

## 7.05 OLAPARIB, Tablet 150 mg, Tablet 100 mg, Lynparza<sup>®</sup>, AstraZeneca Pty Ltd.

### 1 Purpose of submission

- 1.1 The resubmission requested a Section 85, Authority Required listing of olaparib for the treatment of patients with newly diagnosed advanced (FIGO stage III-IV) high grade epithelial ovarian, fallopian tube and primary peritoneal cancer, with evidence of a BRCA1 or BRCA2 gene mutation (BRCAm), and who are in partial or complete response to platinum-based chemotherapy. The first co-dependent submission was considered in November 2019 by the PBAC and MSAC, and the MSAC has since recommended the Medicare Benefits Schedule (MBS) listing for tumour testing in patients treated with olaparib in the second-line (2L) setting. Following the PBAC's decision not to recommend PBS listing of olaparib for first-line (1L) maintenance of ovarian cancer in November 2019, MSAC did not provide advice on BRCA testing for this population. However, the proposed MBS item descriptors for germline and tumour testing do not specify the line of olaparib therapy.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of olaparib and tumour tissue testing for BRCAm compared with current practice. The key components of the clinical issues addressed by the resubmission are summarised below.

**Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)**

Component	Description
Test Population	Patients with newly diagnosed, advanced (FIGO stage III-IV) high grade epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer)
Treatment Population	Patients with newly diagnosed, advanced (FIGO stage III-IV) high grade epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) whose tumour tissue tests positive for a class 4 or 5 BRCA1/2 mutation and who are in response (complete or partial) to platinum-based chemotherapy
Intervention	Test of tumour tissue to determine BRCA1/2 mutation status If BRCA mutation positive, receive olaparib If BRCA mutation negative or unknown, watch and wait (i.e. placebo)
Comparator	Watch and wait following platinum-based chemotherapy
Outcomes	PFS, PFS2, OS TTST <sup>a</sup> , quality of life, safety and tolerability for olaparib vs standard of care (placebo)
Clinical claim	In patients with newly diagnosed, advanced (FIGO stage III-IV) high grade epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) who test positive for a class 4 or class 5 BRCA1/2 mutation and are in complete or partial response to platinum-based chemotherapy, olaparib is superior to placebo (watch and wait) in terms of efficacy and non-inferior in terms of safety and quality of life.

Source: Table 3, p43 of the resubmission.

BRCAm = breast cancer gene 1 and 2 pathological or likely pathological variant; FIGO = Federation of Gynaecology and Obstetrics; PFS = progression free survival; PFS2 = second progression-free survival (time from randomisation to second progression); OS = overall survival; TTST = time to subsequent therapy.

<sup>a</sup> The resubmission included the abbreviation 'TTST', however did not define it, nor discuss it further. This is likely an error in the resubmission, which may have intended to use 'TSST' or 'TFST', however it is unclear what was meant.

## 2 Background

### Registration status

- 2.1 Olaparib was TGA registered on 21 June 2019 as monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to 1L platinum-based chemotherapy. Other regulatory agencies (e.g., FDA, EMA, PMDA) have also approved this indication.
- 2.2 In May 2020, the FDA expanded the indication of olaparib to include its combination with bevacizumab for 1L maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to 1L platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status, defined by either a deleterious or suspected deleterious *BRCA* mutation and/or genomic instability. This was based on the PAOLA-1 trial.

### Previous PBAC consideration

- 2.3 The previous submission was considered by the PBAC in November 2019, in which evidence of BRCAm was either derived from germline testing (Scenario 1) or tumour testing (Scenario 2). The PBAC previously noted concerns regarding the immature overall survival (OS) data in the key trial SOLO1, however, no updated OS data were presented in the resubmission. The resubmission presented updated economic modelling and financial analysis.
- 2.4 The key matters from the previous PBAC considerations and how the resubmission addressed these concerns are summarised below.

**Table 2: Summary of key matters of concern**

Component	Matter of concern	How the resubmission addresses it
Duration of treatment	Paragraph 2.3 advised for a patient to be able to receive a maximum of 24 months of treatment (1 initial and 4 continuing scripts)	Addressed. Proposed PBS listing updated accordingly.
Quality of life	Paragraph 6.21, the PBAC noted no responder analysis was performed on the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire. Reasons for non-response were not provided. Paragraph 6.36, the PBAC noted quality adjusted PFS data, but it was unevaluated at this time.	Not adequately addressed; the resubmission claimed that the quality of life of patients in the olaparib arm was non-inferior to that of patients in the placebo arm of SOLO1, based on Quality Adjusted PFS, and time without symptoms of disease progression or toxicity, and time until subsequent therapy data. These data did not support the conclusion drawn by the resubmission.
Selection of comparator	Paragraph 5.5 The PBAC considered bevacizumab to be an appropriate comparator in the subgroup of patients with sub-optimally debulked stage 3 cancer.	Partially addressed A qualitative analysis was provided using data from trials comparing efficacy of bevacizumab to results of SOLO1.

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Component	Matter of concern	How the resubmission addresses it
<b>Economics</b>		
Model structure and surrogacy of PFS for OS	<p>Paragraph 7.16, 7.17 and 7.25</p> <p>The PBAC agreed with the Commentary that the model structure appeared to be unnecessarily complex, which contributed to uncertainty in the modelled outcomes; a more usual approach, such as a partitioned survival analysis may be more appropriate.</p> <p>The PBAC noted that an OS benefit modelled was not supported by the clinical data currently available. The PBAC agreed with ESC that it was inappropriate to use PFS2 as a surrogate for OS, as no clinical evidence was presented to support the translation of second progression to OS, and the approach was highly favourable to olaparib.</p>	<p>Not adequately addressed.</p> <p>The model structure remained largely unchanged from the previous submission. The resubmission stated that this structure was required given the immaturity of the OS data from SOLO1. Multiple data sources were used to estimate PFS2 and OS from PFS1.</p> <p>The resubmission did not provide a translation study using the framework in Appendix 5 of the PBAC guidelines, for assessing a proposed surrogate measure if the transformation of a change in a proposed surrogate measure (PFS) predicts a change in a target clinical outcome (OS).</p>
Extent of OS benefit	<p>Paragraph 7.19 and 7.25</p> <p>The PBAC considered it would be reasonable for the model to include an OS benefit, consistent with Study 19, for the proportion of patients for whom it is reasonable to accept that olaparib would not have been given in the 2L setting. Alternatively, OS could be extrapolated from more mature survival data for 1L olaparib.</p>	<p>Not adequately addressed.</p> <p>Although the resubmission changed the source of transition probabilities for PFS2 to Death to Study 19, the structure of the economic model and assumed surrogacy of PFS for OS resulted in a large modelled OS gain that was not supported by the clinical evidence from SOLO1.</p>
Cure in 1L placebo group	<p>Paragraph 7.20</p> <p>The PBAC considered that the model should incorporate a proportion of patients cured in the 1L placebo group.</p>	<p>Addressed</p> <p>The resubmission included a mixed cure model for estimating the PFS1 survival curves, and an additional 'cured'<sup>a</sup> health state. The resulting PFS1 survival curve in the 1L placebo group includes a proportion of patients that are cured.</p>
Prevalence of gBRCAm	<p>Paragraph 7.21</p> <p>PBAC considered that using a prevalence for gBRCAm of 20.3% was reasonable.</p>	<p>Addressed</p>
Utilities	<p>Paragraphs 7.21 and 7.25</p> <p>The PBAC noted that future submissions should use the utility values for PFS2 and PD as reported in Study 19.</p>	<p>Not adequately addressed.</p> <p>The resubmission used a weighted utility value. The resubmission assumed that 51% of relapsed patients are healthy enough to receive 2L olaparib and thus have underlying characteristics similar to those enrolled in Study 19. The remaining 49% are considered 'unfit' and are assigned utilities from Havrilesky 2009.</p>

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Component	Matter of concern	How the resubmission addresses it
Costs of olaparib	Paragraphs 6.61, 7. 21, and 7.25 The submission underestimated the cost per course of olaparib in the 1L arm by applying the mean daily dose to calculate the monthly drug costs.	Not adequately addressed  The resubmission used the average daily dose in SOLO1 and SOLO2 to estimate number of tablets required per cycle. This was inappropriate as there is a flat pricing structure for the two tablet strengths of olaparib.
Inclusion of downstream testing costs	Paragraph 7.18, 7.21, and 7.25 The PBAC considered that future resubmission should include downstream germline testing costs in tumour positive patients and private/hospital funded test costs.	Addressed.  The resubmission included downstream germline testing costs in tumour positive patients.
Time horizon	Paragraph 7.22 The PBAC considered that a time horizon of up to 15 years would be appropriate.	Not adequately addressed.  The resubmission revised the time horizon from 25 years to 20 years.
Proportion of patients who receive 2L olaparib.	Paragraph 7.23 The PBAC considered that the proportion of patients who receive 2L olaparib in clinical practice may be higher than in the SOLO1 trial, in which cross-over was not allowed but patients could receive PARP inhibitors outside the trial, and therefore cost-offsets and benefits from 2L olaparib may be underestimated.	Not adequately addressed.  However, the model structure and surrogacy of PFS2 for OS made the impact of sensitivity analyses relating to this variable uncertain.
Impact of bevacizumab for those with sub optimally debulked Stage IIIB/C and all Stage IV patients and are also BRCAm positive.	Paragraph 7.23 and 7.25 The PBAC also noted that bevacizumab was not considered as a comparator, and considered that it may be appropriate to include the impact of bevacizumab in the model for the patient population with sub-optimally debulked Stage IIIB/C and all Stage IV patients who are also BRCAm positive, and would be treated with 1L olaparib maintenance instead of bevacizumab.	Not adequately addressed.  This was not included in the resubmission base case, but as a sensitivity analysis. The sensitivity analysis only impacted the QALYs accrued in the PFS1 health state and did not have any impact on PFS2 or Death.
Incremental cost effectiveness ratio (ICER) should be consistent with that accepted for 2L olaparib	Paragraph 7.25 A reduced price resulting in an ICER consistent with that accepted for olaparib in the 2L setting (\$55,000 to < \$75,000/QALY, Paragraph 7.25, 6.05 olaparib PSD, November 2019 PBAC meeting).	The ICER provided in the resubmission was below the \$55,000 to < \$75,000/QALY as per the 2L olaparib PBAC PSD. However, the ESC considered this did not represent an appropriate base case.
<b>Financial Estimates</b>		
Prevalence of gBRCAm	Paragraph 7.21 The PBAC considered that using a prevalence for gBRCAm of 20.3% was reasonable.	The resubmission adjusted the proportion of patients with gBRCAm to 20.3%.

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Component	Matter of concern	How the resubmission addresses it
Proportion of patients who receive subsequent therapies	Paragraph 7.23 The PBAC considered that the proportion of patients who receive 2L olaparib in clinical practice may be higher than in the SOLO1 trial, in which cross-over was not allowed but patients could receive PARP inhibitors outside the trial, and therefore cost-offsets and benefits from 2L olaparib may be underestimated.	Not adequately addressed.  The use of subsequent therapies was based on that in SOLO1. Sensitivity analyses relating to this variable were considered uncertain.
Impact of bevacizumab for those with sub optimally debulked Stage IIIB/C and all Stage IV patients and are also BRCAm positive.	Paragraph 7.23 and 7.25 The PBAC also noted that bevacizumab was not considered as a comparator, and considered that it may be appropriate to include the impact of bevacizumab in the model for the patient population with sub-optimally debulked Stage IIIB/C and all Stage IV patients who are also BRCAm positive, and would be treated with 1L olaparib maintenance instead of bevacizumab.	This was included as a sensitivity analysis.  Although, this only impacted the estimated cost-offset, and did not impact down-stream costs relating to subsequent therapies.
<b>Other</b>		
Risk-share arrangements	Paragraph 7.25 The PBAC considered that any future submissions for 1L olaparib should include additional details regarding any proposed RSA and estimates of the extent of adjustment to the expenditure caps that would be required.	The submission provided additional details regarding an increase in the subsidisation caps for olaparib, under an RSA.

Source: Compiled during the evaluation

AOCS = The Australian Ovarian Cancer Study; OS = overall survival; PFS2 = progression-free survival after 2L therapy;

<sup>a</sup> The resubmission assumed that patients with a statistical “cure” will never experience progression (e.g. they have zero risk of progression) but remain at risk of death due to other causes.

