6.05 OLAPARIB,

Tablet 150 mg, Tablet 100 mg, Lynparza®, AstraZeneca Pty Ltd.

1 Purpose of submission

1.1 An application has been made requesting MBS listing of germline *BRCA*m testing (Scenario 1) or tumour *BRCA*m testing (Scenario 2) for the evaluation of *BRCA* pathological or likely pathological variants (BRCAm), and PBS listing of olaparib following response to first-line platinum-based chemotherapy for the targeted treatment of advanced, high-grade epithelial ovarian cancer (HGEOC) with a somatic or germline *BRCA*m.

1.2 This is the first submission to the PBAC for the use of olaparib for this indication. Olaparib is currently listed for the treatment of HGEOC following response to a second platinum-based regimen in patients who are g*BRCA*m-positive. At the time of the previous submission, the targeting of patients with a *BRCA*m resulted in a co-dependent process. The MSAC recommended listing of a MBS item number for germline *BRCA*m testing to permit the identification of patients who would be eligible for olaparib, but did not recommend the listing of tumour *BRCA*m testing (Public Summary Document (PSD) for MSAC 1380; MSAC meeting, November 2016).

1.3 Germline *BRCA*m testing is currently listed on the MBS (MBS item 73296). HGEOC patients are eligible for reimbursement using this test at diagnosis. Tumour *BRCA*m testing is not currently MBS listed, however it is available privately in Australia. Tumour *BRCA*m testing identifies patients with both germline and somatic *BRCA*m. The submission proposed that tumour *BRCA*m testing should be available to increase the number of patients identified who are likely to respond to a PARP inhibitor.

1.4 The submission to the PBAC was lodged prior to the TGA decision for first-line olaparib, and it was unknown whether the TGA would approve olaparib for use in both s*BRCA*m and g*BRCA*m or only g*BRCA*m patients. An alternative proposed listing (Scenario 1), which included only germline *BRCA*m testing, was provided in the submission as this would be the appropriate population should the TGA limit the approved indication to g*BRCA*m. The TGA approved indication became available during the evaluation and included both s*BRCA*m and g*BRCA*m. Scenario 1 has minimal testing implications and represents primarily a movement of olaparib for patients with g*BRCA*m from a second-line to a first-line setting.

1.5 The Economics Sub-Committee (ESC) noted that following the TGA approval of olaparib in patients with either s*BRCA*m or g*BRCA*m, scenario 2 may be more relevant,

however, in the event that the MSAC does not recommend tumour testing for *BRCA*m, scenario 1 would be more relevant.

1.6 The submission requested a listing for olaparib and relevant *BRCA*m testing on a cost-effectiveness basis compared with current practice.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description	
	Scenario 1 (g*BRCA*m only)	**Scenario 2 (g*BRCA*m and s*BRCA*m)**
Test Population	Test: patients newly diagnosed with advanced (FIGO stage III-IV) high grade epithelial ovarian, fallopian tube and primary peritoneal cancer The PICO population also included patients who had prior germline BRCAm testing but a negative test result (either at diagnosis or from previous familial cascade testing); these patients were not considered in the submission. These patients may or may not have received tumour BRCAm testing in scenario 2 to identify a sBRCAm.	
Treatment Population	Patients who test positive for a **germline** *BRCA*m and who are in partial or complete response to platinum-based chemotherapy.	Patients whose **tumour** tissue tests positive for a *BRCA*m and who are in partial or complete response to platinum-based chemotherapy.
Intervention	Test: Blood test to determine g*BRCA*m status. Medicine: 1. If g*BRCA*m positive, receive olaparib. 2. If s*BRCA*m, *BRCA*wt or unknown, watch and wait.	Test: Tumour *BRCA*m test on fresh-frozen or FFPE tumour tissue Medicine: 1. If *BRCA*m positive, receive olaparib. 2. If *BRCA*wt or unknown, watch and wait.
Comparator	Test: no change Medicine: Watch and wait following platinum-based chemotherapy, followed by second-line chemotherapy at relapse and maintenance olaparib.	Test: germline *BRCA*m testing Medicine: 1. For patients identified with gBRCAm, comparator is watch and wait, followed by second-line platinum chemotherapy at relapse and olaparib maintenance. 2. For patients without gBRCAm (i.e. possibly sBRCAm, BRCAwt or unknown), comparator is watch and wait, followed by platinum chemotherapy at relapse.
Outcomes	The submission has considered most outcomes related to the test except for the safety of the test; main outcomes considered were sensitivity, specificity and concordance. The submission has selected the following patient relevant outcomes: Overall survival, quality of life and safety. The submission has also nominated progression-free survival, second progression-free survival (time from randomisation to second progression) and time to subsequent therapy as relevant outcomes.	
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 maintenance therapy is superior to placebo (watch and wait) in terms of efficacy and non-inferior in terms of safety and quality of life.	

*BRCA*m = breast cancer gene 1 and 2 pathological or likely pathological variant; *BRCA*wt = *BRCA* wild type; FIGO = Federation of Gynaecology and Obstetrics; FFPE = formalin-fixed paraffin-embedded; g*BRCA*m = germline *BRCA* pathological or likely pathological variant; HGEOC = high grade epithelial ovarian, fallopian tube and primary peritoneal cancer; PICO = population, intervention, comparator, outcomes; s*BRCA*m = somatic *BRCA* pathological or likely pathological variant
Source: Table 1-4 of the submission

1.7 In Scenario 1, germline *BRCA*m testing was proposed to occur at diagnosis of HGEOC. While the sponsor requested a change to an existing MBS item number (currently used to inform access to second-line olaparib) to permit earlier testing, the timing and nature of the testing proposed in Scenario 1 does not represent a large departure from current clinical practice. The submission estimated that 70% of patients with a diagnosis of HGEOC would receive germline testing at baseline as they would be eligible for MBS item number 73296 (that requires a patient to have a 10% or greater risk of a gBRCAm detected). The Pre-Sub-Committee Response (PSCR) noted that although all patients with HGEOC have a greater than 10% risk as soon as they are diagnosed with HGEOC, the Manchester Scoring system does not reflect this for patients aged 60 years and over at diagnosis. The Sponsor's suggested amendment to MBS item 73295 would enable patients aged 60 years and over to access testing if the diagnosis of HGEOC alone is considered insufficient for having a greater than 10% risk. The PBAC considered that almost all patients would currently be tested for *BRCA*m at diagnosis.

1.8 In Scenario 2, tumour *BRCA*m testing was proposed to occur at diagnosis of HGEOC, when a biopsy or surgically excised tissue is available. In patients with inadequate tissue, or for whom tumour testing is not feasible, a germline *BRCA*m test was requested. Patients diagnosed with *BRCA*m on tumour testing will require a subsequent germline *BRCA*m test to differentiate between somatic and germline tumours, and to inform the utility of subsequent family cascade testing. As most patients with a diagnosis of HGEOC would likely be offered a germline *BRCA*m test, the timing of the tumour test will not represent a large change to current clinical practice.

1.9 In both Scenario 1 and Scenario 2, olaparib was proposed to be used in the maintenance setting following response to first-line platinum-based chemotherapy for patients with g*BRCA*m (Scenario 1) or both germline and somatic *BRCA*m (Scenario 2).

1.10 The submission stated that olaparib used in the first-line maintenance setting will not replace any currently subsidised medicine. However, the proposed use of olaparib will be partially offset by a reduction in the currently subsidised use of olaparib in the second-line maintenance setting (for the proportion of patients who progress after first-line treatment and remain eligible to receive it).

1.11 The commentary noted that if the Committees decide against recommending the listing of olaparib for the first-line maintenance setting, the Committees may still decide to support making tumour testing for *BRCA*m available on the MBS and broaden the existing second-line olaparib listing to include s*BRCA*m. This would result in patients with somatic *BRCA* mutations being able to access olaparib in the second-line setting.

2 Requested listing

Proposed PBS Listing

2.1 Suggested additions are in italics and deletions are in strikethrough. The requested PBS restriction has been updated to conform to the electronic requirement for listings.

Name, restriction, manner of administration, form	Max qty packs	Max qty (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Olaparib, tablet, 150mg, 100mg INITIAL TREATMENT	2	112	2	$6961.05 (published) $[redacted] *(effective)*	LYNPARZA® AstraZeneca Pty Ltd
Olaparib, tablet, 150mg, 100mg CONTINUING TREATMENT	2	112	~~6~~ *5*	$6961.05 (published) $[redacted] *(effective)*	LYNPARZA® AstraZeneca Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
~~**Severity:**~~	~~Advanced (FIGO Stage III-IV)~~
Condition:	High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
PBS Indication:	~~Advanced (FIGO Stage III-IV) ovarian cancer~~ high grade epithelial ovarian, fallopian tube or primary peritoneal cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Streamlined
Clinical criteria:	*The condition must be a germline (or somatic) class 4 or 5 BRCA1 or BRCA2 gene mutation,* AND The condition must be platinum sensitive, AND Patient must have received 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
Population criteria:	~~Patient must have evidence of a germline (or somatic) class 4 or 5 BRCA1 or BRCA 2 gene mutation~~

Prescriber Instructions:	*Platinum sensitivity is defined as disease progression greater than 6 months after completion of the penultimate platinum regimen.* *A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.* *Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing.*
Administrative Advice:	*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 8 a.m. to 5 p.m. EST Monday to Friday).* *Special Pricing Arrangements apply.*

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Advanced (FIGO Stage III-IV)
Condition:	High grade epithelial ovarian, fallopian tube or primary peritoneal cancer
PBS Indication:	Advanced (FIGO Stage III-IV) high grade epithelial ovarian
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Clinical criteria:	Patient must have previously received 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 ~~progressive disease~~ *developed disease progression while receiving treatment with this drug for this condition* AND Treatment must not exceed a total of 24 months for patients in complete response
Prescriber instructions:	*A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.*
Administrative Advice:	*Special Pricing Arrangements apply.*

2.2 The sponsor proposed a special pricing arrangement to permit a published price that is [redacted]% higher than the effective price. The requested effective price was the same as the current effective price in the second-line setting.

2.3 The initial treatment restriction proposed 2 repeats, which would be sufficient for 3 months treatment. The body of the submission requested 6 repeats for the continuing restriction, however the executive summary proposed 5 repeats. Five repeats is consistent with the existing listing for olaparib, and is sufficient for 6 months

treatment. Patients who are in complete response may receive up to 24 months (108 weeks) of treatment, which would require 1 initial script and 4 continuing scripts.

2.4 The restriction does not exclude patients who have used bevacizumab as part of their platinum-based chemotherapy. Prior bevacizumab was not permitted in the key trial. Under the current PBS listing patients may be treated with bevacizumab for up to 18 cycles, including initial concurrent treatment with chemotherapy (usually six cycles). The PBAC considered that concurrent treatment with olaparib and bevacizumab would not be appropriate without supporting evidence, and the additional restriction "Must not be used concurrently with bevacizumab" would be appropriate. The PBAC considered that the restriction should not explicitly prohibit patients who have received prior concurrent use of chemotherapy and bevacizumab, as patients eligible for bevacizumab who respond to platinum-based therapy may still benefit from olaparib maintenance treatment.

2.5 The FIGO stage is not specified in the second-line olaparib listings, for which the indications are "High grade serous ovarian cancer", "High grade serous fallopian tube cancer" and "High grade serous primary peritoneal cancer". The listings for second-line olaparib were split into these three separate indications; the same approach may be needed for the proposed listing. The PBAC considered these would be the appropriate indications for the proposed listing.

2.6 The existing olaparib listings have an Authority required (Telephone) restriction level for the initial and grandfathering listings and an Authority required (STREAMLINED) restriction level for the continuing listing. The submission proposed an Authority required (Telephone) restriction level for the initial and grandfathering listings and Authority required (Telephone) or (STREAMLINED) restriction level for the continuing restriction.

