

## 5.05 NIRAPARIB, Capsule 100 mg, Zejula<sup>®</sup>, GlaxoSmithKline Australia Pty Ltd

### 1 Purpose of Submission

- 1.1 The Category 2 submission requested a Section 85 (General schedule), Authority required (streamlined) listing for niraparib for the treatment of newly diagnosed advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (HGEOC), who are in response to platinum-based chemotherapy.
- 1.2 Listing was requested on the basis of a cost-utility analysis (CUA) of niraparib compared with “no active treatment” (referred to as standard medical management (SMM)), as a first-line maintenance therapy in patients with HGEOC, who are in response to platinum-based chemotherapy. The key components of the overall clinical claim addressed by the submission are summarised below.

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

Component	Description
Population	Patients with NDA (FIGO Stage III-IV) HGEOC who are in response (CR/PR) to PBC
Intervention	Niraparib
Comparator	BRCAM: Olaparib; Stage IIIB/IIIC R2 (sub-optimally debulked) and Stage IV: Bevacizumab; Stage IIIA and Stage IIIB/IIIC R0 + R1, non-BRCAM: standard medical management (no active treatment)
Outcomes	PFS, OS TFST, Safety
Clinical claim	In patients with NDA HGEOC who are in CR/PR to PBC, niraparib is superior to placebo (active surveillance) in terms of efficacy, with a manageable safety profile.

Source: Table 2 of the submission, p20

BRCAM = BRCA mutation; CR = complete response; FIGO = International Federation of Gynaecology and Obstetrics; HGEOC = high grade epithelial ovarian cancer; NDA = newly diagnosed advanced; OC = overall survival; PBC = platinum based chemotherapy; PFS = progression free survival; PR = partial response; R0 = nil visible residual disease (0cm); R1 = >0 and ≤1cm residual disease; R2 = >1cm residual disease; TFST = time to first subsequent treatment

### 2 Background

#### Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Second round Clinical Evaluation report, and Delegate’s Overview were available.
- The proposed TGA indication is: “for the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.”

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- 2.2 Niraparib is currently TGA approved as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
- 2.3 The submission proposed the use of niraparib individualised starting dose (ISD) in which patients with body weight <77kg or baseline platelet count <150,000/ $\mu$ L start on 200mg/day, while all other patients start on 300mg/day. The evidence behind the ISD was based on pharmacokinetic modelling and post-hoc exploratory analyses from the NOVA trial<sup>1</sup>. Based on this evidence, the PRIMA trial protocol was changed (see below). The TGA delegate’s overview concluded that interpretation is limited by the small sample size and the post-hoc, indirect nature of the analysis, however, there was no signal of reduced efficacy. The delegate’s overview also concluded that the ISD reduces haematological toxicity and in particular thrombocytopenia.

**Previous PBAC consideration**

- 2.4 This is the first PBAC submission of niraparib for the treatment of newly diagnosed advanced high-grade epithelial ovarian cancer who are in response to platinum-based chemotherapy. Niraparib was considered by the PBAC in March 2021 for the treatment of platinum sensitive relapsed, high-grade serous ovarian, fallopian tube or primary peritoneal cancer, who are in response to platinum-based chemotherapy, but was not recommended for listing in this indication.

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

**3 Requested listing**

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NIRAPARIB					
Niraparib 100 mg capsule, 84	NEW	1	84	2	Zejula
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b>					
<input checked="" type="checkbox"/> Authority Required – Streamlined [new code]					
<input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia					
<b>Administrative Advice:</b>					
<i>Special Pricing Arrangements apply</i>					
<i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333.</i>					

<sup>1</sup>Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *New England Journal of Medicine*. 2016;375(22):2154-64. Post-hoc analyses from this trial showed that low body weight (<77 kg) and low baseline platelet count were predictors of grade 3/4 thrombocytopenia.

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<b>Indication:</b> High grade <i>stage III/IV</i> epithelial ovarian, fallopian tube or primary peritoneal cancer
<b>Treatment Phase:</b> Initial treatment – first line treatment
<b>Clinical criteria</b> Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen prior to commencing treatment with this drug for this condition <b>AND</b> The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition, <b>AND</b> Patient must not have previously received PBS-subsidised treatment with this drug for this condition
<b>Prescribing Instructions:</b> <i>Patients treated under this listing should be receiving a dose of 300 mg/day</i> 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. Patients who have developed intolerance to olaparib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised niraparib. Patients who have developed progressive disease on PBS-subsidised PARP inhibitor as maintenance therapy are not eligible to receive PBS subsidised niraparib for this condition.
<b>Treatment Phase:</b> Continuing treatment – first line treatment
<b>Clinical criteria:</b> The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition, <b>AND</b> Patient must not have developed disease progression while receiving treatment with this drug for this condition <b>AND</b> Patient must have received previous PBS-subsidised treatment with this drug as first line maintenance therapy for this condition <b>AND</b> <i>The treatment must not exceed a total of 24 months of combined non-PBS-subsidised and PBS-subsidised treatment for patients who are in complete response</i>
<b>Prescribing Instructions:</b> <i>Patients treated under this listing should be receiving a dose of 300 mg/day</i>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NIRAPARIB					
Niraparib 100 mg capsule, 56	NEW	1	56	2	Zejula
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code] <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia					
<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply</i> <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333.</i>					
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<b>Clinical criteria</b> Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen prior to commencing treatment with this drug for this condition <b>AND</b> The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition, <b>AND</b> Patient must not have previously received PBS-subsidised treatment with this drug for this condition					
<b>Prescribing Instructions:</b> <i>Patients treated under this listing should be receiving a dose of 200 mg/day</i>					