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

### 3 Requested listing

3.1 The listing suggested by the Secretariat is provided below.

Name, restriction, manner of administration, form	Max qty packs	Max qty (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Olaparib, tablet, 150mg, 100mg INITIAL TREATMENT	2	112	2	\$6962.13 (published) \$ (effective)	LYNPARZA® AstraZeneca Pty Ltd
Olaparib, tablet, 150mg, 100mg CONTINUING TREATMENT	2	112	5	\$6962.13 (published) \$ (effective)	LYNPARZA® AstraZeneca Pty Ltd

<b>Category / Program:</b> Section 85 – General Schedule
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic
<b>Condition:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>PBS Indication:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer

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<b>Treatment phase:</b> Initial treatment
<p><b>Clinical criteria:</b>                  The condition must be a class 4 or 5 BRCA1 or BRCA2 gene mutation                  AND                  The condition must be platinum sensitive                  AND                  Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen                  AND                  The treatment must be the sole PBS-subsidised therapy for this condition                  AND                  The treatment must be maintenance therapy                  AND                  Patient must not have previously received PBS-subsidised treatment with this drug for this condition</p>
<p><b>Prescriber Instructions:</b>                  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 (GCIC) or Response Evaluation in Solid Tumours (RECIST) guidelines                  Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline or somatic testing of a BRCA1 or BRCA2 gene mutation.</p>
<p><b>Administrative Advice:</b>  <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333.</i>                  Special Pricing Arrangements apply</p>

<b>Category / Program:</b> Section 85 – General Schedule
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Streamlined
<b>Condition:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>PBS Indication:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>Treatment phase:</b> Continuing treatment
<p><b>Clinical criteria:</b>                  Patient must have received previous PBS-subsidised treatment with this drug for this condition                  AND                  The treatment must be the sole PBS-subsidised therapy for this condition                  AND                  The treatment must be maintenance therapy                  AND                  Patient must not have developed disease progression while receiving treatment with this drug for this condition                  AND                  Treatment must not exceed at a total of 24 months for patients in complete response</p>
<p><b>Prescriber Instructions:</b> A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIC) or Response Evaluation in Solid Tumours (RECIST) guidelines.</p>
<b>Administrative Advice:</b> Special Pricing Arrangements apply

- 3.2 As in the previous submission, the resubmission proposed a special pricing arrangement. The requested effective price was the same as the current effective price in the 2L setting and the ex-manufacturer price was unchanged from the previous submission.
- 3.3 The PBAC noted the Secretariat’s comment that a line-agnostic listing may be appropriate for olaparib for ovarian cancer. The PBAC noted the different treatment durations for olaparib in the 1L and 2L settings would result in a complex combined listing and recommended separate listings. As a result there would be flow-on changes for the 2L listings to ensure that patients are not re-treated with olaparib where they have recurrence.
- 3.4 The resubmission proposed the PBS indication “High grade or high grade epithelial ovarian, fallopian tube or primary peritoneal cancer”. The existing 2L listing is split into indications: “High grade serous ovarian cancer”, “High grade serous fallopian tube cancer” and “High grade serous primary peritoneal cancer”. The PBAC considered the combined indication appropriate and noted that the 2L listings could be similarly revised.
- 3.5 No separate grandfather restriction was proposed in the resubmission as these patients would be eligible for treatment under the proposed initial treatment listing.

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

## **4 Population and disease**

- 4.1 In Australia, ovarian cancer (including fallopian tube and primary peritoneal) is the sixth most common cause of death from cancer in women. Most patients (70%) are diagnosed at an advanced stage. Despite high rates of response to 1L platinum-based chemotherapy, the majority of patients with advanced ovarian cancer will relapse or progress within 3 years. Recurrent ovarian cancer is estimated to have a 5 year survival rate of less than 30%.
- 4.2 Unchanged from the previous submission, olaparib was proposed as maintenance therapy following response to a 1L platinum-based chemotherapy regimen for patients with a germline or somatic class 4 or 5 BRCA1 or BRCA2 gene mutation. To inform the use of olaparib for this indication, a tumour *BRCAm* test was proposed to occur at diagnosis.
- 4.3 The resubmission considered 3 distinct HGEOC *BRCAm* patient groups, as follow:
- **Subgroup 1: Patients cured with initial platinum-based chemotherapy.** It is assumed that more patients will be cured if olaparib maintenance follows initial chemotherapy treatment. The resubmission did not supply any evidence to support this assumption.
  - **Subgroup 2: Patients who subsequently progress following initial platinum-based chemotherapy but are not eligible for 2L treatment with olaparib.** The resubmission stated this subgroup of patients have the highest unmet clinical

need and will derive a substantial clinical benefit from 1L maintenance treatment with olaparib. The PBAC considered that it may be reasonable to expect that an OS benefit would be achieved with olaparib as 1L maintenance compared with no olaparib at any stage, given the OS benefit for 2L maintenance (as demonstrated in Study 19) (para 6.51, olaparib Public Summary Document (PSD), November 2019 PBAC meeting).

- **Subgroup 3: Patients who subsequently progress following initial platinum-based chemotherapy and are treated with olaparib maintenance as part of their 2L treatment.** The resubmission stated that even in this patient group, maintenance treatment with olaparib following an initial course of chemotherapy, rather than waiting until after relapse, will result in better clinical outcomes. The PBAC previously considered the SOLO1 trial did not support a greater improvement in overall survival for 1L olaparib maintenance versus 2L olaparib maintenance (para 6.51, olaparib PSD, November 2019 PBAC meeting).

- 4.4 The resubmission did not provide economic modelling specific to these subgroups, instead modelling them as a single cohort.

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

## 5 Comparator

- 5.1 The resubmission nominated watch and wait as the main comparator. The PBAC previously specified watch and wait, followed by 2L platinum-based chemotherapy with olaparib maintenance in patients with *gBRCAm* (para 5.4, olaparib PSD, November 2019 PBAC meeting). This population was extended to also include patients with *sBRCAm* (para 7.1, olaparib PSD, March 2020 PBAC meeting).

- 5.2 Given that the PBAC previously considered bevacizumab an appropriate comparator for the subgroup of patients with sub-optimally debulked Stage III ovarian cancer (para 5.5, olaparib PSD, November 2019 PBAC meeting), the resubmission presented a qualitative clinical comparison between olaparib and bevacizumab. Two trials, GOG0218 and ICON7, compared the efficacy of bevacizumab to chemotherapy, and found a statistically significant progression-free survival (PFS) benefit, but no statistically significant OS benefit. The 'high risk' subgroup of ICON7 demonstrated a significant OS benefit, as did the 'Stage IV' subgroup of GOG0218. The heterogeneity of the study designs and populations prevented quantitative comparisons with SOLO1.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented a historical overview of the treatment for women with advanced ovarian cancer and summarised the data from the SOLO1 (1L olaparib) and SOLO2 (2L olaparib) trials. The PBAC

considered the hearing provided a valuable overview of the therapies for ovarian cancer.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed input from patient support organisations (Ovarian Cancer Australia and Rare Cancers Australia) in support of the olaparib submission. The comments noted that a number of patients were self-funding olaparib, with a high financial burden or were unable to access treatment due to the high cost. The comments also noted that patients with ovarian cancer have a high risk of recurrence following standard treatment and many patients experience anxiety and depression or emotional strain related to the fear of recurrence.
- 6.3 The PBAC noted and welcomed input from 69 consumers via the Consumer Comments facility on the PBS website. Patients wishing to access olaparib noted that treatment in the first line setting may delay or prevent recurrence, and patients currently accessing olaparib commented that it had allowed them to live longer than expected. Patients also noted the severe impact of chemotherapy on their quality of life, and access to 1L olaparib may delay the need for chemotherapy. Many patients noted that the cost of self-funding olaparib was prohibitive.
- 6.4 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the olaparib submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the SOLO1 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for olaparib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>, based on a comparison with placebo. The PBAC noted that MOGA upgraded the ESMO-MCBS score to 4 on the basis of a PFS difference >10% at 2 years and a plateau of the PFS curve in the treatment arm.

### **Clinical trial**

- 6.5 The resubmission was based on one head-to-head trial (SOLO1) comparing olaparib to placebo (n=391). The PBAC noted that, with the exception of the updated PFS data provided in the pre-PBAC response, the evidence base remained the same as in the previous submission.
- 6.6 Details of the trial presented in the resubmission are provided in the table below.

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<sup>1</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

**Table 3: Trials and associated reports presented in the resubmission**

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial of olaparib vs placebo		
SOLO1	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following 1L Platinum Based Chemotherapy.	23 August 2018; ClinicalTrials.gov Identifier: NCT01844986
	Gong H. Front-line maintenance therapy for platinum-sensitive ovarian cancer: What's next PARP inhibitors?	Annals of Oncology 2019;30(9):ix81. Abstract 236P
	Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA1/2 mutation (BRCAm): phase III SOLO1 trial.	Annals of Oncology 2018; 29 (9):ix174-ix175.
	Poveda A, Sackeyfio A, Friedlander M. Maintenance olaparib for BRCA-mutated ovarian cancer (OC) patients in 1 <sup>st</sup> line and platinum-sensitive relapsed (PSR) settings: maximizing treatment opportunities.	International Journal of Gynecologic Cancer 2019;29:A133.
	Wu L, Zhu J, Yin R, Wu X, Lou G, Wang J, et al. Olaparib maintenance therapy in patients (pts) with a BRCA1 and/or BRCA2 mutation (BRCAm) and newly diagnosed advanced ovarian cancer (OC): SOLO1 China cohort.	Journal of Clinical Oncology 2019 37:15_suppl, 5554-5554
	Mathews CA, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): efficacy by surgical and tumor status in the Phase III SOLO1 trial	Journal of Clinical Oncology 2019 37:15_suppl, 5541-5541
	Friedlander M, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Efficacy of maintenance olaparib for newly diagnosed, advanced ovarian cancer patients (pts) by BRCA1 or BRCA2 mutation in the phase III SOLO1 trial.	Journal of Clinical Oncology 2019 37:15_suppl, 5551-5551
	Colombo N, Moore KN, Scambia G, Oaknin A, Friedlander M, Lisianskaya AS, et al. Adverse events (Aes) with maintenance olaparib in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): phase III SOLO1 trial.	Journal of Clinical Oncology 2019 37(15_suppl):5539-5539
	Friedlander et al. Patient-centred outcomes with maintenance olaparib in newly diagnosed patients with advanced ovarian cancer and a BRCA mutation in the phase III SOLO1 trial to support the clinical benefit of prolongation of progression-free survival.	POSTER no. 996PD Presented at ESMO Annual Meeting, 27-1 October 2019, Barcelona, Spain.

Source: Table 14, p 65 of the resubmission.

6.7 The key features of the direct randomised trial are unchanged from the previous submission and are summarised in the table below.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
SOLO1	391	R, DB, MC Median 41 months follow up (DCO=17 May 2018)	Low	HGEOC, gBRCAm- positive, responders to 1L platinum-based chemotherapy.	PFS, PFS2, OS, TFST, TSST, TDT, BoR, HRQoL, Safety	PFS (modelled and extrapolated), Time from 1 <sup>st</sup> progression to PFS2 (modelled and extrapolated), OS (within trial only), TDT, QoL while on treatment, subsequent therapies

BoR=best overall response; DB=double blind; DCO=data cut-off; HRQoL=health-related quality of life (on treatment); MC=multi-centre; OS=overall survival; PFS=progression-free survival; PFS2=second progression-free survival; R=randomised; TDT=time to treatment discontinuation; TFST=time to first subsequent therapy (or death); TSST=time to second subsequent therapy (or death).

Source: Table 2-12, pp98, of the previous submission

## Comparative effectiveness

6.8 The results for OS and PFS are summarised below. Updated 5-year PFS data from SOLO1 was provided in the pre-PBAC response. Final OS analyses are event driven and are planned to be conducted at 60% maturity, which is estimated to occur in late 2023 at the earliest and possibly not until 2027.