2.7 The proposed criteria allow patients who are not in complete response to continue olaparib treatment, although patients must not have progressive disease. Patients in complete response must not exceed a total of 24 months of treatment. This was consistent with the SOLO1 trial. The PBAC considered that this approach was appropriate for the first-line maintenance setting.

2.8 The submission stated that patients will only receive one course of treatment with olaparib as there is currently no evidence to support re-treatment with olaparib or another PARP inhibitor. There are currently no other PARP inhibitors listed for ovarian cancer. The PBAC considered that a line-agnostic listing may be a reasonable approach to listings for olaparib in ovarian cancer, provided that the listing ensured a maximum 24 month treatment duration for patients in complete response and did not allow re-treatment with olaparib following relapse.

2.9 The sponsor requested a grandfather restriction for patients accessing olaparib under a compassionate access program, who meet the proposed criteria. These patients

would be eligible for treatment under the proposed initial treatment listing, therefore a separate grandfather listing is not required.

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

3 Background

Registration status

3.1 Olaparib received an ARTG listing effective 21 June 2019 for the following indication:

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

Previous PBAC consideration

3.2 The PBAC has not previously considered olaparib for the proposed indication.

3.3 Olaparib is currently available on the PBS for maintenance use by patients with g*BRCA*m-positive high-grade serous ovarian, fallopian tube and primary peritoneal cancer following response to a second regimen of platinum-based chemotherapy (ie. second-line maintenance).

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

4 Population and disease

4.1 Ovarian (including fallopian tube and primary peritoneal) cancer is projected to affect more than 1,600 patients in Australia in 2020. Most patients (70%) are diagnosed at an advanced (FIGO III/IV) stage[1] and an estimated 23-32% of those will harbour either a germline or somatic *BRCA*m[2].

4.2 Advanced ovarian cancer has a high mortality rate. Despite high rates of response to first-line platinum-based chemotherapy, the majority of patients with advanced

[1] Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012 Jul 20;30(21):2654-63.

[2] Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD, 2nd, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. Ibid. 2010 Aug J Clin Oncol 28(22): 3570-3576

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%.

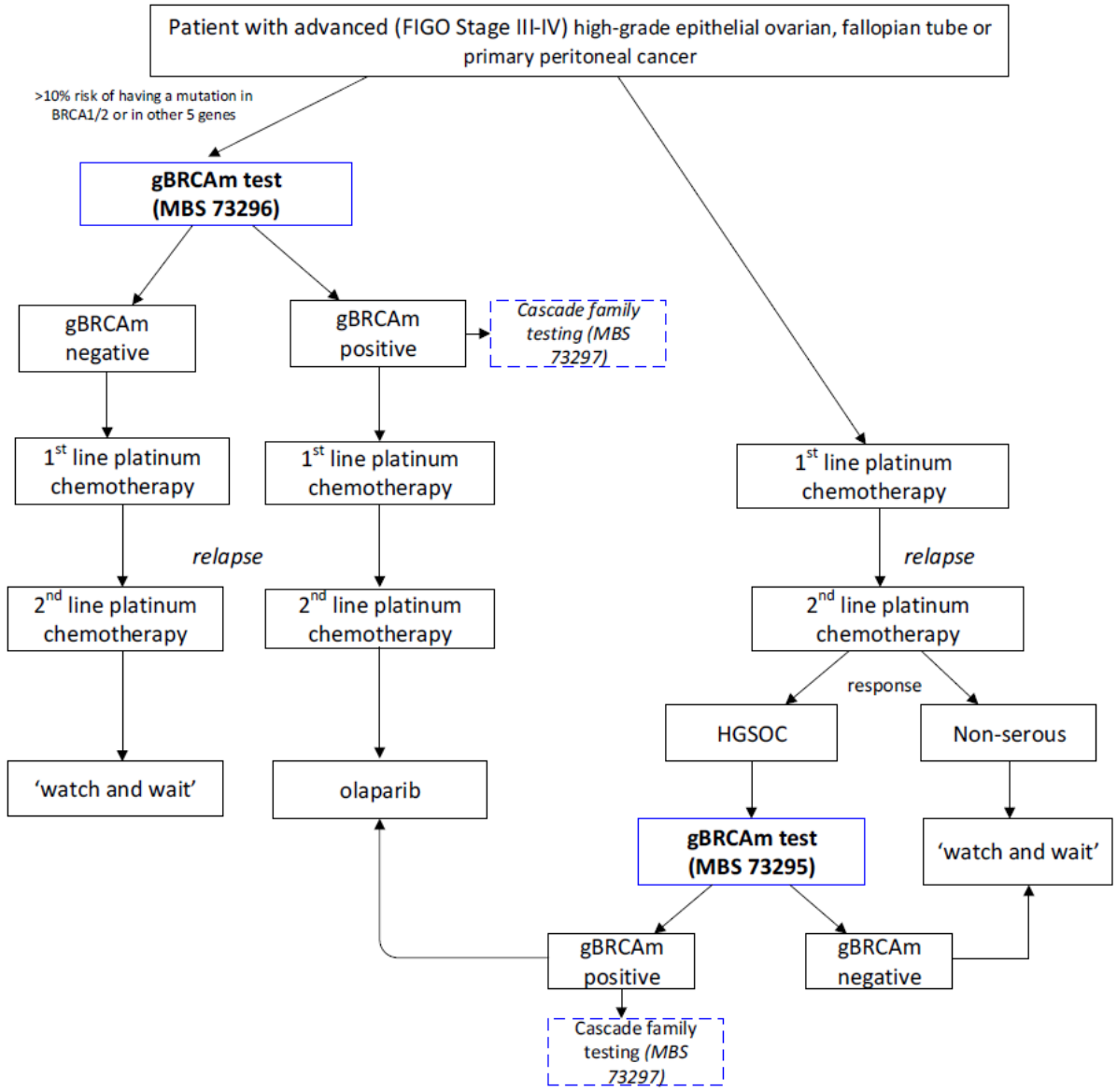
4.3 Olaparib is an orally active inhibitor of human poly ADP ribose polymerase enzymes (PARP inhibitor). PARP enzymes are required for the repair of single DNA strand breaks. Olaparib binds to PARP, preventing dissociation from the DNA and blocking repair. This leads to double strand breaks. In patients with deficient homologous recombination repair (HRR) pathways, such as patients with *BRCA*m, DNA double strand breaks cannot be repaired accurately or effectively. Accumulated genomic instability can lead to cell death.

4.4 The proposed use of olaparib in the current submission was as maintenance therapy following response to a first-line platinum-based chemotherapy regimen for patients with either germline or somatic *BRCA*m-positive tumours. To inform the use of olaparib for this indication, a tumour *BRCA*m test was proposed to occur at diagnosis.

4.5 The starting dose for olaparib is 300 mg bd, taken as two 150 mg tablets, twice daily. Olaparib is to be taken continuously until disease progression, or until 2 years if patients remain in complete response. There is no maximum treatment duration for patients with evidence of disease (partial response or stable disease) and treatment may be ongoing if, in the opinion of the treating physician, the patient may derive further benefit.

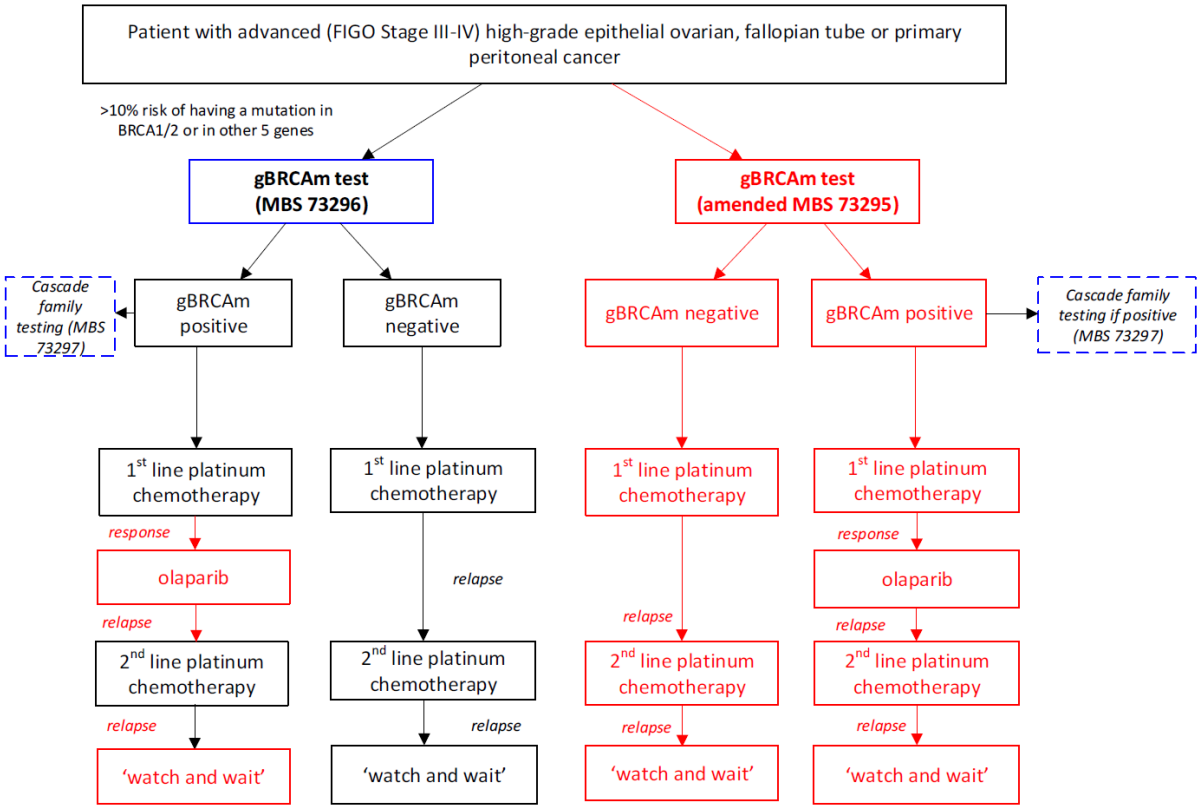
4.6 The current and proposed clinical management algorithms provided in the submission are shown below.