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<p>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.</p> <p>Patients who have developed intolerance to olaparib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised niraparib.</p> <p>Patients who have developed progressive disease on PBS-subsidised PARP inhibitor as maintenance therapy are not eligible to receive PBS subsidised niraparib for this condition.</p>
<p><b>Treatment Phase:</b> Continuing treatment – first line treatment</p>
<p><b>Clinical criteria:</b></p> <p>The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition,</p> <p><b>AND</b></p> <p>Patient must not have developed disease progression while receiving treatment with this drug for this condition</p> <p><b>AND</b></p> <p>Patient must have received previous PBS-subsidised treatment with this drug as first line maintenance therapy for this condition</p> <p><b>AND</b></p> <p><i>The treatment must not exceed a total of 24 months of combined non-PBS-subsidised and PBS-subsidised treatment for patients who are in complete response</i></p>
<p><b>Prescribing Instructions:</b></p> <p><i>Patients treated under this listing should be receiving a dose of 200 mg/day</i></p>

- 3.2 A special pricing arrangement (SPA) was proposed in the submission. The Pre-Sub-Committee Response (PSCR) proposed a new effective ex-manufacturer price for niraparib of \$ [REDACTED] per 56 capsules, as compared with \$ [REDACTED] per 56 capsules proposed in the submission.
- 3.3 The requested restriction is broader than the population included in the key trial PRIMA:
- The proposed PBS indication did not specify advanced stage (FIGO Stage III/IV) HGEOC. The population in PRIMA only included patients with advanced stage HGEOC (Stage III/IV). The requested PBS indication is also inconsistent with the proposed TGA indication. The PSCR agreed to the inclusion of “Stage III/IV” in the proposed PBS indication (consistent with PRIMA and the indication for 1L olaparib) as proposed by the Secretariat. The ESC considered this was appropriate.
  - The requested restriction did not specify patients’ performance status (PS), while the key PRIMA trial only included patients with Eastern Cooperative Oncology Group (ECOG) PS 0-1. Although this is consistent with the olaparib listing, the efficacy and more importantly the toxicity of niraparib in patients with poorer performance status remain unknown. The PSCR argued that clinicians are best placed to determine whether a patient’s level of function is likely to be adequate for treatment with niraparib to be beneficial.
- 3.4 The requested restriction did not define a maximum duration of treatment, which may not be appropriate given that:
- The planned duration of treatment in the PRIMA trial was three years. However, the median treatment duration was 11 months and the maximum treatment duration was 29 months. Thus, the safety of using niraparib beyond three years remains unknown;

- Some of the patients in the target patient population may be cured, thus the benefit/risk of prolonged continuous treatment is uncertain. Note that treatment with olaparib is restricted to 24 months in the first-line setting for patients who are in complete response;
- The economic model presented in the submission assumed a maximum three years of treatment for those patients who are cured, thus the cost-effectiveness of prolonged continuous treatment is uncertain.

The PSCR disagreed with the Secretariat's proposal to add a 24 month stopping rule for patients that are in CR as this was not required in the trial and not specified in the draft PI. The PBAC considered that a maximum treatment period of 3 years would be consistent with the clinical data for niraparib, and that any future resubmission should justify the duration of treatment proposed and ensure consistency with the economic model and financial estimates.

- 3.5 The requested restriction allows niraparib to be used in patients with Stage III, R0 after primary debulking surgery (PDS), while the PRIMA trial excluded these patients. Achieving R0 post PDS is considered to be one of the best prognostic factors, and the additional clinical benefit of using maintenance niraparib in the first-line setting for this group of patients was not captured in the PRIMA trial. The PSCR argued that exclusion of these patients is not appropriate as treatment guidelines recommend maintenance therapy irrespective of prior surgical outcome. The PBAC noted that no clinical evidence was provided for niraparib for this group of patients but considered that in clinical practice it would be reasonable for all stage III/IV patients be treated with PARP inhibitors.
- 3.6 The requested restrictions did not exclude patients with prior treatment with bevacizumab, which was one of the exclusion criteria of the PRIMA trial. The PSCR noted that the same is true for the pivotal evidence for olaparib (SOLO-1). There is inadequate evidence to support the use of niraparib in patients who have received prior treatment with bevacizumab in the first-line setting (based on a very few patients who had bevacizumab as part of the primary treatment within the PRIMA trial<sup>2</sup>).
- 3.7 The requested restrictions would allow switching from one poly (ADP-ribose) polymerase inhibitors (PARPi) to another based on intolerance, however there is no evidence for switching.
- 3.8 The PBAC considered that access to PARPi should be limited to one course per patient lifetime. An analogous restriction should flow on to olaparib, if niraparib is listed. The proposed restriction requested that patients who have developed intolerance to olaparib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised niraparib. If switching is considered appropriate due to

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<sup>2</sup> National Comprehensive Cancer Network (NCCN) Guidelines Ovarian Cancer, version 1.2021, p129

intolerance, the restrictions should require confirmation of no progression on PARPi at time of switching.