**Table 5: SOLO1: PFS, PFS2 and OS results for gBRCAm<sup>f</sup> positive patients (ITT) treated with either olaparib or placebo (DCO 17 May 2018)**

Endpoint	Olaparib	Placebo	HR (95% CI) <sup>a</sup>
<b>PFS</b>			
Events (progression or death) / N (%)	102/260 (39.2%)	96/131 (73.3%)	0.30 (0.23, 0.41) p<0.0001 <sup>e</sup>
Median (95% CI), months <sup>b</sup>	NR (- <sup>d</sup> , NR)	13.8 (11.1, 18.2)	
% of patients event free by time point (95% CI) <sup>b</sup>			
12 months	87.7 (82.9, 91.3)	51.4 (42.4, 59.7)	
24 months	73.6 (67.5, 78.7)	34.6 (46.4, 42.9)	
<b>PFS2<sup>c</sup></b>			
Events (progression or death) / N (%)	69/260 (26.5%)	52/131 (39.7%)	0.50 (0.35, 0.72) p=0.0002 <sup>e</sup>
Median (95% CI), months <sup>b</sup>	NR (NR, NR)	41.9 (36.5, 47.9)	
% of patients event free by time point (95% CI) <sup>b</sup>			
24 months	86.0 (80.8, 89.8)	77.3 (68.2, 84.1)	
36 months	75.1 (68.9, 80.3)	60.2 (50.1, 68.9)	
<b>OS</b>			
Events (death) / N (%)	55/260 (21.2%)	27/131 (20.6%)	0.95 (0.60, 1.53) p=0.8903 <sup>e</sup>
Median (95% CI), months <sup>b</sup>	NR (NR, NR)	NR (NR, NR)	
% of patients event free by time point (95% CI) <sup>b</sup>			
24 months	91.5 (87.3, 94.4)	87.9 (80.8, 92.5)	
36 months	84.0 (78.8, 88.1)	80.5 (72.3, 86.5)	

Source: Table 11.2.1.2, Table 11.2.2.2, Table 11.2.3.2 of the SOLO1 CSR

CI=confidence interval; N=total participants in group; NR=not reached; OS=overall survival; PFS=progression-free survival; PFS2=second progression-free survival.

<sup>a</sup>Estimated from a Cox proportional hazards model including best response to prior chemotherapy (stratification factor) as a covariate

<sup>b</sup>Calculated using Kaplan-Meier techniques

<sup>c</sup>Second progression-free survival is defined as time from randomisation until second progression

<sup>d</sup>The SOLO1 CSR does not report the lower 95% CI for progression-free survival in the olaparib arm, however it is implausible that it has not been reached given that the 95% CI for the landmark analysis of PFS at 42 months is 46.5% - 60.8%.

<sup>e</sup>Determined using log-rank test (stratified by response to platinum based chemotherapy)

<sup>f</sup>SOLO1 contained two patients with somatic BRCA mutations

- 6.9 The SOLO1 trial demonstrated a PFS benefit for maintenance with olaparib compared with placebo with a hazard ratio of 0.30 (95% CI: 0.23, 0.41;  $p < 0.0001$ ). The PBAC previously considered that the gain in PFS is likely to be clinically relevant to patients, based on other supporting measures such as PFS2 and time to subsequent therapy, however, the extent of the clinically relevant benefit may be less than the difference in radiological PFS (para 7.13, olaparib PSD, November 2019 PBAC meeting).
- 6.10 The PBAC noted the updated 5-year PFS results were consistent with those presented in the resubmission with a hazard ratio of 0.33 (95% CI: 0.25, 0.43;  $p < 0.0001$ ), and a difference in the median PFS of 42 months (56 months for olaparib vs 13.8 months for placebo).
- 6.11 There was no difference in OS at median follow-up of 41 months, with a hazard ratio of 0.95 (95% CI: 0.60, 1.53;  $p = 0.89$ ). The PBAC previously noted that the OS data observed in the SOLO1 trial may not reflect the expected OS in the Australian setting because:
- The extent and circumstances of use of PARP inhibitors following progression in the placebo arm may not reflect Australian clinical practice. Approximately 50% of patients who had progressed in the placebo arm received a PARP inhibitor following progression (37% of the ITT placebo population). The Pre-Sub-Committee Response (PSCR) indicated that it was not possible to determine from the SOLO1 data whether the 2L olaparib use followed a response to 2L platinum, but expected that the majority was post 2L platinum, consistent with the marketing indication in most jurisdictions. The PBAC noted the design of SOLO1 did not allow for crossover, meaning only patients who had disengaged from the trial had access to a PARPi in the subsequent-line setting. The PBAC considered that a higher proportion of patients may access 2L olaparib in Australian clinical practice; and
  - PARP inhibitors were used in 20% of patients who had progressed in the olaparib arm. Sequential use of PARP inhibitors would not be subsidised according to the proposed PBS restrictions. Should sequential use of PARP inhibitors confer some benefit, OS in the olaparib arm may be higher in SOLO1 than in clinical practice. The commentary requested the sponsor provide PFS, PFS2 and OS data for the olaparib arm with patients who received subsequent-line PARP inhibitors omitted/censored. The PSCR stated that the subsequent PARP inhibitor use in 20% of progressed patients was equivalent to only 8% of the overall patients in the olaparib arm. The PBAC noted that PFS, PFS2 and OS Kaplan-Meier curves excluding patients who received a subsequent PARP in the olaparib arm were provided in the pre-PBAC response, and that based on the PFS2 results, subsequent PARP inhibitor use in the olaparib arm did not appear to substantially bias the result in favour of olaparib.
- 6.12 The Commentary also requested PFS2 data for the patients in the placebo arm who received a subsequent PARP inhibitor (i.e. subgroup 3, as defined in paragraph 4.3

above). The PSCR argued that a formal comparative analysis of 1L olaparib with placebo patients who received 2L PARP would be biased and that it is not possible to identify the subset of patients in the 1L olaparib arm who would have been eligible to receive 2L olaparib if 1L olaparib had not been given. Similarly, it is not possible to identify the subset of patients in the 1L olaparib arm that would not have received 2L olaparib if 1L olaparib had not been given. The PBAC noted that the PFS2 Kaplan-Meier curve for patients in the placebo arm who received subsequent PARP inhibitors was provided in the pre-PBAC response, and that after the first year, PFS2 was similar to that for the ITT patients. Overall, it was claimed in the pre-PBAC response that use of the PFS2 data from the ITT population in the economic model did not substantially bias the results, and even under the most conservative scenario in which the placebo cohort is restricted to those who received subsequent PARP, the divergence in PFS2 demonstrates that 2L PARP use does not nullify the PFS gains accrued by 1L olaparib.

- 6.13 The resubmission argued that the improvements observed in PFS, disease-free survival (DFS), time-to-first-subsequent-treatment (TFST) and time-to-second-subsequent-treatment (TSST) together may represent an improved chance of long-term remission and cure. Treatment with olaparib reduced the risk of first subsequent therapy or death versus placebo (HR 0.30; 95% CI 0.22, 0.40), and a similar relationship was found for TSST (HR 0.45 95% CI 0.32, 0.63;  $P < 0.0001$ ). This correlation between PFS1 and TFST, and PFS2 and TSST describes the expected treatment decisions (commencing next therapy at time of progression). The TSST was measured from time of randomisation to commencement of second subsequent therapy, which included the TFST, and as such does not provide an accurate assessment of whether the olaparib arm had increased time between first- and second-subsequent treatments. Therefore, this claim cannot be substantiated by the provided data. The PSCR stated that the benefits of olaparib treatment persisted beyond progression and significantly extended time free from chemotherapy treatment. The PSCR argued that olaparib, therefore, preserves a patient's quality of life for a prolonged duration of time by avoiding multiple, increasingly frequent courses of chemotherapy and associated toxicities.
- 6.14 The resubmission presented quality-adjusted PFS (QA-PFS) data, which adjusted the PFS results based on the quality of life experienced by patients, and found a statistically significant improvement in QA-PFS with maintenance olaparib versus placebo (mean QA-PFS was 29.7 months vs 17.5 months respectively,  $p < 0.001$ ). QA-PFS was the product of the mean utility score from the 5-item EuroQol 5D-5L and the mean PFS. The EuroQol utility score is less sensitive to disease-specific QoL differences than the Functional Assessment of Cancer Therapy – Ovarian [FACT-O] questionnaire, which detected a statistically significant (but determined to be clinically irrelevant) difference in QoL which favoured the placebo arm. The PSCR justified using the EQ-5D-5L as the purpose was to document overall health status, rather than disease specific QoL. Another issue with the QA-PFS measure is that the substantial PFS difference between the two arms may have obscured differences in QoL. Patients in

the placebo arm progressed significantly faster than patients in the olaparib maintenance arm and hence there was a substantial imbalance across the arms in the duration of time over which the QA-PFS was measured. This may underestimate the health-related quality of life experienced by patients in the placebo arm, as progression in this disease is usually asymptomatic<sup>2</sup>. The PSCR asserted that most patients with progression in SOLO1 commenced chemotherapy within 5 weeks and that Colombo et al (2017) emphasised the psychological and physical impact of recurrence on patients.

- 6.15 The ESC noted the resubmission also presented time without symptoms of disease progression or toxicity (TWiST) data, which found a significant improvement in the olaparib arm compared to placebo (mean TWiST 33.1 months vs 20.2 months respectively,  $p < 0.001$ ). The TWiST data were calculated based on the mean PFS and time without significant symptoms of toxicity, defined as grade  $\geq 2$  nausea, vomiting or fatigue. These three symptoms do not accurately represent the adverse event profile demonstrated in SOLO1, and two of them are overlapping symptoms (nausea and vomiting). The TWiST data failed to represent large parts of the adverse event profile described in the safety data of SOLO1, including adverse events by organ class, serious adverse events, hospitalisations and discontinuations due to adverse events; all of these measures favoured the placebo arm as being substantially less toxic. The resubmission was also unclear if the TWiST data were weighted to adjust for different severities (e.g. grade 2 vs grade 4). The PSCR acknowledged that symptoms included in the TWiST analysis do not constitute all possible adverse effects, but argued that they are by far the most common and potentially have the greatest impact on patients.

### **Comparative harms**

- 6.16 No new safety data were presented in the resubmission. The PBAC previously noted that olaparib has an inferior safety profile compared with placebo, particularly clinically-relevant anaemia of grade 3 or greater severity, which occurred in 21.2% of patients receiving olaparib and 1.5% of patients in the placebo arm. The PBAC previously considered that the safety profile of olaparib appears manageable but includes clinically important adverse events, particularly as it is used as maintenance treatment (para 7.15, olaparib PSD, November 2019 PBAC meeting).
- 6.17 The PBAC noted that recently published data from SOLO2 indicated that 8% of patients treated with 2L olaparib experienced myelodysplastic syndrome (MDS)<sup>3</sup>, compared with 1.2% treated with 1L olaparib in SOLO1. The PBAC considered that this suggests MDS may become more prevalent the longer patients are treated with olaparib and

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<sup>2</sup> Herzog TJ, Armstrong DK, Brady MF, Coleman RL, Einstein MH, Monk BJ, et al. Ovarian cancer clinical trial endpoints: Society of Gynecologic Oncology white paper. *Gynecologic oncology*. 2014;132(1):8-17.

<sup>3</sup> Poveda, A. 2020. Final overall survival (OS) results from SOLO2/ENGOT-ov21: A phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation. 2020 ASCO Virtual Scientific Program.

that ongoing monitoring of this potentially life-threatening adverse event is warranted.

## Benefits/harms

6.18 The comparison of benefits/harms of olaparib with placebo remained unchanged from the previous submission.

**Table 6: Summary of comparative benefits and harms for olaparib and PBO**

Benefits						
Trial	Median duration of follow up	Event	Olaparib n/N (%)	PBO n/N (%)	Absolute difference (%)	HR (95% CI)
SOLO1	41 months	Progressed	102/260 (39.2)	96/131 (73.3)	24 months: 39	0.30 (0.23, 0.41)
		Dead	55/260 (21.2)	27/131 (20.6)	-	0.95 (0.60, 1.53)
Harms						
Trial	Average duration of treatment <sup>b</sup>	Olaparib n/N (%)	PBO n/N (%)	RR <sup>a</sup> (95% CI)	RD <sup>a</sup> (95% CI)	
Anaemia: CTCAE Grade 3 or greater						
SOLO1	Olaparib: 87 weeks Placebo: 65.3 weeks	55/260 (21.2)	2/130 (1.5)	13.8 (3.4, 55.5)	19.6 (14.2, 25.0)	
Gastrointestinal disorders (SOC): CTCAE Grade 3 or greater						
SOLO1	Olaparib: 87 weeks Placebo: 65.3 weeks	17/260 (6.5)	3/130 (2.3)	2.8 (0.85, 9.49)	4.2 (0.27, 8.19)	

Source: Compiled during the evaluation from Table 2-14, p100, Section 2.2.D.6.1.2.1, pp107-108 and Table 2-23, pp127-128 of the submission.

HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; NR = Not Reported; SOC = system organ class

<sup>a</sup> RR, RD and confidence intervals calculated during the evaluation.

<sup>b</sup>Total treatment duration (includes dose interruptions).

6.19 On the basis of direct evidence presented by the submission, for every 100 patients treated with olaparib in comparison with placebo:

- Approximately 39 more patients would remain progression-free at 24 months, however, there would be no difference in overall survival.

6.20 For every 100 patients treated with olaparib for 87 weeks in comparison to placebo for 65.3 weeks and followed until 30 days after treatment discontinuation:

- Approximately 20 additional patients would experience Grade 3 or greater anaemia; and
- Approximately 4 additional patients would experience Grade 3 or greater gastrointestinal disorders (diarrhoea, abdominal pain, nausea).

## Clinical claim

6.21 The clinical claim presented in the resubmission was that olaparib maintenance treatment following a response to platinum-based chemotherapy in a patient who tests positive for a BRCAm (germline or somatic) is superior in terms of efficacy, and non-inferior in terms of quality of life with a manageable safety and tolerability profile

compared to placebo. The clinical claim in terms of quality of life was an addition compared with the previous submission.

- 6.22 The PBAC reaffirmed its view that in patients with BRCAm, the claim of superior comparative effectiveness for olaparib maintenance compared with placebo followed by 2L platinum-based chemotherapy with olaparib maintenance treatment was reasonable for PFS, but was not adequately supported for OS.
- 6.23 The PBAC reaffirmed its view that the claim of inferior comparative safety was reasonable.
- 6.24 The ESC and PBAC considered the claimed non-inferior quality of life for olaparib compared with placebo was not adequately supported by the evidence. The ESC considered that flaws in the QA-PFS (paragraph 6.14) and TWiST (paragraph 6.15) presented above, undermined the conclusion of non-inferior quality of life.

### **Economic analysis**

- 6.25 As in the original submission, the resubmission presented a modelled economic evaluation, based on the direct randomised trial SOLO1; comparing olaparib versus placebo (watch and wait), in a population of patients with newly diagnosed (tumour) BRCA1/2-mutated advanced ovarian cancer who are in response (complete or partial) after 1L platinum-based chemotherapy. In each arm disease progression is followed by 2L platinum-based treatment in those who are eligible to receive it, and in the comparator arm this may include olaparib maintenance post 2L platinum treatment. The types of economic evaluation presented were cost-utility and cost-effectiveness analyses. A summary of the structure and rationale for the economic model is presented in the table below.

**Table 7: Summary of model structure, key inputs and rationale**

<b>Component</b>	<b>Summary</b>
Treatments	Olaparib 1L maintenance vs watch and wait
Time horizon	20 years in the model base case (15 years in sensitivity analysis) versus 41 months median follow-up in the SOLO1 trial. A time horizon of 25 years was used in the previous submission.
Outcomes	Progression-free years gained; life-years gained; quality-adjusted life years gained. These remained the same as in the previous submission.
Methods used to generate results	The resubmission stated the approach was a 'Modified Markov' model. The resubmission used a partitioned survival model (i.e. area under the curve) to assign costs and QALYs over the time horizon of the model. However, in the extrapolated portion of the model, the PFS2 and OS curves were constructed using Markov-modelling techniques. These methods are the same as those used in the previous submission.
Health states	Cured (i.e. at no risk of progression), progression-free following 1L platinum regimen (PFS1) for uncured, progression-free following 2L platinum regimen (PFS2) for uncured, progressive disease, death. Compared with the previous submission, an additional health state, 'cured', was added.
Cycle length	Monthly. Unchanged from the previous submission.
Transition probabilities and allocation to health states	The methods for determining health state allocation remain the same as the previous submission. The survival curves were constructed using a combination of PFS1, PFS2 and OS KM curves observed from trial data and constructed PFS2 and OS curves. Specifically, for BRCAm patients: <ul style="list-style-type: none"> <li>• The PFS1 curve was based on extrapolated data from SOLO1.</li> </ul>

Component	Summary
	<ul style="list-style-type: none"> <li>The PFS2 curve was derived from SOLO1 until month 47. After month 47 the resubmission applied the constructed PFS curve for uncured patients. This constructed curve is not extrapolated from the SOLO1 PFS2 data but is calculated by applying the observed transition from PFS1 to PFS2 each cycle for each of the respective arms in the SOLO1 trial.</li> <li>Similarly, the OS curve used in the model is based on the SOLO1 curve until month 41. After month 41, the resubmission applied the constructed OS curve. The constructed OS curve was not extrapolated from SOLO1, but was calculated by applying the estimated transition from progressive disease to death (each cycle) from Study 19 to the PFS2 curve in each of the respective arms.</li> </ul> <p>Outcomes for BRCAwt patients were based on modelling of data from AOCS. The PFS1 curve in this patient population is based on a fitted parametric function to AOCS data. For PFS2 and OS, the constructed curves were calculated by applying the estimated transition from that health state to the next, similar to the methods described for the BRCAm population above.</p>
Extrapolation method	<p>For the BRCAm patient population:</p> <p>PFS1: Mixed cure model (log-logistic, jointly estimated, theta + scale + shape), based on SOLO1 data.                      Transitions from PFS1 to PFS2: Log-logistic fitted to SOLO1.                      Transitions from PFS2 to OS: Jointly fitted generalised gamma function (proportional hazards model).</p> <p>86% of the incremental QALYs are generated in the extrapolated period (beyond 41 months).</p>
Health related quality of life	<p>PFS1: 0.8031 sourced from SOLO1 (same as that in the previous submission)                      PFS2: 0.637, derived by weighting the utility value for patients not well enough to receive 2L olaparib maintenance from Havrilesky 2009, and the utility value for those who are healthy enough to receive 2L olaparib maintenance from Study 19.                      PD: 0.557, derived by weighting the utility value for patients not well enough to receive 2L olaparib maintenance from Havrilesky 2009, and the utility value for those who are healthy enough to receive 2L olaparib maintenance from Study 19.</p>

Source: Table 21, Section 3 of the resubmission

AOCS = Australian Ovarian Cancer Study; BRCAm = BRCA1/2 mutation positives; BRCAwt = BRCA 1/2 wildtype; OS = overall survival; PFS1 = progression-free survival after 1L treatment; PFS2 = progression-free survival after 2L treatment; PD = progressive disease.

6.26 In its consideration of the November 2019 submission, the PBAC identified a number of changes that would need to be made to the economic model (para 7.25, olaparib PSD, November 2019 PBAC Meeting).

- A more usual analysis approach to the economic model, for example a partitioned survival analysis.
- Incorporating the following changes to the model inputs:
  - using utility values for PFS2 and PD as reported in Study 19. The resubmission used weighted utility values for these health states based on 51% of ‘healthy’ patients having a utility sourced from Study 19, and the remainder having a utility value sourced from Havrilesky 2009. The use of the weighted utility favoured olaparib 1L maintenance treatment, compared with the use of utility values from Study 19.
  - correcting the modelled cost of olaparib. The resubmission continued to adjust the cost based on the mean daily dose of olaparib, even though the cost for a 400mg or 600mg daily dose is equivalent. The PSCR stated that the reason the planned daily dose of 600mg was not achieved on all days was more frequently

due to treatment interruptions, which would result in a reduction in the cost of treatment. However treatment interruptions were generally short (SOLO1 CSR page 133) and the treatment duration accounting for interruptions is approximately 97% of the total treatment duration, suggesting that treatment interruptions are minor.

- including downstream germline testing costs in tumour positive patients and private/hospital funded test costs. The resubmission included downstream germline testing costs in tumour positive patients.
- using a prevalence for gBRCAm of 20.3%. This proportion was used in the resubmission.
- A revised, more conservative approach to estimating OS benefit, consistent with the OS benefit shown with 2L olaparib for patients who would not have been given olaparib in the 2L setting, or based on more mature survival data for 1L olaparib. The resubmission maintained PFS2 as a surrogate for OS and the implied surrogacy of PFS1 for OS through the use of the constructed PFS2 curve in the extrapolated portion of the model. While the resubmission used Study 19 to inform transitions from PFS2 to death in the extrapolated portion of the curve, the modelled difference in OS between the two treatment arms remained substantial and was not supported by the available clinical evidence for SOLO1.
- A time horizon of up to 15 years. The resubmission argued that a time horizon of 20 years was more appropriate given the likely difference in the proportion of patients experiencing cure. Using a longer time horizon would capture long-term cured survival benefits if they exist, but adds further uncertainty to the modelled results and favoured the olaparib 1L treatment arm. The ESC noted the reduced time horizon of 20 years compared to 25 years in the previous submission and considered that a time horizon of up to 20 years may be reasonable given typical survival for advanced ovarian cancer is 10-15 years and would be longer where patients are considered cured.
- Including the impact of bevacizumab in the model for the patient population with sub-optimally debulked Stage IIIB/C and all Stage IV patients who would be treated with olaparib maintenance instead of bevacizumab. This analysis was not included in the resubmission base case but provided as a sensitivity analysis.
- Consideration of the impact of increased 2L therapies. This was not addressed by the resubmission. Costs associated with the use of 2L therapies remain identical to those considered in the November 2019 submission.
- A reduced price resulting in an ICER consistent with that accepted for olaparib in the 2L setting (\$55,000 to < \$75,000 per QALY). The proposed ex-manufacturer price of olaparib remained unchanged from the previous submission, however, the ICER in the resubmission base case was claimed to be less than \$55,000 to < \$75,000/QALY.

6.27 Overall, the ICER presented in the resubmission was higher (\$35,000 - < \$45,000/QALY) than in the original submission (\$35,000 - < \$45,000/QALY). Compared with the original submission, there was a decrease in the incremental QALYs gained (6.8%), and an increase in the incremental costs (6.3%):

- The reduction in the incremental QALYs gained from the original submission was in part due to a changes in the transition probabilities between PFS2 and OS (based on Study 19 rather than AOCS data), and a reduction in the modelled difference between the PFS1 curves (based on a mixed cure model rather than standard parametric functions alone). The increased utility values for the PFS2 and progressed health states also reduced the incremental QALY gain.
- The increase in incremental costs was mostly driven by an increase in the modelled cost of 1L olaparib (\$25,000 - < \$35,000 vs \$15,000 - < \$25,000), which was partly mediated by an increase in cost-offsets associated with the use of 2L olaparib (\$5,000 to < \$15,000 vs \$5,000 to < \$15,000). These changes are due to the increased prevalence of gBRCAm (updated from 17% to 20.3%, based on PBAC advice).

6.28 The ESC noted that the difference in the model structure between the resubmission and the previous submission is the addition of a “cured” health state, which was based on the PBAC advice that the economic model should incorporate a proportion of patients cured in the 1L placebo group (para 7.20, olaparib PSD, November 2019 PBAC Meeting). The PSCR argued that the revised model structure allows the consideration of outcomes for cured and uncured patients separately, decreasing the uncertainty in the overall modelled OS gain. The ESC considered that the cure rates applied in the model were not adequately supported by the data provided, and may not be applicable to the patient population included in the model.

6.29 The key drivers of the model are summarised below.

**Table 8: Key drivers of the model**

Description	Method/Value	Impact
Extrapolation	OS curves are constructed from a combination of Kaplan Meier data from the SOLO1 trial for the first 41 months, and constructed survival curve of time from PFS2 to death, based on PFS and (adjusted) OS curves from Study 19.	High, favours olaparib
Utilities	Utility values for PFS2 and PD derived by weighting the utility value for patients not well enough to receive 2L olaparib maintenance from Havrilesky, and those who are healthy enough to receive 2L olaparib maintenance from Study 19. The PBAC previously advised to use utility values from Study 19 for these healthy states.	High, favours olaparib
Time horizon	20 years. The PBAC previously advised a 15 year time horizon.	Moderate, favours olaparib

Source: compiled during the evaluation based on data presented in Section 3.9 of the resubmission.