Figure 1: Current management for patient newly diagnosed with advanced (FIGO Stage III-IV) high grade epithelial ovarian cancer



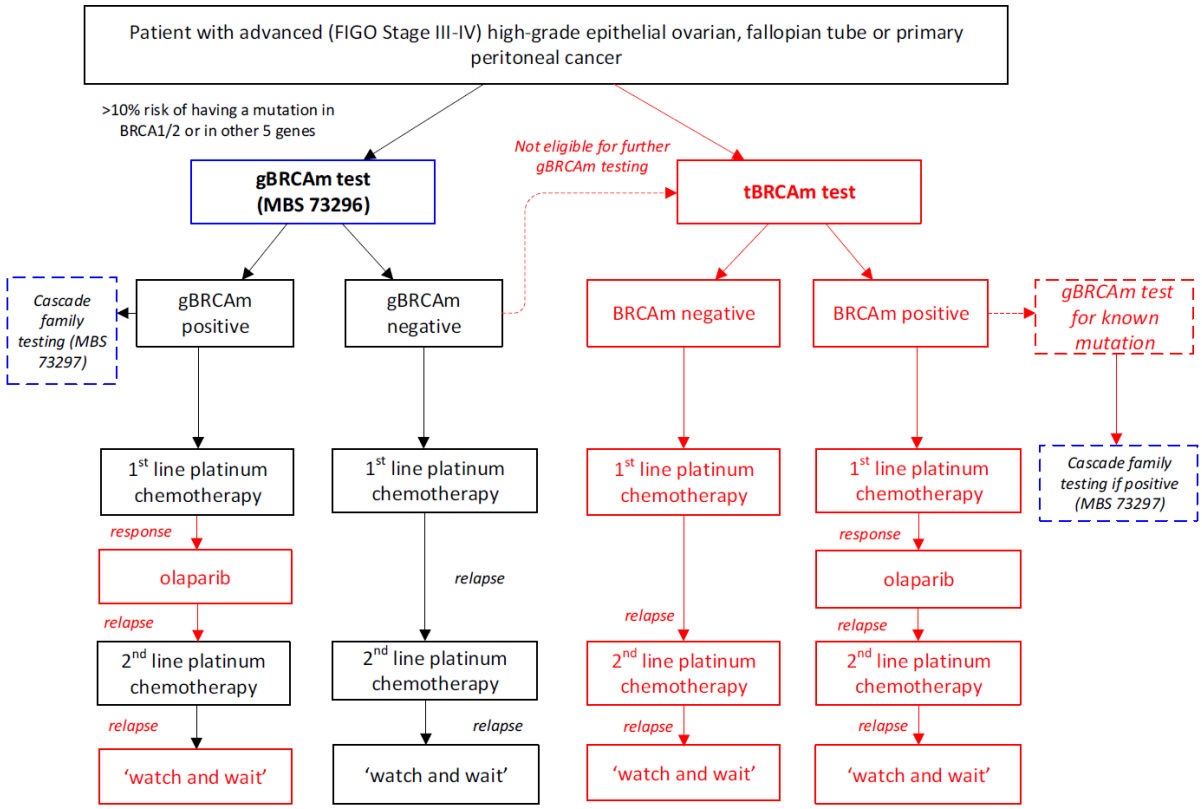
Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; gBRCAm = germline BRCA1 or BRCA2 mutation; HGSOC = high grade serous ovarian cancer

Figure 2: Scenario 1 proposed management including co-dependent test and medicine



Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; gBRCAm = germline BRCA1 or BRCA2 mutation

Figure 3: Scenario 2 proposed management including co-dependent test and medicine



Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; gBRCAm = germline BRCA1 or BRCA2 mutation

4.7 The ESC noted that the current algorithm presented in the submission (Figure 1) omitted the requirement for patients to respond to the immediately preceding platinum-based chemotherapy prior to receiving olaparib. For proposed scenario 1, the separate g*BRCA*m test (amended MBS 73295) pathway was not relevant for the majority of patients, who would be eligible for g*BRCA*m testing at diagnosis under MBS item 73296.

4.8 The ESC noted that the TGA has removed the requirement for presence of *BRCA*m for use of olaparib after 2nd line platinum chemotherapy, and anticipated that if the PBS listing was aligned in the future then all platinum-responding patients would be eligible for olaparib. However, the ESC noted that such a change would require PBAC consideration of a major submission for this broader indication. The ESC noted that the incremental effectiveness of second-line olaparib was reduced in *BRCA*wt patients compared to *BRCA*m patients, consequently a broader second-line PBS listing would increase the ICER/QALY for this additional population. As such, olaparib treatment in the broader second-line population may not be acceptably cost-effective under the current pricing arrangement.

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

5 Comparator

5.1 The proposed comparator in the submission was standard clinical practice. Currently, patients diagnosed with HGEOC will likely receive germline *BRCA*m testing. Following platinum-based chemotherapy, patients are monitored (watch and wait). In the event of progression or relapse, patients who remain suitable receive a second-line of platinum-based chemotherapy. Those patients who respond (either partial or complete response) and who are g*BRCA*m-positive are eligible for maintenance olaparib.

5.2 Patients who did not receive a germline *BRCA*m test at diagnosis receive a germline *BRCA*m test following response to the second-line platinum-based chemotherapy to establish eligibility for maintenance olaparib.

5.3 Patients who do not have a g*BRCA*m receive sequential regimens of platinum-based chemotherapy without second-line maintenance olaparib. This group includes patients who harbour a s*BRCA*m.

5.4 The PBAC considered the appropriate comparator is therefore watch and wait, followed by second-line platinum-based chemotherapy with olaparib maintenance in patients with g*BRCA*m; and watch and wait, followed by second-line platinum-based chemotherapy without olaparib maintenance in patients with s*BRCA*m without g*BRCA*m.

5.5 While bevacizumab is currently available for patients with sub-optimally debulked Stage III ovarian cancer, the submission stated that the populations currently treated

with bevacizumab are less likely to harbour a *BRCA*m, and are less likely to respond to platinum-based chemotherapy. The PBAC noted olaparib is an alternative to bevacizumab maintenance following first-line chemotherapy and bevacizumab. Although the extent to which olaparib would replace bevacizumab is unknown, the PBAC considered that bevacizumab is an appropriate comparator for the subgroup of patients with sub-optimally debulked Stage III ovarian cancer.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the results of the SOLO1 trial, noted that the prolonged PFS and time to next treatment demonstrated in this trial have the potential to make an important difference to patients in terms of quality of life, and anticipated that it was likely to result in survival benefit. The clinician noted that treatment of patients in the first-line setting is the only opportunity to cure patients, and noted changes to treatment approaches in other indications where maintenance treatment with curative intent is the preferred approach, such as immunotherapy for melanoma. The clinician answered questions regarding identification of the broader patient populations likely to benefit from olaparib treatment, and the duration of treatment considered appropriate for patients with complete or partial response, with a preference to focus on the germline and somatic BRCAm population at this time.

Consumer comments

6.2 The PBAC noted and welcomed input from a Consumer Hearing with Ovarian Cancer Australia in support of the olaparib submission, discussing the impact on patients of recurrence, patient interest in and understanding of treatments such as olaparib, and the benefits of first-line maintenance treatment.

6.3 The PBAC noted and welcomed input from patient support organisations Pink Hope, Ovarian Cancer Australia, Rare Cancers Australia and the Centre for Community-Driven Research in support of the olaparib submission. The comments described the benefit to patients of access to medicines that can give extended survival while maintaining quality of life. The comments 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. The comments also noted the impact of ovarian cancer on patients' ability to work. The comments noted that there have been few new treatments for ovarian cancer in the past 20-30 years, and that olaparib maintenance is an effective treatment and well-tolerated compared with chemotherapy.

6.4 The PBAC noted and welcomed input from nine consumers and one healthcare professional via the Consumer Comments facility on the PBS website. These comments noted their support for the olaparib submission, with several patients having participated in clinical trials of olaparib. Patients noted the severe impact of chemotherapy on their quality of life. Patients noted that olaparib had allowed them to live longer than expected, with an improved quality of life compared with chemotherapy. Patients noted that treatment in the first line setting may delay or prevent recurrence, and therefore avoid subsequent chemotherapy regimens and their toll on quality of life. Two of the nine patients noted that they were *BRCA*m negative and therefore had limited treatment options available. These patients suggested that olaparib should be made available to patients regardless of *BRCA* status.

6.5 The Medical Oncology Group of Australia (MOGA) also 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)[3], based on a comparison with placebo. The PBAC did not agree that this score should be updated from 3 to 4, as the PFS difference at 2 years was >10%, but was not convincingly associated with a plateau of the PFS curve in the olaparib arm.

Overview of the evidence base

6.6 The approach taken in the submission was to present evidence that supports the contention that targeting of patients with *BRCA*m (either somatic or germline) with first-line olaparib will result in improved clinical outcomes compared with current germline *BRCA* testing and the use of second-line olaparib in patients with g*BRCA*m.

[3] 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 2: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied
Accuracy and performance of the test (analytical validity)	Level III-2 diagnostic accuracy evidence: a comparison with reference standard that does not meet the criteria required for level II (blinded reference standard among consecutive patients) or level III-1 (blinded reference standard among non-consecutive patients)	☒ k=11, n=2,151
Prognostic evidence	Level I prognostic evidence: SR of level II evidence Level II prospective cohort study	☒ k=1 SR, n=18,396 k=2 cohort, n=702
Clinical utility of the test		
Predictive effect (treatment effect variation)	Four randomised, controlled trials comparing PARP inhibitor maintenance therapy to placebo in the second-line setting	☒ k=4, n=1,138
Change in management	Evidence to show that biomarker determination guides decisions about treatment with the medicine	☐ k=0, n=0
Treatment effect (enriched)	Single randomised controlled trial of olaparib vs placebo in patients that are test positive in both arms	☒ k=1, n=391

k=number of studies, n=number of patients.
Source: Constructed during evaluation

6.7 The submission included a single key trial of olaparib vs placebo in the proposed indication (first-line maintenance therapy of patients with *BRCA*m). The evidence presented in the submission to inform the linked evidence approach is presented in Table 3.

6.8 The submission did not include any direct comparison of olaparib vs placebo in the first-line maintenance setting for patients with s*BRCA*m. The submission presented an indirect comparison of the treatment effect of other PARP inhibitors in the second-line setting for germline vs somatic *BRCA*m, with placebo as a common reference arm.

6.9 The key trial, SOLO1, does not contain sufficient overall survival data to inform the economic model, and data from the Australian Ovarian Cancer Study (AOCS) were applied to the model to estimate incremental OS gains.

6.10 AOCS data were applied to the SOLO1 trial data to inform long term OS. The applicability of the AOCS cohort to that enrolled in the SOLO1 trial was poorly addressed in the submission and was unclear. The evaluation considered the applicability and method of use of the mortality rate associated with second progression derived from the AOCS cohort to the SOLO1 PFS2 curve was not adequately justified.

Table 3: Key data to inform comparisons

Proposed test vs no test	No evidence presented	
Proposed test vs alternative test	11 diagnostic accuracy studies	
	Olaparib maintenance therapy	**Placebo (watch and wait)**
Biomarker test positive	SOLO1	SOLO1
Biomarker test negative	No evidence presented	The Australian Ovarian Cancer Study Registry observational data

Source: Constructed during evaluation

6.11 The key comparative study in patients with identified g*BRCA*m has a low risk of bias. While the safety profile of olaparib may have unmasked some investigators to the allocation of their patients (given the comparator arm was placebo), based on a comparison with blinded assessment of progression events, unmasking does not appear to have affected the investigator assessment of PFS.

6.12 The ESC considered that the data supporting the efficacy of olaparib for patients with s*BRCA*m in the absence of g*BRCA*m was moderately uncertain, given that this population was not included in the key comparative study.

6.13 The ESC considered that the efficacy of maintenance PARP inhibitors in a broader population of first-line patients with *BRCA*wt tumours remained uncertain, but that the field was evolving rapidly, with relevant data from 3 studies – PAOLA-1[4] (olaparib + bevacizumab vs placebo + bevacizumab, PRIMA[5] (niraparib vs placebo), and VELIA[6] (veliparib vs placebo) – recently published or presented at the European Society of Medical Oncology Congress (Barcelona, September 2019). The ESC noted that all three clinical trials reported an improvement in progression-free survival for first-line patients regardless of tumour *BRCA* status, however subgroup analysis reported that olaparib was more effective for *BRCA*m than *BRCA*wt patients, and the benefit for *BRCA*wt patients was reported to be confined to tumours with evidence of homologous repair defects. The ESC therefore considered that any future broader 1st line TGA registration and PBS listing (regardless of *BRCA* status, compared to a *BRCA*m population) would reduce the incremental effectiveness of olaparib in the broader population, and increase the ICER/QALY at a given price. The Pre-PBAC response

[4] Ray-Coquard, I.L., Pautier, P. et al. Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019, mdz394.053, https://doi.org/10.1093/annonc/mdz394.053

[5] González-Martín A, Pothuri B et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019 Sep 28. doi: 10.1056/NEJMoa1910962

[6] Coleman RL, Fleming GF et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. *N Engl J Med.* 2019 Sep 28. doi: 10.1056/NEJMoa1909707.

indicated that the sponsor intends to submit data from the PAOLA-1 study to the PBAC as first-line treatment of advanced ovarian cancer in combination with bevacizumab.