- 3.9 The proposed maximum quantities are consistent with the draft PI, which includes initial dosing of 200 mg for patients who weigh less than 77 kg or who have a baseline platelet count of less than 150,000/ $\mu$ L (ISD). The Secretariat has suggested separate listings with clinical criteria to ensure that patients who meet the ISD criteria or who have had their dose reduced receive the 56 unit pack size rather than the 84 unit pack size, to reduce wastage.
- 3.10 The submission did not propose a grandfather listing, however any patients treated with niraparib prior to PBS listing via private funding or compassionate access programs would be eligible for PBS subsidised treatment under the initial listing.

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

## **4 Population and disease**

- 4.1 HGEOC is the most common and aggressive histological subtype of ovarian cancer (OC). Most patients (>75%) are diagnosed at an advanced stage (Stage III and IV), with a limited long-term survival (7-year survival for FIGO Stage III and IV: 26% and 9% respectively).
- 4.2 Although initial treatment with cytoreductive surgery and platinum-based chemotherapy usually leads to initial response, the majority of patients relapse within the first three years. Post-progression treatment is usually associated with reduced efficacy and prolonged exposure to chemotherapeutic agents (mainly platinum-based chemotherapy) is associated with long-term toxicities and attenuation in quality of life.
- 4.3 In July 2020 the PBAC recommended listing of olaparib as maintenance treatment after an initial response to platinum-based chemotherapy in the first-line setting for patients with a BRCA1/2 pathogenic variant. Bevacizumab is also available on the PBS as first-line maintenance for patients with Stage IIIB/IIIC sub-optimally debulked (R2 resection) or Stage IV ovarian cancer.
- 4.4 The submission requested niraparib to be listed as a first-line maintenance therapy for those who have complete or partial response to platinum-based chemotherapy, irrespective of BRCA mutation status or surgical outcomes. This is consistent with the international guidelines<sup>3</sup>. The ESC noted that patients with homologous recombination deficiency (HRD) positive tumours show a better response to treatment with PARP inhibitors, however HRD testing is not reimbursed on the MBS

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<sup>3</sup> European Society of Medical Oncology (ESMO) guidelines; The National Comprehensive Cancer Network (NCCN) guidelines; The ESMO-European Society of Gynaecology (ESGO) 2019 consensus recommendations on ovarian cancer, and the American Society of Clinical Oncology (ASCO) guidelines

and many patients cannot access due to their location or the prohibitive cost of self-funding the test.

- 4.5 The PBAC noted that the NCCN guidelines include niraparib as an alternative to olaparib in BRCAm patients, and as an alternative to observation in non-BRCAM patients with a footnote that states: “in the absence of a BRCA 1/2 mutation, homologous recombination (HR) status may provide information on the magnitude of benefit of PARPi therapy. The PBAC noted that HRD testing is not currently part of the standard clinical management of HGEOC in Australia.

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

## 5 Comparator

- 5.1 The submission nominated three comparators, depending on BRCA status and surgical outcomes:
- **Olaparib** for patients with BRCA pathological variants (BRCAm). In the PRIMA trial, 30% of the patients enrolled were BRCAm;
  - **Bevacizumab** for patients with Stage IIIB/IIIC sub-optimally debulked (R2) and patients with Stage IV, irrespective of BRCA status. In the PRIMA trial, 43% of the non-BRCAM patients were Stage III, R2 or Stage IV;
  - **No active treatment (referred to as SMM)** for patients with Stage IIIA and Stage IIIB/IIIC with nil visible residual disease (R0) or low volume residual disease (R1) who don’t have BRCA pathological variants and are not treated with bevacizumab. The PBAC considered that SMM was the appropriate comparator for non-BRCAM patients who are not treated with bevacizumab.
- 5.2 The PBAC considered the nominated comparators were appropriate. However, the submission did not present clinical evidence for niraparib versus olaparib or bevacizumab in the relevant populations and did not present an economic model that included these comparators.
- 5.3 The PBAC agreed with the ESC that it was inappropriate that the comparator of SMM was used as the basis for the clinical claim and economic evaluation as it is only relevant to a subset of patients in current clinical practice (under 40% based on PRIMA trial<sup>4</sup>). As a result, the submission failed to make a clinical claim relevant to the majority of the proposed patient population for niraparib and did not present an economic evaluation of niraparib compared to the clinically relevant comparators in Australian practice. The PBAC considered that this was particularly problematic for the 20-25% of patients with a BRCA1/2 pathogenic gene variant, who would be treated with olaparib.