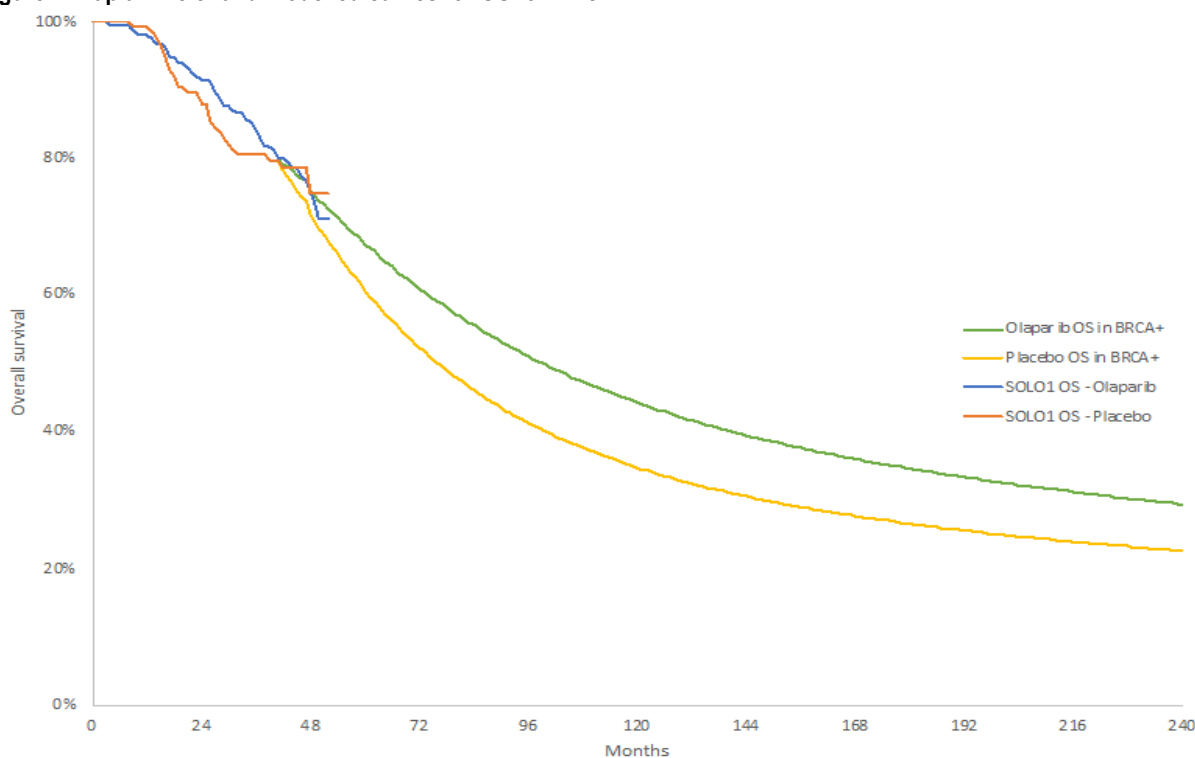
OS = overall survival; PFS2 = Progression-free survival following 2L platinum regimen; PD = progressive disease.

6.30 The ESC agreed with the evaluators that although the data informing the extrapolation of OS in the resubmission was different to that used in the previous submission (i.e. Study 19 rather than AOCS data), the approach was the same in that PFS2 continued

to directly predict OS. Hence the revised model again results in a substantial OS benefit (1.4 years undiscounted for BRCA+ patients) that is not supported by the clinical evidence available for SOLO1. The PBAC previously considered that the extrapolation of OS lacked plausibility, as the OS curves between the two arms diverge further after the trial median follow-up and do not converge within the modelled period, which was not supported by SOLO1 outcomes (para 7.17, olaparib PSD, November 2019 PBAC meeting). The PSCR argued that the lack of convergence within the time horizon reflects cured patients (for whom the curves would not be expected to converge) and that for uncured patients the curves do converge within 20 years (PSCR). The ESC agreed with the commentary that the PBAC’s previous concern regarding the extrapolated OS benefit of olaparib remained applicable to the revised model.

6.31 The modelled OS (including extrapolation) versus the trial data for BRCAm (cured and uncured) patients is presented below.

Figure 1: Kaplan-Meier and modelled curves for OS for BRCAm



Source Compiled during the evaluation based on information presented in Olaparib\_Economic Evaluation\_11032020 Final.xlsx  
 BRCA+ = BRCA1/2 mutation positive; OS = overall survival;

6.32 The results of the stepped analyses for the resubmission’s base case are presented in the table below.

**Table 9: Results of the stepped economic evaluation**

Data	Costs (discounted)			Health outcomes (discounted)			ICER
	Proposed scenario	Current scenario	Increment	Proposed scenario	Current scenario	Increment	
<b>Resubmission</b>							
Step 1 Setting: Trial setting (BRCAm+ only) Time horizon: 49 months <sup>a</sup>	██████	████	██████	3.06	1.82	1.24	\$██████ per PFY gained
Step 2 Setting: Proposed MBS and PBS populations Time horizon: 20 years <sup>b</sup>	██████	██████	██████	4.96	4.61	0.35	\$██████ per LY gained
BRCAm+ population only <sup>c</sup>	██████	██████	██████	7.69	6.84	0.85	\$██████ per LY gained
Step 3 Study evidence transformed from LY to QALY	██████	██████	██████	3.60	3.23	0.37	\$██████ per QALY gained
BRCAm+ population only <sup>c</sup>	██████	██████	██████	5.82	4.76	1.05	\$██████ per QALY gained
<b>November 2019 submission</b>							
Step 1 Setting: Trial setting (BRCAm+ only) Time horizon: 49 months <sup>a</sup>	██████	████	██████	2.81	1.76	1.05	\$██████ per PFY gained
Step 2 Setting: Proposed MBS and PBS populations Time horizon: 25 years <sup>b</sup>	██████	██████	██████	4.71	4.35	0.36	\$██████ per LY gained
Step 3 Study evidence transformed from LY to QALY	██████	██████	██████	3.10	2.70	0.39	\$██████ per QALY gained

Source: Table 48, Table 49 and Table 50, Section 3.A.8 of the resubmission. November 2019 values from Table 3-38, p301 of the submission; Table 3-40, Table 3-41 and Table 3-42, p303 of the submission; Table 3-43 and Table 3-44, p304 of the November 2019 submission.

Blue shading relates to values previously considered by PBAC.

<sup>a</sup> Costs included are those associated with *BRCA* testing, olaparib treatment in 1L for intervention and treatment associated adverse events. Costs and health outcomes presented are for true positives only.

<sup>b</sup> Costs and health outcomes in Step 2 and 3 are modelled for the patients entering the model and are aggregated across both modelled arms over the time horizon of 20 years (25 years in November 2019 submission). Costs included in the modelled analysis are those associated with *BRCA* testing, olaparib treatment, treatment associated adverse events, disease monitoring, disease progression, 2L platinum based chemotherapy and cost of palliative care.

<sup>c</sup> BRCAm true positives

BRCAm = germline *BRCA1/2* mutation positive; LY = life year; PFY = Progression-free years; QALY = quality-adjusted life year.

The redacted table shows ICERs in the range of \$35,000 - \$45,000 to \$75,000 to < \$95,000.

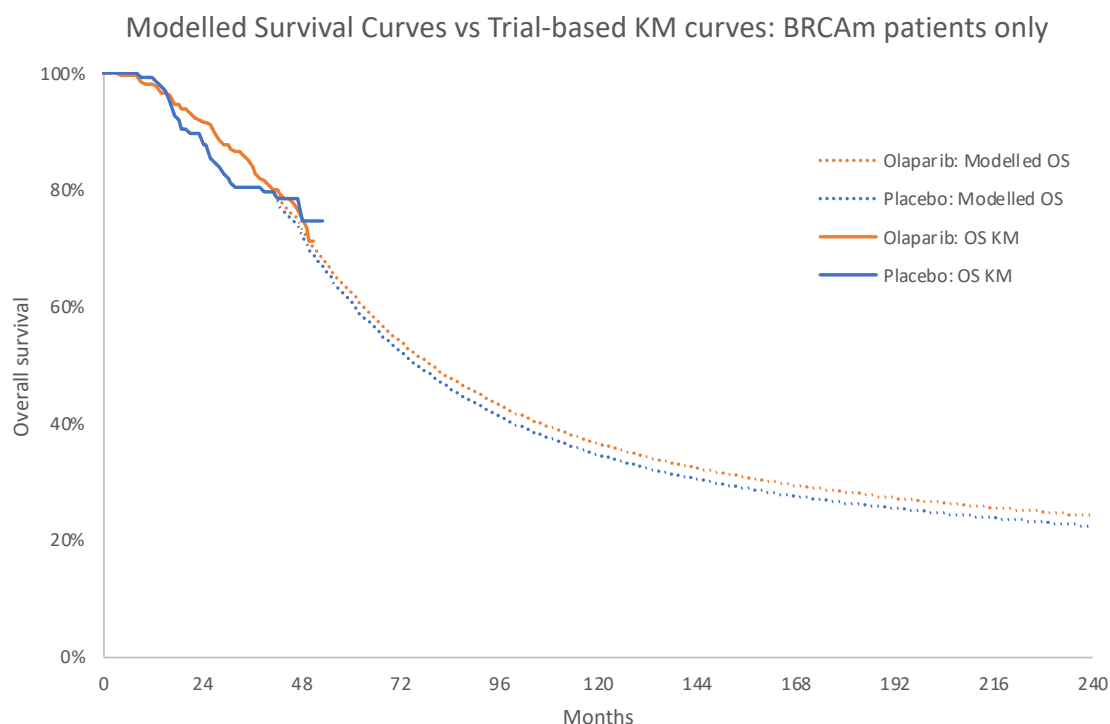
6.33 The PBAC previously considered that the extent of modelled OS benefit was implausibly optimistic. The extent of OS benefit modelled in the resubmission, although slightly smaller than the original submission, remained optimistic and highly uncertain, with 86% of the incremental QALYs generated in the extrapolated period (beyond 41 months). The PBAC previously considered that, although consistent with the evidence from the SOLO1 trial, the revised scenario that removed the OS benefit was overly conservative. The PBAC considered that it would be reasonable for the

model to include an OS benefit, consistent with that observed in Study 19, for the proportion of patients for whom it is reasonable to accept that olaparib would not have been given in the 2L setting (para 7.19, olaparib PSD, November 2019). This suggestion was not addressed in the resubmission. The ESC noted that the model presented in the resubmission did not differentiate between these two patient subgroups (1L placebo patients with and without 2L olaparib), and the complexity of the model structure meant that these changes could not be easily incorporated during evaluation. The PSCR argued that the OS gain generated for uncured patients in the model (HR = 0.87 at 20 years, 0.88 at 15 years) was more conservative than that proposed by the PBAC. The PSCR estimated the HR for the PBAC proposed approach to be 0.765 based on a HR of 0.52 for 49% of the patient population in which the comparison is 1L olaparib vs no olaparib, and a HR of 1 for 51% in which the comparison is 1L vs 2L olaparib.

6.34 The evaluation presented the results of two additional analyses given the absence of mature OS data:

- Option 1: Assuming no difference in OS benefit associated with olaparib 1L maintenance beyond the median follow up (41 months); and
- Option 2: Assuming a HR of 0.95 for OS would apply beyond the median follow up in SOLO1 (41 months) based on the point-estimate for the OS HR in SOLO1 (See Figure 2).