Comparative effectiveness (based on linked evidence)

6.14 Details of the olaparib trial presented in the submission are provided in the table below.

Table 4: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial of olaparib vs placebo		
SOLO1 Moore et al 2018	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 First-line Platinum Based Chemotherapy.	23 August 2018.
	Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Banerjee S, Oza A, González-Martín A, Aghajanian C, Bradley W, Mathews C, Liu J, Lowe ES, Bloomfield R, DiSilvestro P. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.	Epub 2018 Oct 21.N Engl J Med. 2018 Dec 27;379(26):2495-2505. doi: 10.1056/NEJMoa1810858.
	Report describing diagnostic BRCA*m testing used in D0818C00001 (SOLO1)*	Undated

Source: Table 2-7, p78 of the submission

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Patient population	Outcomes	Use in modelled evaluation
Olaparib vs Placebo					
SOLO1	391	R, DB, MC Median 41 months follow up (DCO=17 May 2018)	HGEOC, g*BRCA*m-positive, responders to first-line platinum-based chemotherapy.	PFS, PFS2, OS, TFST, TSST, TDT, BoR, HRQoL, Safety	PFS (modelled and extrapolated), Time from 1st 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 submission.

6.15 A summary of the trial results, conditional on biomarker status, is provided in the table below.

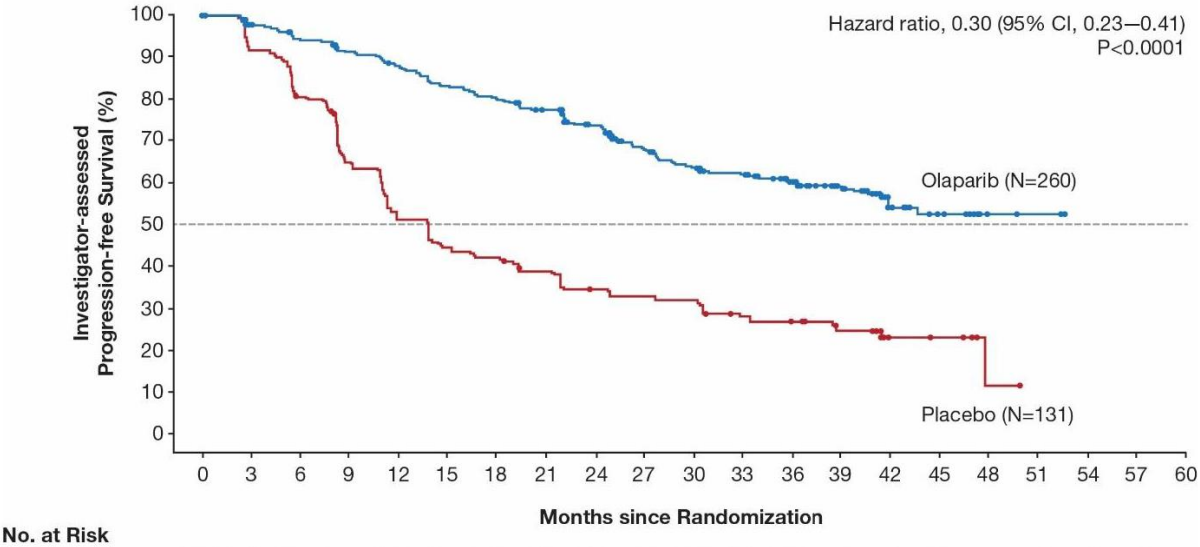
Table 6: SOLO1: PFS, PFS2 and OS results for g*BRCA*m[f] positive patients (ITT) treated with either olaparib or placebo (DCO 17 May 2018)

Endpoint	Olaparib	Placebo	HR (95% CI)[a]
PFS			
Events (progression or death) / N (%)	102/260 (39.2%)	96/131 (73.3%)	0.30 (0.23, 0.41)
Median (95% CI), months[b]	NR (-[d], NR)	13.8 (11.1, 18.2)	
% of patients event free by time point (95% CI)[b]			p<0.0001[e]
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)	
PFS2[c]			
Events (progression or death) / N (%)	69/260 (26.5%)	52/131 (39.7%)	0.50 (0.35, 0.72)
Median (95% CI), months[b]	NR (NR, NR)	41.9 (36.5, 47.9)	
% of patients event free by time point (95% CI)[b]			p=0.0002[e]
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)	
OS			
Events (death) / N (%)	55/260 (21.2%)	27/131 (20.6%)	0.95 (0.60, 1.53)
Median (95% CI), months[b]	NR (NR, NR)	NR (NR, NR)	
% of patients event free by time point (95% CI)[b]			p=0.8903[e]
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)	

[a]Estimated from a Cox proportional hazards model including best response to prior chemotherapy (stratification factor) as a covariate
[b]Calculated using Kaplan-Meier techniques
[c]Second progression-free survival is defined as time from randomisation until second progression
[d]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%.
[e]Determined using log-rank test (stratified by response to platinum based chemotherapy)
[f]SOLO1 contained two patients with somatic BRCA mutations
CI=confidence interval: N=total participants in group; NR=not reached; OS=overall survival; PFS=progression-free survival; PFS2=second progression-free survival.
Source: Table 11.2.1.2, Table 11.2.2.2, Table 11.2.3.2 of the SOLO1 CSR.

6.16 Time to progression was substantially longer in the olaparib arm compared with the placebo arm of the SOLO1 trial. The PFS benefit was consistent across pre-specified subgroups.

Figure 4 : Kaplan-Meier plot of PFS for olaparib vs placebo in the SOLO1 study – FAS (DCO 17 May 2018)



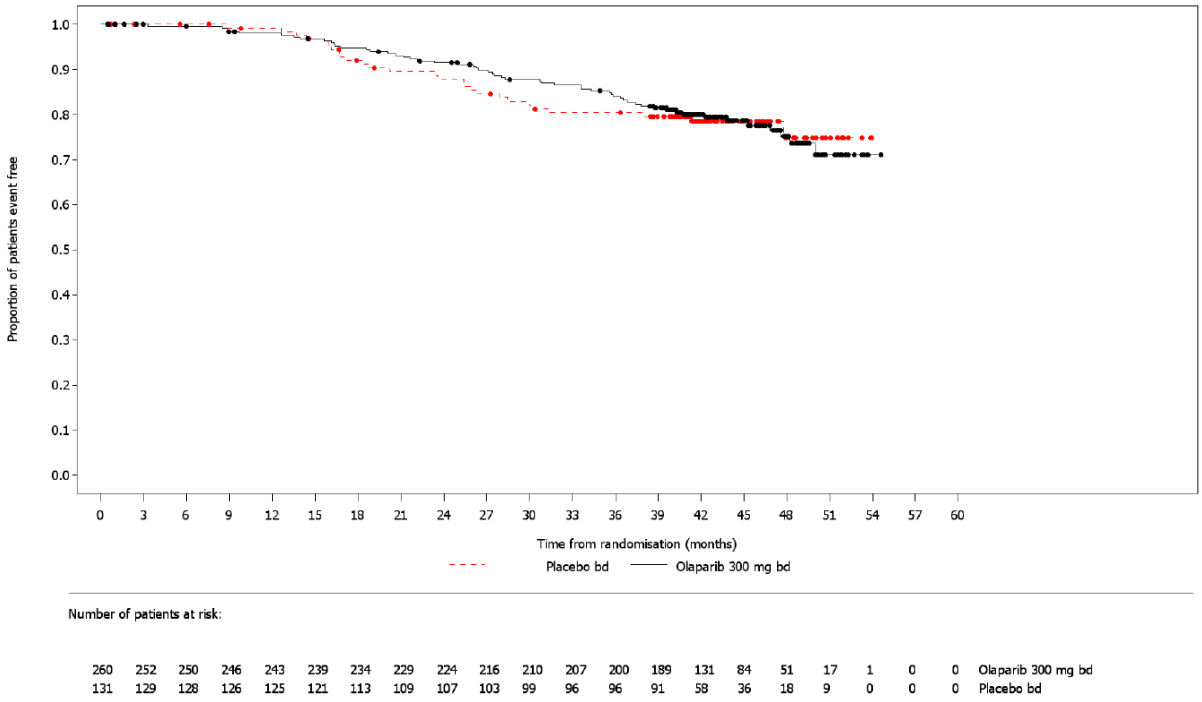
No. at Risk																					
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

DCO = data cut-off; FAS = full analysis set; PFS = progression-free survival.
Source: Figure 2-8, p101, of the submission.

6.17 Some of the gains in progression-free survival in the olaparib arm were subsequently lost in the analysis of time to second progression (indicating a shorter duration of response to subsequent therapies in the olaparib arm). The proportion of patients who respond to subsequent lines of therapy is lower in the olaparib arm compared with the placebo arm. Despite this, time to second progression remained longer in the olaparib arm than in the placebo arm.

6.18 There was no difference in overall survival across the arms. Overall survival remained immature at the data cut-off (17 May 2018) with only 21% of patients having experienced an event. Despite a small early separation in the Kaplan-Meier survival curves, by about 42 months the curves had converged. The data are reasonably mature up to the convergence, and more mature data are unlikely to change the Kaplan-Meier curve prior to this point; however the shape of the Kaplan-Meier curves following 42 months remains uncertain.

Figure 5: Kaplan-Meier plot of OS for olaparib vs placebo in the SOLO1 study – FAS (DCO 17 May 2018)



DCO = data cut-off; FAS = full analysis set; OS = overall survival
Source: Figure 2-13, p108, of the submission.

6.19 The overall survival data observed in the SOLO1 trial may not reflect the expected overall survival 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 at some point following progression (37% of the full ITT placebo population). The submission estimated that 40% of patients would be likely to undergo treatment with a PARP inhibitor as second-line maintenance in current clinical practice. The pre-PBAC response claimed that this was consistent with a recent analysis of second-line PARP inhibitor use (Poveda 2019, poster).
- 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 PBS restriction for second-line maintenance olaparib. Should sequential use of PARP inhibitors confer some benefit, overall survival in the olaparib arm may be higher in SOLO1 than in clinical practice.

6.20 The ESC noted that the proportion of patients who receive subsequent PARP inhibitors following progression on first-line treatments in the Australian setting is unknown, and considered that post-progression use of PARP inhibitors following olaparib treatment is unlikely to reflect clinical practice.

6.21 The SOLO1 study reported no clinically relevant difference in health related quality of life, as measured by the Trial Outcome Index (TOI) score, which is derived from a subset of questions from the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire. No responder analysis has been presented and it is unclear whether any patients, in either arm, experienced a clinically important reduction in TOI score throughout the study. Compliance rates were generally high, but may have been lower in the olaparib arm. Reasons for non-response were not provided.

6.22 The SOLO1 study included only 2 patients with s*BRCA*m. As the comparative treatment effect of olaparib vs placebo in patients with s*BRCA*m tumours cannot be determined from the SOLO1 study, the submission has presented the treatment effect of PARP inhibitors vs placebo in the second-line maintenance setting for patients who have g*BRCA*m and compared them with patients who have s*BRCA*m.

6.23 The pooled analysis of four studies (ARIEL3, NOVA, SOLO2 and Study 19) for PFS resulted in a hazard ratio of 0.27 (95% CI 0.22, 0.33) for PARP inhibitors versus placebo in patients with g*BRCA*m. In a second pooled analysis including 3 of the same studies (ARIEL3, NOVA and Study 19), the hazard ratio was 0.24 (95% CI 0.13, 0.46) for PARP inhibitors versus placebo in patients with s*BRCA*m.

6.24 Despite the key trial in the first-line maintenance setting (SOLO1) including only 2 patients with s*BRCA*m, the TGA, FDA and EMA have approved registration of olaparib for the proposed indication for both germline and somatic *BRCA*m. The TGA delegate's summary noted the deficiency of patients with somatic mutations in SOLO1 and reasoned that:

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

6.25 The ESC agreed with the commentary that the efficacy of olaparib for patients with sBRCAm in the absence of gBRCAm was moderately uncertain, given that this population was not included in the key comparative study.

