24 As noted above (paragraph 4.3 and 4.6), other sources for the prevalence of somatic BRCA mutations are available in the literature. If fewer somatic BRCAm are identified in practice than in Study 19, the financial impact shown in Table 4 will be overestimated.

6.25 As shown in Table 4 (above) there are caps in place for the current olaparib listings. The minor submission requested that, if PBAC recommend the revision to the

restriction to include access for patients with a somatic BRCA mutation, the caps in the current Deed of Agreement be increased in the outer years of the deed, to reflect the additional patients eligible for treatment.

- 6.26 For the full first year of the Deed (1 Dec 2018 – 31 Nov 2019) Commonwealth payment on olaparib (\$ [REDACTED]) was [REDACTED] of its cap (\$ [REDACTED]).

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

7 PBAC Outcome

- 7.1 The PBAC recommended that the existing olaparib PBS listing for the treatment of platinum-sensitive relapsed ovarian, fallopian tube and primary peritoneal cancer in patients with germline BRCA1/2 (BRCA1/2) mutations be amended to also include patients with somatic BRCA1/2 mutations. The PBAC considered that it was reasonable to assume the cost-effectiveness of olaparib in patients with sBRCA1/2 would be similar to that in patients with gBRCA1/2, as previously accepted by the PBAC. This followed MSAC's support for MBS listing of somatic BRCA testing to help identify additional patients who may be suitable for treatment with olaparib at its November 2019 meeting.
- 7.2 The PBAC considered that the prescribing instructions should be amended to "Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline or somatic mutation testing" and the clinical criteria should be amended to "The condition must be a class 4 or 5 BRCA1 or BRCA2 gene mutation".
- 7.3 The PBAC noted that the comparator (standard follow-up care) was as nominated for the previous major submission for olaparib in second-line maintenance, considered by the PBAC in November 2016.
- 7.4 The PBAC noted that clinical evidence for patients with sBRCA1/2 was based on an indirect comparison of the treatment effect for PARP inhibitors in second-line patients with germline vs somatic BRCA1/2, with placebo as a common reference arm, as presented in the November 2019 submission. This analysis included four RCTs comparing PARP inhibitor maintenance therapy with placebo: Study 19 and SOLO2 (olaparib), NOVA (niraparib), and ARIEL3 (rucaparib).
- 7.5 The PBAC noted that, for PFS, the pooled analysis of these studies resulted in a hazard ratio of 0.27 (95% CI 0.22, 0.33) for PARP inhibitors versus placebo in patients with gBRCA1/2. In a second pooled analysis including 3 of the same studies (ARIEL3, NOVA and Study 19), the hazard ratio was 0.24 (95% CI 0.13, 0.46) for PARP inhibitors versus placebo in patients with sBRCA1/2. The indirect treatment comparison for gBRCA1/2 vs sBRCA1/2 for PFS gave a hazard ratio of 1.125 (95% CI 0.579, 2.184). As was noted in consideration of the evidence presented in the November 2019 submission the PBAC maintained that this "supported the efficacy of olaparib in the second-line setting for patients with sBRCA1/2 in the absence of gBRCA1/2" (paragraph 7.9, olaparib PSD, November 2019).

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- 7.6 The PBAC considered that it is reasonable to conclude sBRCA patients will derive similar benefit from olaparib as gBRCA patients, based on the pooled analysis of trial data for PARP inhibitors in the second line setting.
- 7.7 The PBAC considered that it is reasonable to conclude that the safety profile of olaparib in patients with sBRCAm patients would be not be different from the safety profile in patients with gBRCAm.
- 7.8 Given the conclusion of similar effectiveness and safety in the sBRCAm population as the gBRCAm population, the PBAC considered that it was reasonable to assume the cost-effectiveness in patients with sBRCAm would be similar to that in patients with gBRCAm, as previously accepted by the PBAC.
- 7.9 The PBAC noted that utilisation estimates provided in the minor submission were based on an additional 10% of patients identified through somatic testing, based on 20/209 (9.6%) platinum-sensitive HGSOc patients in Study 19 identified as having sBRCAm. The PBAC noted that the prevalence of sBRCAm varies in the literature. The PBAC identified four large studies, in which the prevalence of sBRCA ranged from 3% to 7%. The PBAC considered that 5% was the most reasonable estimate of additional patients who would be identified through somatic BRCAm testing based on the available literature and consistent with MSAC's advice. The PBAC considered the financial estimates, for calculation of risk sharing agreement caps, should be adjusted to account for an additional 5% of patients identified through testing for sBRCAm.
- 7.10 Olaparib is not currently included in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only/within a shared care model.
- 7.11 Olaparib should not be exempt from the Early Supply Rule as it currently applies to the existing listings for olaparib.
- 7.12 Olaparib is not currently considered as interchangeable with any other drugs on an individual patient basis.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as this is a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend the relevant prescriber instruction and clinical criterion in the existing listing to read as follows:

Prescribing Instruction: Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline or somatic mutation testing
Clinical criterion: The condition must be a class 4 or 5 BRCA1 or BRCA2 gene mutation

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.