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<sup>4</sup> In PRIMA, 57% of the non-BRCAM patients (37% of the whole study population) had Stage III, R0-1 resection.

- 5.4 The pre-PBAC response argued that a proportion of patients in the BRCAm population have unknown BRCAm status due to unwillingness to have genetic testing or do not have a viable sample for somatic testing following NACT. The PBAC noted that for these patients the appropriate comparator would be SMM or bevacizumab.
- 5.5 The ESC considered that there may also be some non-BRCAm patients eligible for, but not treated with bevacizumab due to risk/benefit considerations. For these patients SMM may also be a reasonable comparator. In its consideration of olaparib the PBAC previously considered that up to 40% of first-line patients may be treated with bevacizumab (paragraph 7.19 olaparib Public Summary Document (PSD), July 2020 PBAC meeting). The pre-PBAC response argued that the proportion of patients for which bevacizumab is an appropriate comparator (Stage IIIB/IIIC R2 and Stage IV) is likely to further reduce in the future, due to improvements in surgical cytoreduction rates to R0 over time and increasing utilisation of NACT-IDS, however the PBAC noted that following its recommendation at the March 2021 PBAC meeting, bevacizumab now has an unrestricted listing.
- 5.6 The PSCR defended the approach to the submission stating that the comparative effectiveness and safety of niraparib vs olaparib or bevacizumab was unable to be reliably quantified based on the available evidence (PRIMA, SOLO-1, ICON-7); and that mandating a corresponding clinical conclusion is unwarranted, citing decisions made in other jurisdictions including NICE and CADTH (see also paragraphs 6.6-6.9).
- 5.7 The PBAC considered that the comparative clinical effectiveness and cost-effectiveness of niraparib in the proposed PBS population could not be assessed based on the clinical evidence and economic evaluation presented in the submission. Importantly, the PBAC considered there may be differences in benefits and harms in the different patient subgroups, if niraparib is used in place of olaparib, bevacizumab or SMM.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented an overview of Stage III/IV disease and the PRIMA trial. In addition, the clinician commented that the change in PBS requirements for bevacizumab (unrestricted benefit listing that commenced on 1 June 2021) might lead to more use of bevacizumab in the relapsed setting. The clinician compared the adverse event profiles of niraparib and olaparib and supported the approach of using an individualised starting dose for niraparib based on the results of the PRIMA trial. The clinician also noted that some patients choose not to undertake BRCAm testing, which is currently a barrier to treatment with PARP inhibitors.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (11), and organisations (3) via the Consumer Comments facility on the PBS website. The comments noted that patients with ovarian cancer without evidence of a BRCA pathogenic variant are not currently able to access PARP inhibitors. Individuals considered that maintenance with niraparib may prolong survival and improve quality of life. Individuals reported that self-funding PARP inhibitors was not possible for most patients due to their high cost. Patients also noted the impact on quality of life of chemotherapy which can be poorly tolerated. Support for the niraparib listing was also communicated by individuals with personal experience of olaparib treatment because they felt it was important to advocate for other patients who are not eligible for olaparib due to BRCA status.
- 6.3 The PBAC noted the advice received from the Ovarian Cancer Research Foundation (OCRF), Ovarian Cancer Australia (OCA) and Rare Cancers Australia (RCA) in support of the niraparib submission. The comments from these organisations focussed on the impact of ovarian cancer on patients' mental health and quality of life and the hope of new treatments that prevent or delay relapse and extend survival. RCA and OCA reported that issues impacting patients with ovarian cancer included: the burden of indignity, impacts on fertility, the fear of recurrence, and the impact on families. In addition, patients felt there was a lack of equity of access, with PARP inhibitors PBS currently subsidised only for patients with BRCA pathogenic variants.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the niraparib submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the PRIMA trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for niraparib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>5</sup>, based on a comparison with placebo. The PBAC noted that this score was based on the PFS benefit for niraparib as OS data from PRIMA are immature.

### **Clinical trials**

- 6.5 The submission presented three randomised phase III trials:
- PRIMA: a placebo controlled, double blind, randomised phase III trial, which compared niraparib to placebo in patients with newly diagnosed, advanced, high-grade ovarian cancer who are in partial or complete response after 6 to 9 cycles of platinum-based chemotherapy;
  - SOLO-1: a phase III, placebo controlled, double blind randomised trial, which compared olaparib to placebo in patients with newly diagnosed, advanced, high-

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<sup>5</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

grade ovarian cancer, with BRCA1/2 mutation, who are in complete or partial response after 6 to 9 cycles of platinum-based chemotherapy;