6.26 The SOLO1 study does not contain *BRCA*wt patients. Therefore, a treatment effect variation (different treatment effects of olaparib by *BRCA*m status) cannot be derived from SOLO1. The clinical utility of either germline or tumour BRCAm testing in the first-line setting remains unknown, however, it may be reasonable to leverage evidence from the second-line maintenance setting. A statistical test for treatment effect variation by *BRCA*m status for PFS in the second-line setting was reported as significant (p=0.03) in the Olaparib PSD, March 2016. The ESC also noted results of related clinical trials in the first-line setting suggest that PARP inhibitors are less

effective for *BRCA*wt patients compared to BRCAm patients (refer paragraph 6.13 above).

Comparative harms

6.27 Olaparib was associated with a greater number of gastrointestinal and blood related adverse events than placebo. Adverse events of grade 3 or greater severity were relatively uncommon, with the exception of anaemia, which occurred in 21.2% of patients receiving olaparib, and 1.5% of patients receiving placebo. Anaemia uncommonly led to discontinuation, but was a common cause of dose interruption and dose reduction.

Table 7: Summary of adverse events for olaparib and PBO

	Olaparib 300 mg bd (N=260)		Placebo (N=130)	
MedDRA preferred term	**Number (%) of patients**		**Number (%) of patients**	
Patients with any AE	256 (98.5)		120 (92.3)	
Any AE of CTCAE Grade 3 or higher	102 (39.2)		24 (18.5)	
Any SAE	54 (20.8)		16 (12.3)	
Any AE leading to discontinuation	30 (11.5)		3 (2.3)	
Any AE leading to dose interruption	135 (51.9)		22 (16.9)	
Any AE leading to dose reduction	74 (28.5)		4 (3.1)	
	Number (%) of patients	**Event rate (per 1000 pt years)**	**Number (%) of patients**	**Event rate (per 1000 pt years)**
Nausea	201 (77.3)	1747.27	49 (37.7)	420.42
Fatigue	106 (40.8)	375.75	39 (30.0)	306.10
Vomiting	104 (40.0)	346.03	19 (14.6)	124.91
Anaemia	99 (38.1)	321.48	12 (9.2)	72.78
Dysgeusia	68 (26.2)	199.23	5 (3.8)	30.55
Asthenia	63 (24.2)	176.10	16 (12.3)	101.63
Neutropenia	41 (15.8)	104.13	9 (6.9)	54.89
Dyspnoea	39 (15.0)	95.57	7 (5.4)	41.63

AE = adverse event, CTCAE = common terminology criteria for adverse events, SAE = serious adverse events
Source: Table 39, p139, Olaparib CSR.

6.28 While dose interruptions were common (occurring in 51.9% of patients receiving olaparib compared with 16.9% of patients receiving placebo), interruptions were typically short.

6.29 The safety in SOLO1 does not capture adverse events associated with later-line treatments, which may be greater in the placebo arm. For instance, a proportion of

patients who progress in the placebo arm will be exposed to olaparib in the later-line setting.

6.30 Olaparib may be associated with myelodysplastic syndrome or acute myeloid leukaemia. As presented in the periodic benefit-risk evaluation report (8 February 2019), the cumulative incidence of MDS/AML in patients known to have been treated with olaparib is approximately 0.59%. The ESC noted that the PBAC previously advised that concerns regarding the long-term safety of olaparib in the context of MDS and AML were not sufficient to impede support for subsidising olaparib in the 2nd line setting, particularly given that MDS and AML are also recognised side effects of conventional chemotherapy (paragraph 7.4, olaparib PSD, March 2016).

Benefits and harms

6.31 A summary of the comparative benefits and harms for olaparib versus placebo is presented in the table below.

Table 8: 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 mo	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)	36 months: 3.5	0.95 (0.60, 1.53)
Harms						
Trial	**Average duration of treatment[b]**	**Olaparib n/N (%)**		**PBO n/N (%)**	**RR[a] (95% CI)**	**RD[a] (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)

[a] RR, RD and confidence intervals calculated during the evaluation.
[b]Total treatment duration (includes dose interruptions).
Abbreviations: HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; NR = Not Reported; SOC = system organ class.
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.

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

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

For every 100 patients treated with olaparib for 87 weeks in comparison to PBO 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).

6.33 The diagnostic accuracy of tumour *BRCA*m testing is very high and the proportion of patients who would be wrongly classified is likely to be negligible. However, if BRCAwt patients were treated with olaparib, the benefit remains unknown (benefits were less than observed in patients with BRCAm in the second-line setting). Additionally, patients would be exposed to the adverse events associated with olaparib.

Interpretation of clinical evidence

6.34 The clinical claim presented in the submission was that olaparib maintenance treatment following a response to platinum-based chemotherapy in a patient who tests positive for a *BRCA*m (germline or somatic) is superior in terms of efficacy, with a manageable safety and tolerability profile compared to placebo.

6.35 The clinical claim for superior effectiveness remains uncertain, but may be reasonable, based on time to progression. The ESC agreed with the commentary that the submission did not adequately address the patient relevance of this endpoint. Patients who progressed in SOLO1 did so radiologically rather than clinically, and therefore patients were likely to be without symptoms at the time of progression in SOLO1. The ESC considered that, at a median follow-up of 41 months, the increment in progression-free survival (HR 0.30 95%CI: 0.23, 0.41, p<0.0001, 39% difference in progression at 24 months) was statistically significant but of uncertain clinical importance, noting patients were likely to be without symptoms at the time of progression, and noting that this would be rated as grade of 3 on the ESMO-Magnitude of Clinical Benefit Scale version 1.1, where grades 4 and 5 represent the grades with substantial improvement. The ESC also noted that there was no clinically important difference in health-related quality of life between treatment arms.

6.36 Regarding the relevance to patients of progression-free survival, the ESC noted that the PSCR provided a supporting statement from the European Medical Agency, expert clinician advice and patient surveys arguing that PFS is considered to be of benefit to patients. The PSCR stated that on average the time to subsequent chemotherapy was extended from 13.8 months to 4 years. The PSCR also referenced unevaluated data reporting improvements in Quality Adjusted PFS, and time without symptoms of disease progression or toxicity (TWiST). The PBAC agreed with the ESC that these outcomes were of clinical importance.

6.37 The ESC agreed with the commentary that the clinical claim for superior effectiveness was not supported for overall survival, which appeared similar across the arms and was not mature. The ESC considered that the increment in overall survival was not statistically significant, and the presence of any benefit in overall survival was questionable (HR 0.95, 95%CI: 0.60, 1.53, p=0.89, 3.5% difference in deaths at 36 months).

6.38 In regard to lack of overall survival benefit, the ESC noted that the PSCR stated that it is unlikely final OS analyses will become available before late 2023, but that the demonstrated improvement in time to second progression or death (PFS2) and second subsequent therapy or death (TSST) support a future demonstrated survival benefit. The ESC considered that the presence and magnitude of any survival benefit remained highly uncertain. The Pre-PBAC response argued that advice from medical oncologists indicates that improvement in PFS will extend survival and potentially increase the rate of cure.

6.39 The ESC agreed with the commentary that safety was inferior for olaparib compared to placebo, and considered that increases in grade 3/4 gastrointestinal disorders, and increases in grade 3/4 anaemia (associated with increase in proportion of patients requiring blood transfusions from 2% to 23%) were both clinically important.

6.40 The ESC noted that the PBAC's recommendation for olaparib in the second-line setting was based on outcomes from Study 19. When compared to SOLO1 in the *BRCA*m subgroup, Study 19 demonstrated a more substantial improvement in progression-free survival (HR 0.18 95%CI: 0.11, 0.31), a more substantial but non-significant improvement in overall survival (unadjusted HR 0.73 95%CI: 0.45, 1.17), and a more substantial and statistically significant improvement in overall survival after taking into account cross-over in the placebo arm to olaparib as post-progression therapy (adjusted HR 0.52 95%CI: 0.28, 0.97) (PSD Olaparib March 2016 PBAC Meeting).

6.41 The PBAC considered that in patients with g*BRCA*m, the claim of superior comparative effectiveness for olaparib maintenance compared with placebo followed by second-line platinum-based chemotherapy with olaparib maintenance treatment was reasonable for PFS benefit, but was not adequately supported by the data for OS benefit. The PBAC considered the claim of superior comparative effectiveness for first-line olaparib maintenance treatment in patients who test positive for a s*BRCA*m was not supported by the direct trial data, and was somewhat uncertain.

6.42 The PBAC considered that the claim of inferior comparative safety was reasonable.

Claim of codependence

6.43 A treatment effect modification by *BRCA* status (pathological variant vs wild-type) for the use of olaparib in the second-line setting has been established. However, the clinical utility of the test (either g*BRCA*m or s*BRCA*m testing) remains uncertain. There is evidence of benefit of olaparib (vs placebo) in *BRCA*wt in the second-line setting.

There is currently no evidence for the use of olaparib in *BRCA*wt in the first-line setting. The ESC noted that the lack of evidence in *BRCA*wt patients in the first-line setting was a key omission in the claim of co-dependence. The ESC noted that if olaparib were PBS listed in *BRCA*m and *BRCA*wt patients the claim of co-dependence would not be required.

Economic analysis

6.44 The submission presented a modelled cost-utility analysis, using the randomised trial (SOLO1, which compared olaparib versus placebo (watch and wait), in a population of patients with newly diagnosed *BRCA1/2*-mutated advanced ovarian cancer who are in response (complete or partial) after first-line platinum-based chemotherapy). A summary of the structure and rationale for the economic model is presented in the table below.

6.45 The PBAC noted the unnecessary complexity of the model's structure, and suggested that a more usual partitioned survival analysis may have been a more transparent modelling approach.

Table 9: Summary of model structure and rationale

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis (base case) Cost-effectiveness analysis	This is appropriate.
Outcomes	Progression-free years gained, life-years gained, quality-adjusted life years gained	These are appropriate health outcomes for cost-effectiveness and cost-utility analyses.
Time horizon	25 years in the model base case (vs 41 months median follow-up in the SOLO1 trial)	25 years in the model base-case. The modelled difference in overall survival over the long time horizon is a key driver of the model, but this is unsupported by the trial evidence. The ESC agreed with the commentary that the modelled long-term difference in survival between arms is highly uncertain.
Methods used to generate results	Modified Markov A cohort analysis of partitioned survival (i.e. area under the curve) is also used to generate the results	The approach used is reasonable, but the ESC agreed with the commentary that this approach was unnecessarily complex compared to a routine partitioned survival analysis.
Health states	4 health states are modelled: Progression-free following 1st line platinum regimen (PFS1), Progression-free following 2nd line platinum regimen (PFS2), Progressive disease, and Death	The ESC agreed with the commentary that the health states modelled were reasonable. In this model, the two progression free states accommodate use of olaparib maintenance treatment either after 1st or 2nd line platinum therapy, in the intervention and comparator arms, respectively.

Component	Description	Justification/comments
Cycle length	30.4 days	This is appropriate.
Transition probabilities	Health state allocation over time is determined using area under the PFS1, PFS2 and OS curves in a partitioned survival model. PFS1 and "time from first progression to second-progression" curves are extrapolated from the Kaplan-Meier curves from SOLO1 in the BRCAm patients, and AOCS data in the BRCAwt patients. OS curves are taken directly from the Kaplan-Meier curves from SOLO1 up to 41 months followed by a monthly probability of death derived from AOCS registry data for BRCAm patients. PFS1, "time from first progression to second-progression" and "OS after second progression" for BRCAwt arms are derived from AOCS Kaplan-Meier curves. All curves are extrapolated using log-logistic or log-normal parametric survival functions.	The limitations in the available clinical trial evidence – particularly with respect to the immaturity of the data result in a highly uncertain model that relies heavily on extrapolation. In the case of overall survival beyond the immature trial data, rather than extrapolate from the OS data, the model uses the (predominantly extrapolated) PFS2 as a direct predictor of survival. The observed difference in PFS2 between the treatment arms therefore generates diverging OS curves between the treatment arms. This is highly favourable to olaparib and does not appear consistent with the limited clinical trial data on OS that is available but does not show divergence. Overall, there is substantial uncertainty around the partitioned survival estimates generated in the model.
Discounting	5% per annum for outcomes and costs	This is appropriate.
Software package	Microsoft Excel 2016	This is appropriate.