**Figure 2: Option 2: Including all changes requested by the PBAC, using OS KM from SOLO1 until median follow up (41 months) and assuming a difference (HR=0.95) in OS beyond median follow up.**



Source: Compiled during the evaluation based on information presented in 'Olaparib\_Economic evaluation\_11032020 Final.xlsx'

6.35 Both additional analyses conducted during the evaluation also included a number of changes as requested by the PBAC:

- Allowing use of olaparib in 2L setting for sBRCAm patients, consistent with the PBAC recommendation in March 2020 (7.12 Olaparib PSD, March 2020 PBAC Meeting);
- Assuming a time horizon of 15 years (para 7.25, olaparib PSD, November 2019 PBAC Meeting);
- Use of utility values for PFS2 and PD from Study 19 (para 7.25, olaparib PSD, November 2019 PBAC Meeting);
- Correcting the modelled costs of olaparib (para 7.25, olaparib PSD, November 2019 PBAC Meeting);
- Including bevacizumab as a comparator for the relevant subpopulation (para 7.25, olaparib PSD, November 2019 PBAC Meeting) (assumed in the resubmission to be 7% of patients).

Table 10: Options for a respecified base case

#	Parameter	Base case value	Value used in analysis	Incremental Costs	Incremental QALYs	ICER (\$/QALY)
	Resubmission base case			\$ [REDACTED]	0.365	\$ [REDACTED]
<b>Univariate Analyses</b>						
1	Availability of 2L treatment	Patients with sBRCA mutations not eligible for treatment with 2L olaparib	sBRCA patients eligible for 2L olaparib <sup>a</sup>	\$ [REDACTED]	0.27	\$ [REDACTED]
2	Time horizon	20 years	15 years <sup>b</sup>	\$ [REDACTED]	0.308	\$ [REDACTED]
3	Utilities	PFS2: 0.637 Progressive disease: 0.557 Weighted between Study 19, and Havrilesky et al, assuming 51% of patients would be healthy enough to receive 2L olaparib.	Utilities from Study 19: PFS2: 0.768 Progressive disease: 0.708 <sup>c</sup>	\$ [REDACTED]	0.310	\$ [REDACTED]
4	Cost of olaparib	Average daily dose of 1L treatment (558.8mg) from SOLO1 and 2L treatment (568.20mg) SOLO2 used to determine cost	No adjustment to cost to reflect same price for each tablet strength <sup>d</sup>	\$ [REDACTED]	0.365	\$ [REDACTED]
5	Bevacizumab use in comparator arm	Bevacizumab not included in BRCAm+ placebo patients	Bevacizumab included in BRCAm+ placebo patients (7%); <sup>e</sup>	\$ [REDACTED]	0.358	\$ [REDACTED]
6	OS Gain	Assumed surrogacy of PFS for OS	No OS benefit after median follow up (41 months)	\$ [REDACTED]	0.251	\$ [REDACTED]
7			Assume OS HR of 0.95 after median follow up (41 months)	\$ [REDACTED]	0.276	\$ [REDACTED]
8	Duration of 2L treatment	Final data cut for study 19 (21.52 months)	Truncated mean in SOLO2 (16.92 months)	\$ [REDACTED]	0.365	\$ [REDACTED]
			16.3 months as per Nov 2016 submission	\$ [REDACTED]	0.365	\$ [REDACTED]

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#	Parameter	Base case value	Value used in analysis	Incremental Costs	Incremental QALYs	ICER (\$/QALY)
<b>Multivariate Analyses</b>						
9	Option 1: #1 to #6 Includes changes requested by the PBAC, and no difference in OS beyond median follow up.			\$ [REDACTED]	0.046	\$ [REDACTED]
10	Option 2a: #1 to #5 and #7 (15 year time horizon) Option 2b: as above, 20 year time horizon Includes all changes requested by the PBAC and a difference in OS assuming a HR of 0.95			\$ [REDACTED]	0.070	\$ [REDACTED]
				\$ [REDACTED]	0.081	\$ [REDACTED]
11	Option 3a: #1, #2, #4, #5, #7 (15 year time horizon) Option 3b: #1, #2, #4, #5, #7 (20 year time horizon) As per Option 2 but with resubmission base case utilities			\$ [REDACTED]	0.153	\$ [REDACTED]
				\$ [REDACTED]	0.172	\$ [REDACTED]

Source: Constructed during the evaluation based on information presented in 'Olaparib\_Economic evaluation\_11032020 Final.xlsx'

<sup>a</sup> Analysis conducted by setting the value in Cell C63 in 'Input Assumptions' worksheet equal to 26.3%, and the value in D63 in the 'input assumptions' worksheet to 0%.

<sup>b</sup> Cell E13 in 'Input Assumptions' set equal to 15.

<sup>c</sup> Cell B6 and C7 in 'Utilities' worksheet set to 0.768 and 0.708, respectively.

<sup>d</sup> Cell D13 and D14 in "resource inputs" worksheet set to '4'.

<sup>e</sup> Cell D209 in 'Input Assumptions worksheet set to "Yes". Impact limited to an adjustment on QALYs gained in the PFS1 health state (ie % reduction in time spent in PFS1). Submission estimated a 1.33% average improvement in PFS1-associated QALYs (calculation: (1- HRf or PFS in ICON7) \* proportion of patients to receive bevacizumab; (1-0.81)\*7%). This sensitivity analysis may not accurately reflect the true impact of including bevacizumab in the comparator arm for patients with sub-optimally debulked, but may be informative to the PBAC.

The redacted table shows ICERs in the range of \$35,000 - < \$45,000 to \$255,000 - < \$355,000.

6.36 Noting revision to both the OS gain and utility values, the ESC considered that Option 1 was unrealistically conservative, while Option 2 was hypothetical and relied on the point estimate of the OS HR in SOLO1 being the true benefit. The ESC noted that olaparib was recommended by NICE for inclusion in the Cancer Drugs Fund on the basis of the NHS England version of a Managed Access Program (MAP) in which the uncertainty related to modelling of OS is to be addressed through the collection of long-term OS data from SOLO1. The pre-PBAC response indicated that that the sponsor would be willing to enter a MAP.

6.37 The ESC noted that the ICER was sensitive to the utility values used when a smaller (or no) OS benefit for olaparib was assumed. The ESC noted that use of the Study 19 utility values resulted in a value of 0.71 for progressive disease which seemed high, and considered that the approach used in the resubmission where the Study 19 values were applied to the proportion of patients healthy enough to receive 2L olaparib maintenance may be reasonable. The ICER for the scenario with a survival gain based on a HR of 0.95 and the utility values from the resubmission (Option 3) was \$75,000 to < \$95,000 with a 15 year time horizon and \$75,000 to < \$95,000 with a 20 year time horizon.

6.38 The ESC noted that the assumed duration of 2L olaparib treatment (based on the final data cut for Study 19) was longer than that accepted by the PBAC in November 2016 based on an earlier analysis of Study 19 (paragraph 6.8, olaparib PSD, November 2016 PBAC meeting) (21.5 months vs 16.3 months). The ESC noted that the ICER was

somewhat sensitive to the 2L olaparib treatment duration, with the ICER increasing to \$45,000 to < \$55,000 per QALY when the duration accepted in November 2016 was used (Table 10).

6.39 The pre-PBAC response included an alternative model scenario which differed from the options presented in the ESC advice (see Table 10). The PBAC noted that compared with the base case scenario in the resubmission, the pre-PBAC scenario:

- accepted the inclusion of sBRCA patients in 2L and bevacizumab in the comparator arm;
- maintained use of the weighted utility values and 20 year time horizon (the ESC considered these assumptions may be reasonable);
- continued to use PFS2 as a surrogate for OS (the ESC considered this to be inappropriate noting it resulted in a large gain in OS);
- revised the approach for adjusting the cost of olaparib to account for treatment interruptions; and
- reduced the duration of 2L olaparib to be consistent with that included in the PBAC submission for the 2L listing of olaparib.

6.40 The ICER for the pre-PBAC scenario was \$55,000 - \$75,000/QALY. The PBAC considered the approach for estimating OS should be revised based on that presented in the evaluation using a HR of 0.95 and 2L olaparib use should be based on the final analysis of Study 19. The resulting ICER was \$55,000 - \$75,000/QALY.

**Table 11: Respecified base cases in ESC advice and pre-PBAC response**

Model parameter	ESC advice	Pre-PBAC revised scenario
sBRCA patients in 2L included	Yes	Yes <sup>a</sup>
Time horizon	15 <b>OR</b> 20 years	20 years
Utilities PFS2 and PD	Utilities from Study 19 (Options 1 and 2): PFS2=0.768; PD=0.708 <b>OR</b> Weighted Study 19 & Havrilesky 2009 (Option 3): PFS2=0.637; PD=0.557	Weighted Study 19 & Havrilesky 2009: PFS2=0.637; PD=0.557
Cost of olaparib	No adjustment to cost to reflect same price for each tablet strength	4.9 weeks treatment interruption approximated by setting zero cost for olaparib for cycle 1.
Bevacizumab (7%) included	Yes	Yes
OS	HR=1 (Option 1) <b>OR</b> HR=0.95 (Option 2 and 3) after median follow-up	Based on PFS, PFS2 from SOLO1
Duration of 2L treatment	Final data cut for Study 19 (21.52 months)	16.3 months as per Nov 2016 submission

<sup>a</sup> The pre-PBAC response revised scenario also incorporates the cost of downstream germline testing in both the proposed and comparator arms of the model given that the March 2020 PBAC recommendation assumes tumour testing occurs in the comparator arm

## Drug cost/patient/course

Table 12: Drug cost per patient

	Olaparib 1L			Olaparib 2L (as would be received in 51% of progressed patients in the 1L comparator population) <sup>a</sup>	
	1L olaparib SOLO1 dose and duration	Proposed drug Model	Proposed drug Financial estimates	Comparator Model	Comparator Financial estimates <sup>g</sup>
Mean dose (mg/day)	558.80	558.80 <sup>b</sup>	558.80	568.2 <sup>a</sup>	NR
Mean duration (months)	20.65	20.04 <sup>c</sup>	20.65 <sup>b</sup>	21.52 <sup>d</sup>	NR
Cost/patient/month Revised	NR	\$ [REDACTED] <sup>e</sup>	\$ [REDACTED] <sup>f</sup>	\$ [REDACTED] <sup>e</sup>	NR
Cost/patient/course Revised	NR	\$ [REDACTED] <sup>e</sup>	\$ [REDACTED] <sup>f</sup>	\$ [REDACTED] <sup>e</sup>	NR

Source: Compiled during the evaluation based on information presented in Section 3 and Section 4 of the resubmission.

<sup>a</sup> Mean dose of 2L olaparib was taken from SOLO1.

<sup>b</sup> Based on area under the (digitized) time to treatment discontinuation curve from SOLO1. Included approximately 10% of patients who had received treatment beyond 24 months.

<sup>c</sup> This includes the error where the economic model applied the time to treatment discontinuation Kaplan Meier curve from month 1, rather than the beginning of month 0.

<sup>d</sup> Mean duration in model based on area under the curve of the time to treatment discontinuation Kaplan Meier curve from Study 19. This is longer than the treatment duration for 2L olaparib accepted in the November 2016 submission (16.3 months, based on an earlier analysis of Study 19).

<sup>e</sup> Corrected to account for flat pricing across doses. The accepted cost for 2L olaparib was \$ [REDACTED], based on the shorter treatment duration.

<sup>f</sup> Corrected calculation for converting treatment months into the number of packs required is: # months x (365.25/12) / 28.

<sup>g</sup> The approach used does not identify the number of patients who receive olaparib in the 2L setting, but estimates the number of patient-years of 2L olaparib treatment that would be avoided per patient treated with 1L olaparib.