- ICON-7: a phase III, open label, active control trial, which compared platinum-based chemotherapy plus bevacizumab followed by maintenance bevacizumab to only six cycles of platinum-based chemotherapy in patients with newly diagnosed high-risk Stage III (R2) or Stage IV ovarian cancer.
- 6.6 The submission claimed that indirect comparisons between niraparib and olaparib or bevacizumab could not be performed due to significant issues of heterogeneity between trials. The submission stated that, consequently, the interpretation of the clinical evidence was primarily informed by the head-to-head comparison of niraparib versus placebo (PRIMA) in the overall, intent to treat (ITT) population.
- 6.7 The ESC agreed with the Commentary that an indirect comparison between niraparib and bevacizumab was problematic because the ICON-7 study was a considerably older study and included a substantially different patient population than SOLO-1 and PRIMA trials. The PSCR argued that prior consideration of olaparib in the 1L setting recognised bevacizumab as a main comparator, with the PBAC's July 2020 recommendation being made in the absence of a clinical conclusion for olaparib vs. bevacizumab. The PBAC recalled that it had previously recognised bevacizumab as a relevant comparator to olaparib in a subgroup of patients in the 1L setting during its consideration of olaparib in July 2020. The PBAC noted that the sponsor of olaparib provided a qualitative analysis using data from trials comparing efficacy of bevacizumab to olaparib (from SOLO-1) (paragraph 2.4, olaparib PSD, July 2020 PBAC Meeting).
- 6.8 The ESC noted that in clinical practice bevacizumab is not used in all eligible patients due to safety concerns and the modest benefit of treatment. As such, the ESC considered that the lack of comparison presented for niraparib and bevacizumab was less of a concern than the lack of comparison with olaparib.
- 6.9 However, the ESC agreed with the Commentary that the infeasibility of performing a comparison between niraparib and olaparib was poorly justified because:
- The claim that the patient population in the PRIMA trial may have poorer prognosis based on higher proportion of patients treated with neoadjuvant chemotherapy with interval debulking surgery (NACT-IDS) and the exclusion of patients with Stage III R0 post PDS, may be overstated. Although PDS may have better survival compared to NACT-IDS, this may be confounded by the patients' performance status<sup>6</sup>. All patients included in both the SOLO-1 and PRIMA trials had good performance status (0-1), thus it is expected that the differences in prognosis between the two trial populations would be modest, conditioned on

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<sup>6</sup> Rauh-Hain JA, Melamed A, Wright A, Gockley A, Clemmer JT, Schorge JO, et al. Overall survival following neoadjuvant chemotherapy vs primary cytoreductive surgery in women with epithelial ovarian cancer: analysis of the National Cancer Database. *JAMA oncology*. 2017;3(1):76-82

similar surgical outcome. In addition, a post-hoc subgroup analysis including only patients post NACT-IDS was consistent with the overall results. The ESC noted that NACT-IDS is now employed commonly in patients who could have previously had upfront surgery. Therefore, the ESC considered that the increased rate of NACT-IDS in PRIMA vs SOLO-1 (68% vs 35%) is likely to also be reflective of the change in clinical practice with greater uptake of NACT-IDS for the enrolment periods of PRIMA (2016-18) compared to that of SOLO-1 (2013-15) rather than simply due to the inclusion of patients with higher volume disease.

- The claim that the differences in baseline demographics between the SOLO-1 trial and the BRCAm patient population in the PRIMA trial would make indirect comparison inappropriate may also be unreasonable. Overall, the difference in median age between the two studies was negligible (57 years in PRIMA and 53 years in SOLO-1).
  - The prognostic effect of having a higher proportion of patients with Stage III, and in complete response in the SOLO-1 trial compared to the PRIMA BRCAm subgroup may be compensated for by the higher proportion of patients with R2 resection in the SOLO-1 trial.
  - Although the median PFS in the control arm of the SOLO-1 trial was ~ 3 months longer than that of the PRIMA (BRCAm population), there was an overlap in the confidence intervals which preclude the presence of substantial prognostic differences between the two patient populations.
  - The submission claimed that the differences between the PRIMA trial and the SOLO-1 trial in terms of primary and secondary outcomes made the performance of a formal indirect comparison between them not feasible. The differences between the PRIMA and SOLO-1 trials' primary outcome analyses in terms of: i) Blinded independent central review (BICR) versus investigator assessment (INV), ii) way of defining progressive disease (RECIST v1.1 versus clinical assessment), and iii) the censoring rules, are not expected to markedly affect the validity of an indirect comparison. Sensitivity analyses of these factors were provided in the submission, and they had little impact on the relative treatment effect of niraparib.
- 6.10 The PSCR noted that the CODR expert review committee for CADTH reported that clinical heterogeneity observed across the trials was a “valid concern that would preclude a meaningful analysis and unbiased estimates of relative treatment effect” between niraparib and other maintenance therapies (i.e., olaparib, bevacizumab; pCODR expert review committee final recommendation, p11). Whilst acknowledging that there were some areas of heterogeneity across the trials, the ESC considered that a comparison between niraparib and olaparib may have been achievable with the PRIMA and SOLO-1 trials.
- 6.11 Details of the trial presented in the submission are provided in the table below.