Source: Table 3–1, p217 of the submission.
AOCS = Australian Ovarian Cancer Study; *BRCA*m = *BRCA1/2* mutation positives; *BRCA*wt = *BRCA 1/2* wildtype; OS = overall survival; PFS = progression-free survival

6.46 The structure of the economic evaluation was adequate to convey and assess the claim of codependence, however there was inadequate clinical data in the appropriate setting to run an economic evaluation on an untested population.

6.47 The key drivers of the model were the extrapolated difference in OS and the utility value of PFS2, as per the table below. The ESC noted that the time horizon was also a key driver of the model.

Table 10: 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 monthly death rate (estimated from OS stratified by BRCAm status in AOCS) added equivalently to each arm of the PFS2 curve (after 41 months trial period), rather than an estimate or extrapolation of overall survival time from the randomisation (or the start of the model).	High, favours olaparib
Utilities	Relatively low values for PFS and PD modelled health states are used from Havrilesky et al (2009)[7] rather than more recent, applicable sources.	High, favours olaparib
Time horizon	25 years, long relative to other submissions in advanced ovarian cancer and relative to trial follow-up.	High, favours olaparib

OS = overall survival; PFS2 = progression-free survival after second-line therapy
Source: Compiled during the evaluation based on Section 3.9 of the submission

6.48 The results of the stepped analysis of the base case presented in the submission are presented in the table below.

[7] Havrilesky LJ, Broadwater G, Davis DM, Nolte KC, Barnett JC, Myers ER, et al. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. Gynecol Oncol 2009 May;113(2):216-20.

Table 11: Results of the stepped economic evaluation

Data	Costs (discounted)			Health outcomes (discounted)			ICER
	Proposed scenario	***Current scenario***	**Increment**	***Proposed scenario***	***Current scenario***	**Increment**	
Step 1 Setting: Trial setting (***BRCA*m+ only**) Time horizon: 49 months [a]	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per PFY gained**
Proposed scenario 1 (available to first-line *gBRCAm* patients only – 17% *BRCA*m positives)							
Step 2 Setting: Proposed MBS and PBS populations Time horizon: 25 years [b]	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per LY gained**
Step 3 Study evidence transformed from LY to QALY	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per QALY gained**
Proposed scenario 2 (available to all first-line *BRCAm* patients (g+s) – 23% *BRCA*m positives) – submission base case							
Step 2 Setting: Proposed MBS and PBS populations Time horizon: 25 years	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per LY gained**
Step 3 Study evidence transformed from LY to QALY	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per QALY gained**

[a] Costs included are those associated with *BRCA* testing, olaparib treatment in first-line for intervention and treatment associated adverse events. Costs and health outcomes presented are for true positives only.

[b] 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 25 years. Costs included in the modelled analysis are those associated with *BRCA* testing, olaparib treatment, treatment associated adverse events, disease monitoring, disease progression, second-line platinum based chemotherapy and cost of palliative care.g*BRCA*m = germline *BRCA1/2* mutation positive; g+s = germline and somatic; LY = life year; PFY = Progression-free years; QALY = quality-adjusted life year.

Source: 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 submission.

6.49 The results presented as Step 1 in the submission (see table above) are not strictly trial-based. These are modelled analysis results over the trial time horizon of 49 months for true BRCAm positive patients only. Only the OS KM is taken from the trial data, the PFS1 and PFS2 curves are based on modelled functions, not empirical data. Costs included are those associated with BRCA testing, olaparib treatment in first-line for intervention and treatment associated adverse events.

6.50 The modelled health outcomes (including extrapolations) versus trial data over the model time horizon for *BRCA*m are presented in Figure 6.

Figure 6: Kaplan-Meier and modelled curves for PFS1, PFS2 and OS for *BRCA*m

*BRCA*m = *BRCA1/2* mutation positive; KM = Kaplan-Meier; MT = Modelled traces; OS = overall survival; Olap = olaparib; PFS1 = progression-free survival after first-line; PFS2 = progression-free survival after second-line
Source: Constructed during the evaluation using Economic Evaluation.xlsx, Attachment 7.1

6.51 The ESC considered 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. The ESC noted that 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. The ESC noted that the model manufactured substantial survival gain (0.22 life years in scenario 1 and 0.36 life years in scenario 2) despite no survival benefit demonstrated in SOLO1. A survival benefit was not supported by the clinical data currently available due to its immaturity and the ESC agreed with the commentary that the extrapolation lacks plausibility. The pre-PBAC response argued that data from ovarian cancer patient registries show a very strong association between remaining disease-free for 5 years and long-term survival outcomes. The PBAC considered that it may be reasonable to expect that an OS benefit would be achieved with olaparib as first-line maintenance compared with no olaparib at any stage, given the OS benefit for second-line maintenance (as demonstrated in Study 19). The pre-PBAC response noted that this population (patients not treated with second-line olaparib as they are not well enough or do not respond to second-line platinum-based chemotherapy) would account for 60% of the proposed population, or 66% including patients with s*BRCA*m who are not currently eligible for second-line treatment. The pre-PBAC

response maintained that all patients treated with first-line olaparib maintenance will achieve a survival gain, compared to the current treatment pathway in which it is only available to g*BRCA* patients in the second-line setting. However, the PBAC considered that the data available for SOLO1 study did not support a greater improvement in survival for first-line versus second-line olaparib maintenance.

6.52 The ESC noted that the model applied a 25 year time horizon based on 41 months of median follow-up. The ESC considered that the 25-year time horizon used in the model introduced additional uncertainty, as the model relied heavily on extrapolated outcomes. The ESC recalled that the PBAC previously accepted a 10 year time horizon for first line treatment of advanced ovarian cancer (page 8, bevacizumab PSD, November 2013), where trial follow-up was 49 months. The pre-PBAC response noted that AOCS data demonstrates that approximately 2% of *BRCA*m patients remain progression-free 15 years after diagnosis, and 1-2% of *BRCA*m patients remain alive 23 years after diagnosis. The PBAC considered that patients eligible for treatment with bevacizumab are likely to have a poorer prognosis than the proposed population, and considered that a time horizon of up to 15 years would be appropriate.

6.53 The commentary noted that relatively low utility values for PFS and PD modelled health states from the literature (Havrilessky et al 2009) are used, rather than more recent, applicable sources. The ESC noted that the utility values used for PFS2 and PD in the submission were low relative to PFS1, which favoured olaparib. The commentary noted that first progression is determined by radiological criteria, and is not likely to be associated with clinical change or disease symptoms. It is plausible that utility after first progression (but before second progression) is almost the same as utility prior to first progression, as identified by other literature sources. The PSCR argued that it is not appropriate to use utility scores observed in Study 19, as these patients are a healthier subgroup of the second-line population than in the current model. The ESC noted that 98% of patients who progressed in the placebo arm of SOLO1 received subsequent therapy, therefore they are fit for treatment and would likely have similar utility to those in Study 19. The ESC considered that the selection of utility values from the literature was not adequately justified and considered that the use of utility values from Study 19 would be appropriate. The pre-PBAC response disagreed with the ESC that use of Study 19 utilities would be appropriate but acknowledged that utilities from Havrilesky et al (2009) may underestimate utilities for PFS2 and PD. The sponsor proposed using utilities that were elicited using TTO from women undergoing second-line or subsequent treatment for advanced ovarian cancer rather than restricting to those who remain platinum sensitive from NICE review TA91 (PFS2: 0.63; PD: 0.34).

6.54 A stepped analysis was performed during the evaluation to address concerns regarding the inputs used in the base case, where possible, and respecify the base-case; (i) assuming OS in *BRCA*m positive patients is the same across both olaparib and placebo arms in the model; (ii) using utility values for PFS2 and PD as reported in Study 19; (iii) correcting the modelled cost of olaparib; (iv) including downstream germline

testing costs in tumour positive patients and private/hospital funded test costs; and (v) using a prevalence for g*BRCA*m of 20.3%.

6.55 The re-specified analysis conducted during the evaluation resulted in a substantially higher ICER and highlighted that overall survival gains and PFS2 and PD utility weights were key drivers of the model. The ESC considered that the respecified base case was a more appropriate basis for assessment of the cost-effectiveness of olaparib in both scenarios presented.

Table 12: Results of re-specification of base-case performed during the evaluation

	Variable or assumption	Costs (discounted)		QALYs (discounted)		∆costs	∆QALY	ICER
	Stepped analyses to respecify the base-case	**Proposed**	**Current**	**Proposed**	**Current**			
1	Same OS curve in BRCAm positives (after 41 months)	$[redacted]	$[redacted]	[redacted]	[redacted]	$[redacted]	0.3083	$[redacted]
2	(1) and utility values for PFS2 (0.768) and PD (0.708) reported in Study 19	$[redacted]	$[redacted]	[redacted]	[redacted]	$[redacted]	0.1563	$[redacted]
3	(2) and corrected modelled cost of olaparib ($5,514.28 per monthly cycle)	$[redacted]	$[redacted]	[redacted]	[redacted]	$[redacted]	0.1563	$[redacted]
4	(3) and including germline testing costs in tumour positive patients[a] and costs for hospital/private funded test ($1,200)	$[redacted]	$[redacted]	[redacted]	[redacted]	$[redacted]	0.1563	$[redacted]
5	**(4) and prevalence of gBRCAm increased to 20.3%**	**$[redacted]**	**$[redacted]**	[redacted]	[redacted]	**$[redacted]**	**0.1647**	**$[redacted]**
6	**(5) only for gBRCAm testing (scenario 1)**	**$[redacted]**	**$[redacted]**	[redacted]	[redacted]	**$[redacted]**	**0.0512**	**$[redacted]**

[a]Additional germline testing costs included for tumour BRCAm test-positives only; calculated as $1400 × prevalence of BRCAm×$400 which equates to $1,492 for prevalence 23% or $1,505 when prevalence is 26.3%.
∆ = incremental; gBRCAm = germline BRCA mutation; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; PD = progressive disease; QALY = quality adjusted life year
Source: Constructed during the evaluation using Economic Evaluation.xlsx, Attachment 7.1

6.56 A summary of the ICERs (where calculable from the data provided) and other issues relevant to test/medicine accessibility is shown in the table below.