## Estimated PBS usage & financial implications

6.41 This resubmission was not considered by DUSC.

6.42 The key inputs for the updated financial estimates presented in the resubmission are summarised below.

**Table 13: Key inputs for the updated financial estimates in the resubmission**

Data	Values and source	Comment
<b>Eligible population</b>		
% patients who test positive for gBRCAm	20.3% Australian Ovarian Cancer Study	Based on PBAC advice (para 7.25, olaparib, PSD, November 2019 PBAC meeting), a prevalence of 20.3% for gBRCA was used in the resubmission.
<b>Utilisation and cost of olaparib in the 1L setting</b>		
Average duration of treatment (months) per patient	Yr 1:10.3 Yr 2: 8.2 Yr 3: 1.4 Yr 4: 0.6 Yr 5: 0.4 Yr 6: 0.0 Based on SOLO1 trial	The resubmission applied the Kaplan-Meier estimates for time to treatment discontinuation observed in the SOLO1 trial, which allowed treatment beyond 24 months for patients with residual disease who may have continued to receive benefit according to the investigator's discretion. The requested restriction specifies a maximum treatment duration of 24 months for patients in complete response who have not experienced relapsed disease. To calculate the duration of therapy for grandfathered patients, the resubmission assumed that all patients have been on treatment for 12 months and will receive a total of 8.2 months of PBS-subsidised olaparib treatment.
<b>Utilisation and cost of olaparib in the 2L setting</b>		
The number of patient-years on 2L treatment per patient in the current clinical practice for those who are eligible for 1L olaparib if it is listed	Yr 1: 0.1104 Yr 2: 0.2042 Yr 3: 0.1528 Yr 4: 0.1148 Yr 5: 0.0913 Yr 6: 0.0772 PFS in the placebo arm of SOLO1 (Kaplan Meier Data) multiplied by 51% (the proportion of patients who progressed in the placebo arm of SOLO1 and treated with 2L olaparib). Each cycle the proportion starting subsequent olaparib is multiplied by the Kaplan-Meier duration of olaparib from Study19 (2L). The resulting value above is the estimated number of patient-years on 2L treatment per patient (for those not receiving 1L maintenance treatment).	The PBAC previously considered that the proportion of patients who receive 2L olaparib in clinical practice may be higher than in the SOLO1 trial, and therefore cost-offsets from 2L olaparib may be underestimated (Para 7.23, olaparib PSD, November 2019 PBAC meeting).

Source: Constructed during the evaluation based on Section 4 of the resubmission.

- 6.43 As for the previous submission, the resubmission used an epidemiological approach to estimate the number of patients diagnosed with FIGO Stage III/IV ovarian, fallopian tube and primary peritoneal cancer.
- 6.44 The PBAC noted that the incidence of ovarian cancer was based on AIHW data and likely included tumour types other than epithelial tumours (e.g. germ cell tumours), which would account for around 16% of ovarian cancers<sup>4</sup>. The PBAC considered that the patient numbers should be revised to remove non-epithelial cancers.

<sup>4</sup> Australian Institute of Health and Welfare & National Breast and Ovarian Cancer Centre 2010. Ovarian cancer in Australia: an overview, 2010. Cancer series no. 52. Cat. no. CAN 48. Canberra: AIHW.

- 6.45 The PBAC noted that the estimated patient numbers were multiplied by a factor of 1.14 to include patients with primary peritoneal and fallopian tube cancer. The PBAC noted that this factor was not justified in the submission and considered that the AIHW data is likely to encompass primary peritoneal cancer and to some extent, fallopian tube cancer, as distinguishing between these subtypes is often not practical.
- 6.46 The assumed prevalence of BRCA mutations was increased to 26.3% (20.3% for gBRCAm and 6% for sBRCAm) in the resubmission from 22.6% (16.6% for gBRCAm and 6% for sBRCAm) in the previous submission. The prevalence of 20.3% for gBRCAm is consistent with the previous PBAC advice (para 7.25, olaparib PSD, November 2019 PBAC meeting). The PBAC considered that the prevalence of sBRCAm should be reduced to 5% consistent with the PBAC's advice at the March 2020 meeting (paragraph 7.9 olaparib PSD March 2020 PBAC meeting).
- 6.47 The resubmission estimated that 95% of eligible patients would undertake tumour BRCAm testing. During the evaluation, it was assumed that the remaining 5% of patients underwent a germline BRCAm test and the subsequently identified gBRCAm patients were included in the evaluation's re-analyses. The PBAC considered it was reasonable to assume that 5% of patients would not undergo testing where patients are elderly or frail and do not undergo surgery and commence platinum based chemotherapy.
- 6.48 The resubmission estimated the average duration of 1L olaparib maintenance based on the time to treatment discontinuation curve from SOLO1. The resubmission appeared to make an error in converting the number of packs required (28 day supply) to the average number of months of treatment in a calendar year (assuming an average of  $365.25/12 = 30.4$  days per month). The PBAC noted, as for the economic model, the cost of 1L olaparib should be reduced to account for treatment interruptions. Treatment interruptions were estimated to account for 1 month (1 model cycle, Table 11) out of a total of 21.5 months of treatment. Thus the prescription numbers have been reduced by 4.7%.
- 6.49 As in the November 2019 submission, the resubmission estimated the displacement of 2L olaparib using the PFS Kaplan-Meier estimates from the placebo arm in SOLO1 and assuming 51% of progressed patients on placebo would receive 2L olaparib maintenance. To estimate the treatment duration for 2L olaparib, the resubmission applied the time until discontinuation of 2L olaparib from Study 19. The resubmission stated that it was assumed that 12 packs were required per treatment year for 2L olaparib. The number of scripts required per patient year is actually 13.04 scripts ( $365.25 \text{ days} / 28 \text{ days per script}$ ). Further to this, the resubmission assumed that 3 scripts would also be required in the second year. This calculation was not explained by the resubmission and appeared incorrect.
- 6.50 The PBAC noted that for the calculation of the cost of 1L olaparib, and for the cost offsets associated with 2L olaparib, it was assumed that 75% of patients would be treated in year 1. The PBAC considered that the uptake rate should be reduced in

Year 1 to account for patients commencing treatment throughout the year and, on average, receiving a lower number of prescriptions per patient.

- 6.51 The number of grandfathered patients was estimated as <500 in the resubmission, compared with <500 in the previous submission. The ESC previously noted that the displacement of 2L olaparib did not account for grandfathered patients who would no longer access olaparib in the 2L setting (para 6.71, olaparib, PSD, November 2019 PBAC meeting). Grandfathered patients had been included in the estimated displacement of 2L olaparib in the resubmission.
- 6.52 The estimated use and financial implications are summarised below. The estimates presented in the resubmission have been adjusted as follows:
- Patient numbers revised to exclude non-epithelial ovarian cancers (16%) (paragraph 6.44);
  - 1.14 multiplication factor removed (paragraph 6.45);
  - The prevalence of somatic BRCAm reduced from 6% to 5% (paragraph 6.46);
  - Correction to the number of packs for 1L olaparib (paragraph 6.48);
  - Reduction in the number of prescription per patient for 1L olaparib to account for dose interruptions (paragraph 6.48);
  - Correction to the number of packs for 2L olaparib (paragraph 6.49);
  - Inclusion of the <500 grandfathered patients (not <500 germline patients) for the calculation of the 2L olaparib offsets.
- 6.53 The PBAC noted the resubmission's sensitivity analyses for the financial estimates included cost offsets for reduced bevacizumab use. As for the economic model this was based on use in 7% of patients. The PBAC considered it reasonable for offsets for the reduced use of bevacizumab to be included in the financial estimates, noting that the offset had been underestimated due to underestimating the proportion of patients treated with bevacizumab, and this was likely in the region of up to 40% of the total 1L patients.

**Table 14: Estimated use and financial implications (PBAC revised estimates)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated (resubmission estimates)	■ <sup>a</sup>	■	■	■	■	■
PBAC revised number of patients treated <sup>e</sup>	■	■	■	■	■	■
PBAC revised number of scripts <sup>b</sup>	■	■	■	■	■	■
<b>Estimated financial implications of 1L olaparib treatment</b>						
PBAC revised cost to PBS/RPBS less copayments (A)	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
<b>Estimated financial implications for offset 2L olaparib</b>						
PBAC revised cost to PBS/RPBS less copayments <sup>c,d</sup> (B)	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Net cost to MBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Net cost to PBS/RPBS/MBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
<b>Previous submission: November 2019</b>						
Net cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: Table 56, Table 59 and information presented in 'Olaparib\_Economic evaluation\_11032020 Final.xlsx'. Previous submission values from Table PBAC.15 6.05 olaparib PSD, November 2019 PBAC Meeting

<sup>a</sup> Figure also includes <500 grandfathered patients.

<sup>b</sup> Number of scripts based on TTD curve from SOLO1, which allowed treatment beyond 24 months which was permitted according to the protocol for patients with residual disease who may continue to receive benefit according to investigator's discretion. The resubmission appeared to make an error in converting the number of packs required (28 day supply) to the average number of months treatment in a calendar year (365.25/12= 30.4 days per month), this error has been corrected. The resubmission estimated that the average duration of therapy was 20.65 months, which would require 22.1 scripts. However, 22.44 scripts would actually be required for a treatment duration of 20.65 months. This included approximately 10% of patients who received treatment beyond 24 months. 1L script numbers reduced to account for treatment interruptions.

<sup>c</sup> The resubmission only accounted for 82 germline GF patients. Revised to include <500 GF patients.

<sup>d</sup> The resubmission stated that it was assumed that 12 packs were required per treatment per year. The number of scripts required per patient year is actually 13.04 scripts (365.25 days / 28 days per script). Further to this, the resubmission assumed that 3 scripts would also be required in the second year. This calculation was not explained by the resubmission and appeared incorrect.

<sup>e</sup> Patient numbers revised to exclude non-epithelial ovarian cancers (16%), 1.14 multiplication factor removed, 5% somatic BRCAm, 100% of patients treated in year 1 but 64% uptake).

6.54 The net cost to the PBS/RPBS of listing olaparib as 1L maintenance therapy was estimated to be approximately \$10 million to < \$20 million in Year 6, and a total of \$60 million to <\$70 million in the first 6 years of listing.

### Quality Use of Medicines

6.55 The resubmission noted duration of therapy (and stopping rules for patients in complete response) as a potential quality use of medicine issue.

### Financial Management – Risk Sharing Arrangements

6.56 The resubmission proposed that the existing Deed between the sponsor and the government for olaparib supply as a 2L maintenance therapy be amended to reflect

the increased supply of olaparib for 1L treatment. The PBAC considered that for the RSA to be effective offsets from reduced 2L use would need to be factored into calculation of the subsidisation caps. Neither the current subsidisation caps, nor the estimate of the revised subsidisation caps included in the resubmission take into consideration PBAC's recommendation to allow 2L olaparib treatment in patients with sBRCA mutations. The ESC considered that it may be reasonable to assume that, in time, all potential 2L patients will be treated in the 1L setting and therefore the current 2L caps should reduce to \$0.

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of olaparib for the treatment of high grade epithelial ovarian, fallopian tube and primary peritoneal cancers as maintenance following a partial or complete response to first line (1L) platinum-based chemotherapy in a patient with evidence of a BRCA1 or BRCA2 gene mutation (BRCAm) via germline or somatic testing. The PBAC was satisfied that 1L maintenance with olaparib provides, for some patients, a significant delay in the time to progression. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of olaparib would be acceptable if the ICER was less than \$55,000 - \$75,000/QALY for the revised economic model scenario as described in paragraph 7.17 below.
- 7.2 The PBAC recognised the clinical need for effective treatments for patients with ovarian cancer prior to disease relapse. The PBAC noted the input from patient support organisations (Ovarian Cancer Australia and Rare Cancers Australia) and consumers regarding the high risk of recurrence without olaparib maintenance and the associated anxiety and depression related to the fear of recurrence. The PBAC noted the strong support of the MOGA for the olaparib submission, and that the ESMO-MCBS score was upgraded to 4 on the basis of a PFS difference >10% at 2 years and a plateau of the PFS curve in the treatment arm.
- 7.3 The PBAC noted that in November 2019 MSAC recommended the MBS listing for tumour BRCA testing in patients treated with olaparib in the 2L setting but did not provide advice on BRCA testing for the 1L population. Although, the proposed MBS item descriptors for germline and tumour testing do not specify the line of olaparib therapy, the PBAC noted that the July 2020 MSAC meeting was scheduled to consider a streamlined co-dependent submission to ensure that these descriptors are appropriate for the 1L population, and to provide any advice on the consequential financial implications to the MBS.
- 7.4 The PBAC considered that the restriction should specify that treatment is for patients with stage III or IV epithelial ovarian cancer, consistent with the SOLO1 trial. The PBAC recommended new separate listings for 1L olaparib noting that combining the 1L and 2L olaparib listings would be complex due to the different dosing regimens for the two settings. The PBAC noted there would be flow-on changes for the 2L listings to ensure

that patients are not re-treated with olaparib following recurrence on 1L olaparib. The existing 2L listing is split into indications: “High grade serous ovarian cancer”, “High grade serous fallopian tube cancer” and “High grade serous primary peritoneal cancer”. The PBAC considered a combined indication appropriate for 1L and noted that the 2L listings could be similarly revised. As previously advised for the 2L olaparib listing, 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”.