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**Table 2: Key trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
PRIMA	Clinical study report: Niraparib PR-30-5017-C A phase 3, randomised, double-blind, placebo-controlled, multicentre study of niraparib maintenance treatment in patients with advanced ovarian cancer following response of front-line platinum-based chemotherapy González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. González-Martín A, Mirza MR, Vergote I, Li Y, Hazard S, Clark R et al. A prospective evaluation of tolerability of niraparib dosing based upon baseline body weight (wt) and platelet (blplt) count: Blinded pooled interim safety data from the PRIMA Study. Monk BJ, Mirza MR, Vergote I, Li Y, Malinowska I, Gupta D et al. A prospective evaluation of tolerability of niraparib dosing based upon baseline body weight and platelet count: Blinded pooled interim safety data from the ENGOT-OV26/PRIMA study. Valabrega G, Pothuri B, Oaknin A, Graybill W, Sánchez AB, McCormick C et al. Efficacy and safety of niraparib in older patients (pts) with advanced ovarian cancer (OC): Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Pothuri B, Han S, Chase D, Heitz F, Burger R, Gaba L et al. Patient-reported outcomes (PROs) in patients (pts) receiving niraparib in the PRIMA/ENGOT-OV26/GOG-3012 trial. Mirza MR, Martin AG, Graybill W, O'Malley DM, Gaba L, Yap OWS et al. Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. Han SN, Monk BJ, Gonzalez-Martin A. Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer.	November 2019  New England Journal of Medicine 2019;381(25):2391-2402  Annals of Oncology 2018;29:viii335-viii336  Gynecologic Oncology 2019;154:3-4  Annals of Oncology 2020;31:S619  Annals of Oncology 2020;31:S612-S613  Journal of Clinical Oncology 2020;38(15 Suppl)  Gynecologic Oncology 2020;159:18-19

Source: Table 19, p44 of the submission.

6.12 The key features of the direct randomised trial are summarised in the table below.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Niraparib versus placebo</b>						
PRIMA	Niraparib (n=487); Placebo (n=246)	R <sup>^</sup> , DB, MC 15 mths*	Low	Patients with NDA, high-grade ovarian cancer who are in PR or CR to PBC	PFS; OS	Used

Source: in the submission.

R = randomised; DB = double blind; MC = multi-centre; mths = months; NDA = newly diagnosed, advanced; PR = partial response; CR = complete response; PBC = platinum based chemotherapy; OS = overall survival; PFS = progression-free survival.

<sup>^</sup>Patients were stratified by the use of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (positive or negative/not determined)

\*Median duration of follow up for OS. Median duration follow-up for PFS was 13.8 months

6.13 There were two important amendments to the PRIMA study protocol (PRIMA CSR, Table 12, p92) during the course of the trial:

- As per the original PRIMA protocol, only patients who had homologous recombination deficiency (HRD) positive tumours (Myriad myChoice Score  $\geq 42$ ) were eligible to enter the study, however, as per Amendment 1 (December 2016);

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the study allowed the inclusion of all patients irrespective of the HRD status (after 44 subjects were enrolled regardless of the HRD status).

- As per the original PRIMA protocol, all patients initiated treatment with fixed starting dose (FSD, 300mg niraparib); however as per Amendment 2 (November 2017), dosing was changed to the ISD regimen based on baseline body weight and platelet count – 200mg/day for patients with body weight <77kg or baseline platelet count <150,000/ $\mu$ L, while all other patients will be given 300mg/day. Dose reductions were allowed by 100mg/day decrement.

### Comparative effectiveness

6.14 A summary of progression free survival (PFS) and overall survival (OS) results in the PRIMA trial for the ITT population at data cut-off (DCO) May 2019 is presented below.

Table 4: PFS and OS of the PRIMA trial (DCO May 2019)

		Niraparib 487/733 (66%)	Placebo 246/733 (34%)	Absolute difference	HR (95% CI)
<b>Primary outcome: Progression-free survival per BICR at DCO May 2019</b>					
Patients with event		232 (47.6)	155 (63.0)	15.4%	-
Median PFS months (95% CI)		13.8 (11.5, 14.9)	8.2 (7.3, 8.5)	5.6 months	<b>0.62 (0.50, 0.76)</b>
PFS (95% CI) at <sup>^</sup>	6 months	0.73 (0.69, 0.77)	0.60 (0.53, 0.66)	13%*	-
	12 months	0.53 (0.48, 0.58)	0.35 (0.29, 0.42)	18%*	-
	18 months	0.42 (0.36, 0.47)	0.28 (0.21, 0.35)	14%*	-
	24 months	0.32 (0.25, 0.39)	0.23 (0.14, 0.32)	9%*	-
<b>Secondary outcome: Overall survival at DCO May 2019</b>					
Patients with event		48 (9.9)	31 (12.6)	2.7%	-
Median months OS (95% CI)		NR	NR	NA	0.70 (0.44, 1.11)
OS (95% CI) at <sup>^</sup>	6 months	1.00 (0.98, 1.00)	0.99 (0.97, 1.00)	1%#	-
	12 months	0.94 (0.91, 0.96)	0.92 (0.88, 0.95)	2%#	-
	18 months	0.89 (0.84, 0.92)	0.84 (0.76, 0.89)	5%#	-
	24 months	0.84 (0.78, 0.89)	0.77 (0.63, 0.86)	7%#	-
	30 months	0.76 (0.62, 0.86)	0.68 (0.46, 0.83)	8%#	-