Table 13: ICERs and considerations of various BRCA1/2 testing and olaparib funding scenarios

	Proposed PBAC funded first-line maintenance olaparib
No MSAC funded test	Not modelled and inadequate clinical evidence available to estimate
MSAC funded test: Restricted to germline mutation testing only	Sponsor estimated ICER: $[redacted]/QALY. (or $[redacted]LY) Evaluation re-specified model: $[redacted]/QALY (or $[redacted]/LY)
MSAC funded test: Proposed tumour testing (identifying germline and somatic mutations)	Sponsor estimated ICER: $[redacted]/QALY. (or $[redacted]/LY) Evaluation re-specified model: $[redacted]/QALY (or $[redacted]/LY)

*BRCA*m = *BRCA1/2* mutation; ICER= incremental cost-effectiveness ratio; LY = life year; MSAC = Medical Services Advisory Committee; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life year
Source: Constructed during the evaluation based on results presented in Section 3A.8 of the submission

6.57 When the base-case in the economic analysis presented in the submission was re-specified such that survival is no different across the arms, and more reasonable estimates of utility (quality of life) for patients following progression or second progression were applied, there was reduced benefit related to early (first-line) use of olaparib compared with the second-line use of olaparib (scenario 1). The move from second-line to first-line use is associated with small QALY gains from reduced time in PFS2 (0.0512 QALYs). This move also is associated with significant additional cost ($[redacted]) due to an increase in the proportion of patients receiving olaparib, resulting in a high ICER. The ESC noted that the submission model assumed that, of patients not treated with olaparib in the first-line setting, 51% of patients who progressed (37.4% of patients overall) would receive olaparib in the second-line treatment setting. The ESC noted that the respecified base case used the same monthly costs for first-line and second-line olaparib. The ESC also noted that in the proposed listing for the first-line setting, patients with complete response stop olaparib treatment after 24 months, whereas patients receiving second-line olaparib maintenance remain on treatment until disease progression. In the model, the proportion of patients on treatment was based on TTD data from SOLO1 for first-line use and TTD data from Study 19 for second-line use. As such, the incremental cost for the olaparib arm appears to be due to the additional patients treated with first-line olaparib rather than a higher cost per patient.

6.58 The PSCR argued that the remaining patients in the comparator arm, who do not receive a second-line PARP inhibitor (for example patients who are not well enough or do not respond to second-line platinum-based chemotherapy) would be expected to have outcomes consistent with the AOCS cohort. The ESC considered that there are likely to be patients who receive olaparib first-line who would otherwise not be eligible for second-line olaparib treatment, and it may be reasonable to assume that access to first-line olaparib would result in a survival benefit for these patients. However, the ESC considered that the modelled difference in OS was not supported

by the observed data from SOLO1 and the approach to modelling OS in the submission relied on assumptions that may not be reasonable.

6.59 The model predicts moving a patient with s*BRCA*m from not receiving olaparib to receiving olaparib in the first-line setting would be associated with an average increase of more than two additional life years (2.33 life years gained; or 2.82 progression free life years gained), 1.91 additional QALYs, and an ICER of $45,000 - $75,000 per QALY. The ESC noted that in the s*BRCA*m patients, who would move from no treatment with olaparib to first-line treatment with olaparib, it may be reasonable to assume an OS benefit in line with that shown in Study 19. The ESC noted that the overall ICER in scenario 2 is substantially reduced by the introduction of olaparib maintenance therapy to s*BRCA*m patients, who previously had no access to olaparib first or second line. The ESC noted that the benefits associated with olaparib treatment for patients with s*BRCA*m were consistent with those presented for g*BRCA*m patients in the March 2016 PBAC submission for the second-line setting (1.73 QALYs).

6.60 Results of univariate sensitivity analyses around the respecified base case conducted during the evaluation are presented in the table below.

Table 14: Results of sensitivity analyses around re-specified base case (scenario 2) performed during the evaluation

Variable or assumption	∆ costs	∆ QALY	ICER
Respecifed base-case Scenario 2	**$**		**$**
Time horizon 10 years; base-case 25 years	$		$
Time horizon 15 years; base-case 25 years	$		$
Time horizon 20 years; base-case 25 years	$		$
Diagnostic accuracy of tumour test 100%, base-case 99%	$		$
Utility score for PFS2 (0.803) and PD (0.739) reported in SOLO2 trial	$		$
Adverse event costs not accrued for olaparib maintenance in 2L	$		$

∆ = incremental; 1L= in response to first-line platinum regimen; 2L = in response to second-line platinum regimen; *gBRCAm* = germline *BRCA* mutation; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; PD = progressive disease; QALY = quality adjusted life year;
Source: Constructed during the evaluation using Economic Evaluation.xlsx, Attachment 7.1

The redacted table shows ICERs in the range of $105,000/QALY - $200,000/QALY.

Drug cost/patient/course: $

6.61 The drug cost (undiscounted) for first-line olaparib in *tumour BRCAm* test true positives was estimated to be $, using the proposed effective DPMQ (28 days treatment length adjusted for monthly cycle by applying mean daily dosage) and the modelled SOLO1 TTD curve. The submission underestimated the cost per course of olaparib in the first-line arm by applying mean daily dose to calculate monthly drug costs. The undiscounted drug cost per course for first-line olaparib (scenario 2) for true positives would be $.

Estimated PBS & financial implications

6.62 This submission was not considered by DUSC.

6.63 The submission used an epidemiological approach to estimate the number of patients diagnosed with FIGO Stage III/IV ovarian, fallopian tube and primary peritoneal cancer. The assumed prevalence of *BRCA* mutations is 23%. The prevalence of BRCA mutations used in the submission may be an underestimate. The submission proposed the listing of olaparib in the first-line maintenance setting in patients with *BRCA*m according to tumour testing (and germline testing if tumour testing is not feasible). Tumour testing is estimated to identify a further 3% - 9% of patients with a *BRCA* mutation, in addition to the 20% to 23% of patients who would be identified using a germline *BRCA* test.

6.64 The duration of therapy of first-line maintenance with olaparib applied in the analysis is modelled from the SOLO1 data for patients on olaparib. Patients in SOLO1 with a partial response were able to continue beyond the trial duration of 24 months, and approximately 10% of patients continued treatment. The submission adjusted the estimates for treatment duration from 25 months onwards, noting that a higher proportion of partial responders (33%) was reported in the AOCS (AZ AOCS2) data report compared to SOLO1 (18%). The impact on the use of olaparib in the second-line maintenance setting is determined using an estimate of the rate at which patients progress in the placebo arm of SOLO1 trial, and applying 51% of progressed patients to receive second-line olaparib (reflecting second-line PARP inhibitor use in the SOLO1 trial). The duration of therapy in second-line maintenance is captured by the number of patients in each year, which is based on TTD from Study 19.

6.65 Approximately 75% of patients were assumed to be tested using tumour *BRCA*m testing, with the remainder accessing germline *BRCA*m testing.

6.66 The estimated financial implications of listing olaparib were based on the proposed effective price of olaparib (DPMQ = $[redacted]) and a proposed MBS fee for tumour testing of $1400.

6.67 In year 6 the estimated number of patients treated with olaparib was less than 10,000 and the net cost to the PBS based on the effective price would be $10 - $20 million.

Table 15: Estimated use and financial implications of listing olaparib for first-line maintenance setting in patients with BRCAm

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of tumour BRCAm testing and financial implications						
Number of patients tested with tumour or germline *BRCA*m testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Number of patients no longer tested with germline *BRCA*m test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Saving to MBS[a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated extent of use of olaparib for *BRCA*m patients in the first-line maintenance setting						
Number of patients likely to receive a positive test result[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients likely to be treated with proposed medicine[b,c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of olaparib used in the first-line maintenance setting						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for the reduction of olaparib used in the second-line maintenance setting						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications to the PBS						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a]The estimate of the number of patients receiving a positive *BRCA*m test has been adjusted to include those patients who would receive a germline test if tissue testing is not feasible.
[b]Re-calculated during the evaluation to account for a higher proportion of patients receiving a germline test at baseline.
[c]Includes an estimated [redacted] grandfathered patients (in year 1) and an increase in the number of patients treated (approximately 8 per year) based on the use of a germline *BRCA*m test when tissue testing is not feasible.
[d]The submission has not applied a calculation of average number of scripts per year per patient. The method for calculating scripts is based on the number of patients receiving olaparib each month based on a time to treatment discontinuation curve. On average, patients who begin treatment in month 1 of year 1 are calculated to receive approximately 22 scripts over six years. A small number of patients are estimated to still be receiving olaparib after 4 years of treatment.
Source: Table 4-9, Table 4-10, Table 4-11, Table 4-12, Table 4-14, Table 4-15, Table 4-17, Table 4-21, Table 4-22, Table 4-23, Table 4-24, Table 4-25, Table 4-28, Table 4-29, pp321-34.

6.68 The submission estimated the number of scripts for the proposed first-line listing of olaparib based on staggering the initiation of patients across each month. This approach was inconsistent with the method for calculating the reduction of use of second-line olaparib. The methodology used in the financial model was particularly complex, and appeared to deviate from the approach described in the submission in some aspects. The methods used to estimate utilisation of first-line olaparib were

appropriate, but were inconsistent with the methods used to estimate other model outputs (such as the expected number of authorisations and the displacement of second-line use of olaparib). Due to the complexity of the approach, it was difficult to make amendments to the financial model to incorporate alternative data or assumptions. It remained unclear whether the approach taken in the model resulted in a meaningful improvement in the precision of the estimates beyond the first year. The ESC considered that it would be preferable in any future submissions that the approach be simplified, as the current approach is complicated and the complexity has resulted in different approaches being applied to costs vs cost-offsets.

6.69 A higher proportion of patients treated beyond 2 years was applied in the financial model than was observed in the SOLO1 trial. This was stated to be based on a report from the Australian Ovarian Cancer Study (AOCS) that was commissioned by the sponsor. The PSCR confirmed that the proportion of patients with partial response should be 23-24% rather than 33% as estimated in the submission.

6.70 The submission assumed that each month on treatment in the first-line setting represents one script (or 12 scripts per year). Scripts will provide 28 days of supply and 13 scripts would be required for each year of supply.

6.71 The ESC also noted that the displacement of second-line olaparib was underestimated as it did not account for grandfathered patients in year 1 who would no longer access olaparib in the second-line setting.

Quality use of medicines

6.72 The sponsor identified appropriate duration of treatment with olaparib as a quality use of medicines issue. No further details were provided.

Financial management – risk sharing arrangements

6.73 The submission noted that there is an existing agreement between the Government and AstraZeneca Pty Ltd in relation to risk sharing for the supply of olaparib. It is the sponsor's understanding that the supply of olaparib in the first-line setting would be subject to the Agreement, and an adjustment to the expenditure caps would be required.

Other considerations for the committees

Clinical utility of the test in the second-line setting

6.74 There is currently no evidence of a survival benefit for the effectiveness of olaparib in the first-line setting in an unselected or *BRCA*wt population. However, it appears that olaparib may confer some benefit (at least in terms of progression-free survival) in *BRCA*wt patients in the second-line setting compared with no treatment. Regulatory agencies have removed reference to *BRCA*m in the indication for second-line olaparib

in HGEOC, and the NCCN Ovarian Guidelines (2019) only require that patients are in response to platinum-based chemotherapy. There is still a treatment effect variation associated with BRCAm in the second-line setting, however the test may not be necessary. Patients who respond to platinum-based chemotherapy, an eligibility criterion for second-line treatment, appear likely to respond to olaparib.

6.75 There is little difference in observed overall survival in *BRCA*wt patients treated with olaparib vs placebo in the second-line maintenance setting (HR 0.83 [95% CI 0.55, 1.24], there is clear violation of the proportional hazards assumption and the HR may not be an accurate measure of relative survival.)

6.76 While Study 19 was not stratified by *BRCA* status, the results are consistent with those from NOVA (niraparib) and ARIEL3 (rucaparib), which both reported favourable progression-free survival treatment effects of a PARP inhibitor in patients with *BRCA*wt.

6.77 The ESC considered that the efficacy of maintenance PARP inhibitors in first-line patients with BRCAwt tumours remained uncertain, but that the field was evolving rapidly, with recently published data from 3 studies of olaparib, niraparib, and veliparib presented at the European Society of Medical Oncology Congress, Barcelona September 2019 reporting benefit in some subgroups.