- 7.5 The PBAC reaffirmed that watch and wait (placebo), followed by 2L platinum-based chemotherapy with olaparib maintenance, is the appropriate comparator, and that for the subgroup of patients with sub-optimally debulked Stage III ovarian cancer, bevacizumab is also an appropriate comparator (paragraph 5.5, olaparib PSD, November 2019 PBAC meeting).
- 7.6 The PBAC noted the key evidence to support the clinical claim (the SOLO1 trial) remained unchanged from the previous submission. The PBAC noted that updated 5-year PFS results were provided in the pre-PBAC response and that they were consistent with those presented in the resubmission with a hazard ratio of 0.33 (95% CI: 0.25, 0.43;  $p < 0.0001$ ) and a median difference of 42 months (56 months for olaparib vs 13.8 months for placebo). The OS data were the same as provided in the November 2019 submission with a median follow-up of 41 months. The OS data were immature (events in 21% of patients) and a difference across the treatment groups was not demonstrated (HR 0.95, 95% CI: 0.60, 1.53;  $p = 0.89$ ). The final analysis of the OS data is to be undertaken when 60% of death events have occurred and this is not expected until after 2023, and possibly not until 2027.
- 7.7 The PBAC reaffirmed that the claim of superior effectiveness for olaparib 1L maintenance compared with placebo followed by subsequent therapy (including olaparib 2L maintenance in patients who remain eligible) is reasonable based on the PFS results.
- 7.8 No new safety data were presented in the resubmission and the PBAC reaffirmed that the claim of inferior safety is reasonable. The PBAC noted that longer term follow-up data for the Phase III 2L olaparib trial (SOLO2) indicated that 8% of patients treated with 2L olaparib experienced MDS, compared with 1.2% of patients treated with 1L olaparib in SOLO1. The PBAC noted this may suggest that MDS becomes more prevalent the longer patients are treated with olaparib, and that ongoing monitoring of this potentially life-threatening adverse event is warranted.
- 7.9 The PBAC considered the resubmission’s claim of non-inferior quality of life for olaparib compared with placebo was not adequately supported by the evidence presented. The PBAC noted the Quality-adjusted PFS (QA-PFS) outcome was based on metrics that censored patients at progression, and hence did not provide an estimate of comparative quality of life across the arms over a similar time period. Regarding the

‘Time without symptoms or toxicity’ (TWiST) metric the PBAC noted this factored in only three symptoms (nausea, vomiting and fatigue), and hence did not accurately capture the adverse event profile of olaparib.

- 7.10 The PBAC noted the economic model included in the resubmission was revised to include a ‘cured’ health state, however PFS2 continued to be used as a direct predictor of OS and this resulted in a large increase in OS (a mean of 1.4 years in BRCAM patients) that was not supported by the SOLO1 results. The PBAC noted in the final analysis of SOLO2<sup>5</sup>, compared with placebo, 2L olaparib resulted in a 12.9 month increase in median OS (HR 0.74, 95% CI: 0.54, 1.00; p=0.0537) with 38% of patients in the placebo arm receiving subsequent PARP inhibitor therapy. The PBAC considered, as was observed with longer follow-up of the SOLO2 trial, that a difference in OS may be observed with 1L olaparib with more mature data, however currently the magnitude of any OS gain is highly uncertain.
- 7.11 The pre-PBAC response indicated that the sponsor would be willing to enter a MAP with reference to these planned analyses for the SOLO1 trial, however the PBAC did not recommend this, because the timing of the final OS analysis is event driven and the relevant data may not be available until 2027, which falls outside a reasonable timeframe for a MAP.
- 7.12 The PBAC noted the alternative approach to modelling OS in the evaluation in which the OS HR was applied directly beyond the median trial follow-up (41 months). Two scenarios were presented, one in which the point estimate for the OS HR from SOLO1 was applied (HR=0.95) and one in which no difference in OS was assumed (HR=1). The PBAC considered it reasonable to apply the point estimate from SOLO1 (HR=0.95), even though not statistically significant, given the large difference in PFS, and that the results from SOLO2 suggest a difference in OS may be observed with longer follow-up.
- 7.13 The PBAC agreed with ESC that the 20-year model time horizon was reasonable. The PBAC also agreed with ESC that use of the utility values for PFS2 and PD from Study 19 only for the proportion of patients considered fit for 2L olaparib to be reasonable.
- 7.14 The PBAC noted that the ESC modelled scenarios, and the scenario included in the pre-PBAC response, assumed 7% of patients in the comparator arm are treated with bevacizumab. The PBAC considered that a substantially higher proportion of patients would be treated with bevacizumab in clinical practice. However, the PBAC noted that the adjustments made to the model to capture the outcomes associated with bevacizumab treatment reduced the reliability of the ICER, and hence accepted the assumed low use of bevacizumab in the economic model.
- 7.15 The PBAC noted that the ESC modelled scenarios removed the resubmission’s adjustment to cost of 1L olaparib to account for dose reductions or treatment

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<sup>5</sup> Poveda, A. et al 2020 suppl.6002 *Journal of Clinical Oncology* 38, no. 15\_suppl (May 20, 2020) 6002-6002. DOI: 10.1200/JCO.2020.38.15\_

interruptions on the basis that the daily cost was the same regardless of dose. The pre-PBAC response argued that treatment interruptions were associated with a reduced cost and stated that the mean duration of treatment interruptions in SOLO1 was 4.9 weeks per patient. This was applied in the pre-PBAC model by removing the 1L olaparib drug cost for the first monthly cycle. The PBAC considered this adjustment to be reasonable and that an equivalent adjustment should be made for the calculation of the financial estimates.

- 7.16 The PBAC noted the duration of 2L olaparib in the pre-PBAC modelled scenario was 16.3 months, and although consistent with that assumed in the November 2016 submission for 2L olaparib (paragraph 6.8, olaparib PSD, November 2016 PBAC meeting), was substantially less than that based on the final analysis of Study 19 (21.5 months). The PBAC further noted that in SOLO2 patients remained on 2L olaparib for a longer duration than in Study 19 (65% versus 40% on treatment at year 1, 45% versus 24% at year 2, data sourced from the economic model). The PBAC considered that it was reasonable for the duration of 2L treatment in the economic model to be based on the final analysis of Study 19, as was done in the resubmission and the ESC modelled scenarios.
- 7.17 In summary, the PBAC considered the following model inputs applied in the pre-PBAC model to be reasonable: (a) 20 year time horizon (paragraph 7.13); (b) weighted utility values for PFS2 and PD based on those reported in Study 19 and Havrilesky 2009 (0.637 and 0.557, respectively, paragraph 7.13); (c) inclusion of bevacizumab as a comparator for 7% of patients (paragraph 7.14); and (d) adjustment to the cost of 1L olaparib to account for treatment interruptions (paragraph 7.15). However, the PBAC considered OS should be estimated using a HR of 0.95 (paragraph 7.12) and the duration of 2L olaparib should be based on the final analysis of Study 19 (paragraph 7.16). The resulting ICER was \$55,000 - \$75,000/QALY. The PBAC considered the cost-effectiveness of olaparib would be acceptable if the ICER was less than \$55,000 - \$75,000/QALY. The PBAC noted that this would need to be achieved through a 10% reduction in the treatment cost of olaparib for 1L treatment.
- 7.18 The PBAC considered that the number of patients estimated to receive 1L olaparib was overestimated and as outlined in paragraphs 6.44-6.52 the financial estimates should be revised as follows: (a) remove patients with non-epithelial cancers (16%); (b) remove the adjustment (1.14 multiplication factor) to account for patients with primary peritoneal and fallopian tube cancer; and (c) assume a prevalence of 5% for sBRCAm. The PBAC noted the number of prescriptions had been underestimated due to calculation errors, but this was partly countered by treatment interruptions not being accounted for (paragraph 7.15).
- 7.19 The PBAC noted the resubmission's sensitivity analyses for the financial estimates included cost offsets for reduced bevacizumab use. As for the economic model this was based on use in 7% of patients. The PBAC considered it reasonable for offsets for the reduced use of bevacizumab to be included in the financial estimates, noting that the offset had been underestimated due to underestimating the proportion of

patients treated with bevacizumab, and this was likely in the region of up to 40% of the total 1L patients.

- 7.20 The PBAC noted the resubmission proposed the current RSA for 2L olaparib be revised to include the use of olaparib as 1L. The PBAC considered that for the RSA to be effective, the combined caps for 1L and 2L olaparib would need to be based on the net effective increase in the cost of olaparib to the PBS due to the addition of 1L patients, and would be calculated as (i) the existing 2L caps, plus (ii) the effective total cost of 1L olaparib, minus (iii) the cost of reduced 2L olaparib use, taking into account the changes to the financial estimates modelling as described above, including paragraph 7.18. The PBAC considered that 6 years after listing 1L olaparib, it is likely that all patients would be treated with 1L olaparib and that it was unlikely that there would be a market for use of 2L olaparib.
- 7.21 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for first line olaparib maintenance:
- a) Treatment with olaparib is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies;
  - b) Treatment with olaparib is not expected to address a high and urgent unmet clinical need because other subsidised therapies (including olaparib in the second-line setting) are available;
  - 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.
- 7.22 The PBAC noted the flow-on restriction changes to olaparib second line.
- 7.23 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new PBS indication/listing as follows:

Name, restriction, manner of administration, form	Max packs	qty	Max (units)	qty	No. of repeats	Proprietary name and manufacturer
Olaparib, tablet, 150mg, 100mg INITIAL TREATMENT	2		112		2	LYNPARZA® AstraZeneca Pty Ltd
Olaparib, tablet, 150mg, 100mg CONTINUING TREATMENT	2		112		5	LYNPARZA® AstraZeneca Pty Ltd

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Category / Program	Section 85 – General Schedule
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Condition	High grade stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer
PBS Indication	High grade stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer
Treatment phase	Initial treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Electronic
Clinical criteria	The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation, AND Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition.
Prescriber Instructions	A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIC) or Response Evaluation in Solid Tumours (RECIST) guidelines. Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline or somatic testing for a BRCA1 or BRCA2 gene mutation.
Administrative Advice	Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8a.m. to 5p.m. EST Monday to Friday). Special Pricing Arrangements apply

Category / Program	Section 85 – General Schedule
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Condition	High grade stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer
PBS Indication	High grade stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer
Treatment phase	Continuing treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Electronic
Clinical criteria	Patient must have received previous PBS-subsidised treatment with this drug as first line maintenance therapy for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND Treatment must not exceed at a total of 24 months for patients in complete response
Administrative Advice	Special Pricing Arrangements apply

8.2 Amend existing listings with flow-on changes:

*Combine ovarian/fallopian/peritoneal treatment restriction into one:*

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**Restriction Summary 8131 / ToC: 8132: Authority Required**

<b>Category / Program:</b> Section 85 – General Schedule
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic
<b>Condition:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>PBS Indication:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>Treatment phase:</b> Initial treatment
<b>Clinical criteria:</b> The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation AND 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 the sole PBS-subsidised therapy for this condition AND The treatment must be maintenance therapy AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition
<b>Prescriber Instructions:</b> 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 (GCIC) or Response Evaluation in Solid Tumours (RECIST) guidelines Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline or somatic testing
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.  Special Pricing Arrangements apply

**Restriction Summary 8130 / ToC: 8169: Authority Required: Streamlined**

<b>Category / Program:</b> Section 85 – General Schedule
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Streamlined
<b>Condition:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>PBS Indication:</b> High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>Treatment phase:</b> Continuing treatment – <i>second line treatment</i>
<b>Clinical criteria:</b> Patient must have previously received PBS-subsidised treatment with this drug <i>as a second line therapy</i> for this condition AND Patient must have received at least two previous platinum-containing regimens

AND
The treatment must be the sole PBS-subsidised therapy for this condition
AND
The treatment must be maintenance therapy
AND
Patient must not have developed disease progression while receiving treatment with this drug for this condition
<b>Prescriber Instructions:</b> A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIC) or Response Evaluation in Solid Tumours (RECIST) guidelines.
<b>Administrative Advice:</b> Special Pricing Arrangements apply

***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.