Source: Table 48, p81 and Table 49, p84 of the submission

BICR = blinded independent central review; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NA= not applicable; NR= not reported; OS= overall survival; PFS= progression free survival

\*Absolute difference in risk of progression or death at each time point (calculated during the evaluation)

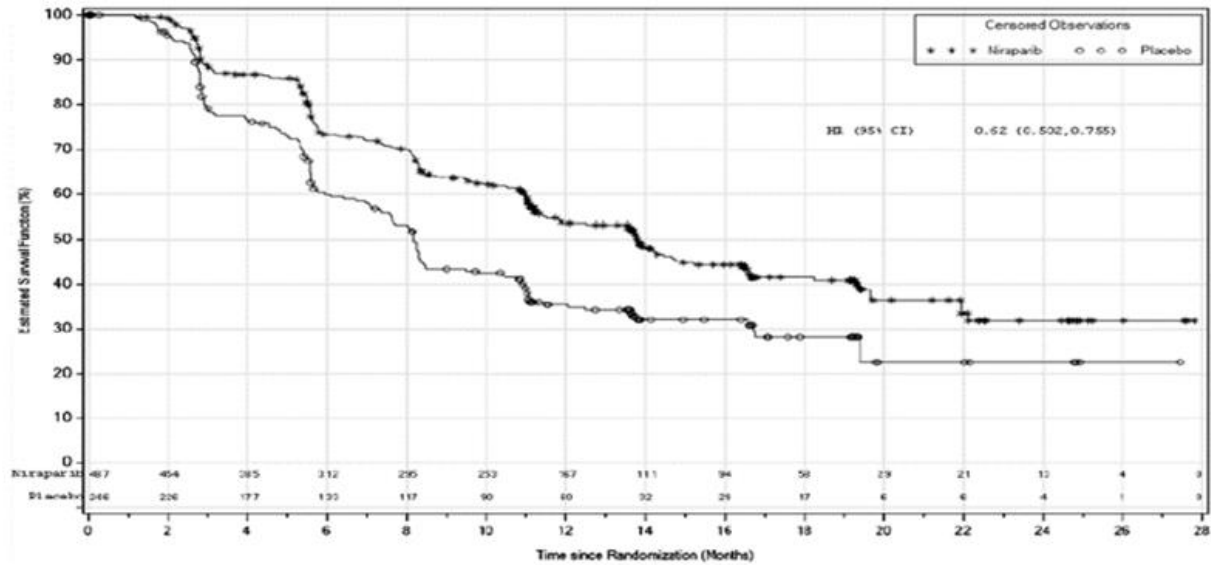
#Absolute difference in risk of death at each time point (calculated during the evaluation)

<sup>^</sup> Results were presented in the submission as survival distribution function with estimates calculated from product-limit (Kaplan-Meier) method. Confidence intervals constructed using log-log transformation

Note that the results denoted by (\*,#) presented in Table 4 are derived from post-hoc analyses conducted by the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for PRIMA. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.15 The Kaplan-Meier plots of PFS and OS for the ITT population in PRIMA are presented below.

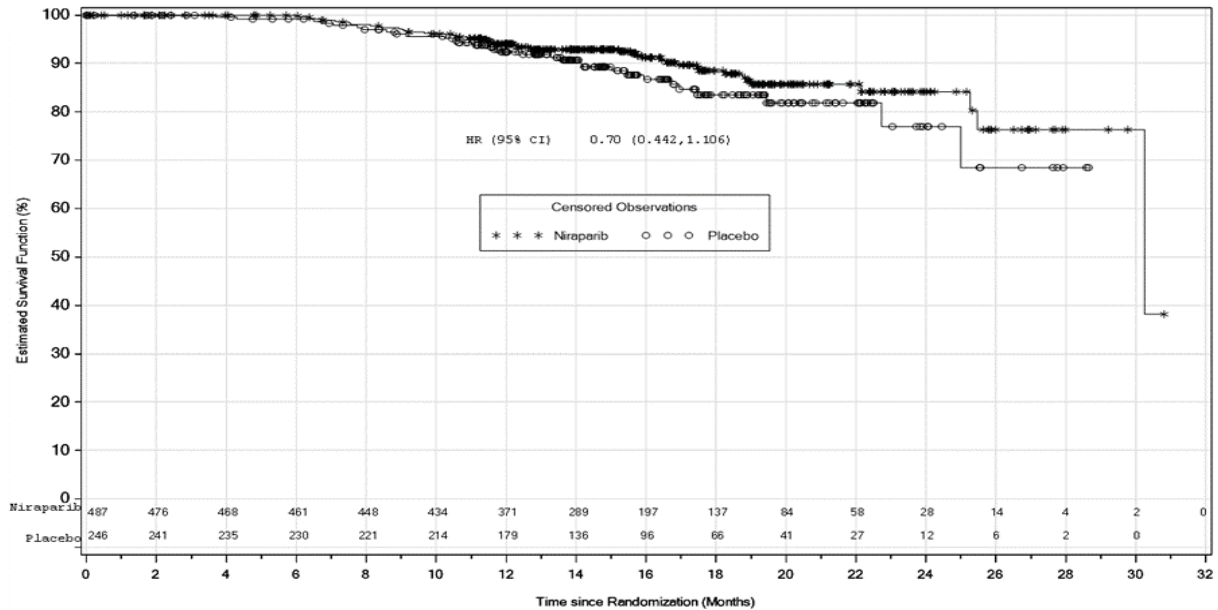
Figure 1: Kaplan-Meier plot for PFS per BICR assessment – primary analyses (PRIMA, overall ITT population, DCO: May 2019)