6.78 The ESC considered that broader listing for olaparib in the second-line setting would involve a revised value proposition for olaparib as it would be used in a greater number of patients, but would, on average, result in less benefit per patient. This would also negate the need for tumour *BRCA*m testing.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of olaparib (Lynparza®) for the first-line maintenance treatment of ovarian, fallopian tube or primary peritoneal cancer. The PBAC considered that olaparib provided a substantial benefit to some patients in delaying recurrence, which it considered is likely to be a clinically important outcome. The PBAC considered that the modelled cost-effectiveness was uncertain due to an overly complex model including optimistic assumptions of the extent of the overall survival benefit which were not supported by the clinical evidence. The PBAC advised that the ICER was high at the sponsor's proposed price. The PBAC considered the extent of use in the first-line setting was overestimated, and the reduction in use in the second-line setting was underestimated.

7.2 The PBAC noted that there are a range of systemic therapies currently available for the second-line treatment of ovarian cancer, including olaparib, however recognised the ongoing clinical need for effective first-line treatments for ovarian cancer that can delay or prevent recurrence. The PBAC acknowledged the social and emotional impact of high rates of recurrence on patients diagnosed with ovarian cancer. The PBAC noted the support from patients, several patient representative organisations, and MOGA for making olaparib available as first-line maintenance for ovarian cancer.

7.3 The PBAC considered that "High grade serous ovarian cancer", "High grade serous fallopian tube cancer" and "High grade serous primary peritoneal cancer" are the appropriate indications for the listing, consistent with the indications for second-line listings.

7.4 The PBAC considered that 2 repeats for the initial restriction and 5 repeats for the continuing restriction would be appropriate, consistent with the existing listing for second-line maintenance. The PBAC considered that the proposed Authority required (Telephone) restriction level for the initial listings and Authority required (STREAMLINED) restriction level for the continuing listings were appropriate.

7.5 The PBAC considered that concurrent treatment with olaparib and bevacizumab would not be appropriate without supporting evidence, and an additional restriction "Must not be used concurrently with bevacizumab" is appropriate. The PBAC considered that the restriction should not explicitly prohibit patients who have used bevacizumab concurrently with their platinum-based chemotherapy. The PBAC considered that patients with a *BRCA*m who are also eligible for bevacizumab and respond to platinum-based therapy may still benefit from olaparib maintenance treatment.

7.6 The proposed restrictions allow patients who are not in complete response to continue olaparib treatment, while patients with complete response must not exceed a total of 24 months of treatment. The PBAC considered that this approach was appropriate for the first-line maintenance setting, as it was consistent with SOLO1 and it would be unnecessary for patients with complete response to have ongoing therapy

beyond 24 months. The PBAC considered that a line-agnostic listing may be a reasonable approach to listings for olaparib in ovarian cancer, provided that the listing ensured a maximum 24 month treatment duration for patients in complete response and did not allow re-treatment with olaparib following relapse.

7.7 The PBAC noted that patients accessing first-line olaparib under a compassionate access program would be eligible for treatment under the proposed initial treatment listing, therefore a separate grandfather listing is not required.

7.8 The PBAC considered that the proposed clinical place for olaparib as first-line maintenance with olaparib in patients with BRCAm who are in response to platinum treatment was appropriate. The PBAC noted that there are a substantial proportion of patients who are no longer suitable for treatment with olaparib following a subsequent relapse and chemotherapy and as such, first-line maintenance is a clinically appropriate approach.

7.9 The PBAC agreed with the ESC that there was a lack of direct trial data supporting the efficacy of olaparib in the first-line setting for patients with s*BRCA*m in the absence of g*BRCA*m, as only two such patients were included in the key comparative study. The PBAC also noted that the pooled analysis of studies in the second-line setting found similar hazard ratios for PARP inhibitors versus placebo in patients with g*BRCA*m and s*BRCA*m (paragraph 6.23), which supported the efficacy of olaparib in the second-line setting for patients with s*BRCA*m in the absence of g*BRCA*m.

7.10 The PBAC noted that *BRCA*m status is used as a surrogate for homologous DNA repair deficiency, and considered that although an imperfect marker of homologous DNA repair deficiency, BRCAm status and platinum sensitivity are currently the most appropriate means to identify patients likely to benefit the most from olaparib maintenance.

7.11 The PBAC considered the appropriate main comparator is watch and wait, followed by second-line platinum-based chemotherapy and olaparib maintenance in patients with g*BRCA*m. While bevacizumab is currently available for patients with sub-optimally debulked Stage III ovarian cancer, the submission stated that the populations currently treated with bevacizumab are less likely to harbour a *BRCA*m, and are less likely to respond to platinum-based chemotherapy. The PBAC noted olaparib is an alternative to bevacizumab maintenance following first-line chemotherapy and bevacizumab. Although the extent to which olaparib would replace bevacizumab is unknown, the PBAC considered that bevacizumab is an appropriate comparator for the subgroup of patients with sub-optimally debulked Stage III ovarian cancer.

7.12 The PBAC considered that the key comparative study in patients with identified g*BRCA*m (SOLO1) has a low risk of bias for the primary outcome of PFS. The PBAC considered the use of post-progression PARP inhibitors in the olaparib arm may have

biased the overall survival results in favour of olaparib, as it would not reflect clinical practice in Australia.

7.13 The PBAC noted that the SOLO1 trial demonstrated a substantial 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 noted that there was no difference in health-related QoL as measured by the trial outcome index (TOI) in the SOLO1 trial. The PBAC noted that the PSCR presented recently published quality-adjusted PFS and TWiST data from the SOLO1 trial. Although these results supported the claim that prolongation of PFS in SOLO1 was not at the expense of reduced HRQoL due to toxicity, these data were not evaluated. The PBAC 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 PBAC considered that the extent of the clinically relevant benefit may be less than the difference in radiological PFS.

7.14 The PBAC noted that there was no difference in overall survival 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 noted that OS data was not mature, and was impacted by subsequent treatment with PARP inhibitors in the control arm, which reflects the current PBS listing for olaparib. The PBAC noted that Study 19, assessing the efficacy of olaparib as second-line maintenance therapy, demonstrated a larger although also non-significant improvement in OS with an increase in median OS of 3 months (34.9 vs 31.9 months, unadjusted HR 0.73 95%CI: 0.45, 1.17). However with adjustment for post-progression therapy the gain in OS further increased and was statistically significant (34.9 vs 26.6 months, adjusted HR 0.52 95%CI: 0.28, 0.97) (Table 6, olaparib PSD, March 2016). The PBAC considered that it may be reasonable to assume that, compared with no olaparib treatment, patients treated with olaparib as first-line maintenance had a survival benefit equivalent to that demonstrated in second-line maintenance in Study 19, but that it would not be reasonable to assume additional survival benefit for first-line maintenance compared with second-line maintenance as this was not supported by the clinical evidence.

7.15 The PBAC 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 considered that the safety profile of olaparib appears manageable but includes clinically important AEs, particularly as it is used as maintenance treatment.

7.16 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 have been more appropriate.

7.17 The PBAC noted that an overall survival benefit was not supported by the clinical data currently available. The committee agreed with the 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. The PBAC 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. The PBAC noted that AOCS data were applied to the SOLO1 trial data to inform long term OS, which was not available from the SOLO1 trial. The PBAC considered that the applicability and method of use of the mortality rate associated with second progression derived from the AOCS cohort to the SOLO1 PFS2 curve was not adequately justified.

7.18 The PBAC noted that the evaluation conducted a revised analysis assuming (i) OS in *BRCA*m positive patients is the same across both olaparib and placebo arms in the model; (ii) using utility values for PFS2 and PD as reported in Study 19; (iii) correcting the modelled cost of olaparib; (iv) including downstream germline testing costs in tumour positive patients and private/hospital funded test costs; and (v) using a prevalence for g*BRCA*m of 20.3%. This increased the ICER to more than $200,000 per QALY for the g*BRCA*m population.

7.19 The PBAC considered that assuming OS is the same across both olaparib and placebo arms in the model was conservative, although it was consistent with evidence from the SOLO1 trial which showed no OS benefit in the overall population. 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 second-line setting. The PBAC considered that the scenario presented in the submission was implausibly optimistic, but the revised scenario presented in the evaluation was overly conservative.

7.20 The PBAC also noted that a proportion of patients in the placebo arm would not progress without olaparib maintenance treatment, and considered that the model should incorporate a proportion of patients cured in the first-line placebo group.

7.21 The PBAC considered that the evaluation's approach to PFS2 and PD utilities, correction of the cost of olaparib, inclusion of downstream testing costs and using a prevalence for g*BRCA*m of 20.3% were reasonable.

7.22 The PBAC noted that the submission model used a 25 year time horizon and relied heavily on extrapolated outcomes. The PBAC considered that this introduced additional uncertainty in the modelled outcomes. The PBAC previously accepted a 10 year time horizon for first-line treatment of advanced ovarian cancer (page 8, bevacizumab PSD, November 2013). The PBAC considered that patients eligible for treatment with bevacizumab are likely to have a poorer prognosis than the proposed population, and considered that a time horizon of up to 15 years would be appropriate.

7.23 The PBAC noted that the model assumed that 51% of patients who progressed in the placebo arm (37.4% of the overall placebo arm) were treated with second-line olaparib. The submission calculated the expected use of second-line olaparib as 40%, based on AOCS data for second-line platinum-based chemotherapy uptake and a number of assumptions regarding platinum sensitivity and expected uptake. The PBAC considered that it is unknown what proportion of *BRCA*m patients who progress would receive olaparib in the Australian setting. The PBAC considered that the proportion of patients who receive second-line 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 second-line olaparib may be underestimated. 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 suboptimally debulked Stage IIIB/C and all Stage IV patients who are also *BRCA*m positive, and would be treated with first-line olaparib maintenance instead of bevacizumab.

7.24 The PBAC noted that by year 6 the estimated number of patients treated with olaparib was less than 10,000, and the net cost to the PBS based on the effective price would be $10 - $20 million per year. The PBAC considered that the financial impact appears to be overestimated due to underestimated cost-offsets from reduced second-line therapies, as the proportion of patients who receive second-line olaparib in clinical practice may be higher than in the SOLO1 trial. The PBAC considered the financial impact also appears to be overestimated, due to application of a higher proportion of first-line olaparib patients assumed to be treated beyond 2 years in the financial model than was observed in the SOLO1 trial. The PBAC noted that the financial estimates included *BRCA*m prevalence of 23%, which included somatic mutations.

7.25 The PBAC considered that any re-submission for first-line olaparib maintenance treatment should be a major submission and incorporate the following changes:

- A more usual analysis approach to the economic model, for example a partitioned survival analysis;
- Incorporating changes to the economic model in the evaluation's revised analysis: (i) using utility values for PFS2 and PD as reported in Study 19; (ii) correcting the modelled cost of olaparib; (iii) including downstream germline testing costs in tumour positive patients and private/hospital funded test costs; and (iv) using a prevalence for gBRCAm of 20.3%.
- A revised, more conservative approach to estimating overall survival benefit, consistent with the OS benefit shown in second-line olaparib for patients who would not have been given olaparib in the second-line setting, or based on more mature survival data for first-line olaparib;
- A time horizon of up to 15 years;

- Inclusion of bevacizumab as a comparator in the relevant population, including the impact of bevacizumab in the model for the patient population with suboptimally debulked Stage IIIB/C and all Stage IV patients who would be treated with olaparib maintenance instead of bevacizumab;
- Consideration of the impact of increased second-line therapies;
- A reduced price resulting in an ICER consistent with that accepted for olaparib in the second-line setting ($45,000 - $75,000 per QALY);
- Revised and simplified financial impact estimates addressing the issues outlined in paragraph 7.23, and ensuring that the same approach is applied to costs and cost-offsets; and
- Additional details regarding any proposed RSA and estimates of the extent of adjustment to the expenditure caps that would be required.

7.26 The PBAC considered that a future submission for olaparib regardless of *BRCA*m status would be welcomed, but given the incremental effectiveness of olaparib appears to be reduced in BRCAwt patients compared to BRCAm patients, it is anticipated that a broader listing would require a lower price to achieve a cost-effective listing.

7.27 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.