Source: Figure 10, p82 of the submission.

PFS = progression free survival; BICR = blinded independent central review; ITT = intention to treat; DCO = data cut off.

Figure 2: Kaplan-Meier plot for overall survival (PRIMA, overall ITT population, DCO: May 2019)



Source: Figure 13, p84 of the submission.

ITT = intention to treat; DCO = data cut off

6.16 Over a median follow-up of 14 months (for PFS), there was a 38% reduction in the risk of progression or death according to the blinded independent central review (BICR) assessment in the niraparib arm compared to the placebo arm. The median PFS was extended by 5.6 months in favour of niraparib. The PFS Kaplan-Meier plot demonstrated a distinct separation in the curves in favour of niraparib.

- 6.17 OS data were immature. Over a median follow-up of 15.3 months, a total of 79 patients had died, including 48 of 487 (9.9%) and 31 of 246 (12.6%) randomised to the niraparib and placebo arms, respectively. The median OS was not reached in either arm of the trial, with hazard ratio showing no statistically significant OS benefit (HR = 0.70, 95% CI: 0.44, 1.11). The PSCR noted that further reporting of OS from PRIMA is not expected until 2025 and acknowledged that the current estimates from the primary data cut are based on limited event rates.
- 6.18 Baseline global health status/quality of life per EORTC-QLQ-C30 were similar between placebo and niraparib subjects in the overall population. No statistically significant differences ( $p > 0.05$ ) were observed between the two treatment arms during the treatment period for most assessment visits. The QLQ-C30 supplement specifically for ovarian cancer patients, OV28, also did not indicate any consistent differences in health-related quality of life scores between niraparib- and placebo treated subjects in the overall population.
- 6.19 The submission noted that the ISD is expected to be used in practice. The Commentary noted that the HR was superior for the FSD compared with the HR for the ISD subgroup (HR= 0.59, 95% CI: 0.46, 0.76 for the FSD and HR= 0.69, 95% CI: 0.48, 0.98 for the ISD), though the PRIMA trial was not powered to detect differences between the ISD and the FSD. The TGA delegate noted that the comparison of ISD to FSD was limited by the small sample size and the post-hoc, indirect nature of the analysis. However, there was no signal of reduced efficacy and haematological toxicity was significantly reduced. The ESC noted that in PRIMA 76% of patients on FSD had dose reductions, suggesting that the doses between groups were likely to be similar. The ESC considered that the ISD approach is unlikely to have had a major impact on efficacy outcomes and differences in the HR for the subgroups are likely to be due to chance rather than any true underlying differences in efficacy based on the approach to dosing. The PBAC agreed with the ESC that in clinical practice, efficacy is likely to be similar for ISD and FSD approaches because a high rate of dose reductions would be expected for the latter approach, as seen in PRIMA.
- 6.20 The benefit of niraparib versus placebo in terms of PFS in clinical practice may have been overestimated, based on the results in the ITT analysis in PRIMA:
- About 30% (223/733) of patients in PRIMA had BRCAm and the treatment benefit of niraparib in the BRCAm subgroup was larger than that in the ITT population. There was a 60% reduction in the risk of progression or death (per BICR) for patients randomised to receive niraparib compared to placebo for BRCAm subgroup (HR = 0.40, 95% CI: 0.265, 0.618). Comparing niraparib with placebo within the BRCAm patients in PRIMA biased the results in favour of niraparib, since placebo is an inferior comparator for these patients in current clinical practice.
  - Fifty one percent of patients in PRIMA had HRD positive tumours. Niraparib appears to be more effective in terms of PFS among patients with HRD positive tumours (HR= 0.43, 95% CI: 0.31, 0.59) compared to patients with HRD negative

tumours (HR= 0.68, 95% CI: 0.49, 0.94) or not determined (HR= 0.85, 95% CI: 0.51, 1.43).

- PRIMA was only relevant to Stage III R0-1 non-BRCAM patients in clinical practice and higher risk non-BRCAM patients who do not elect to be treated with bevacizumab, as this was the group for which placebo is an appropriate comparator. The submission presented the subgroup analysis for Stage III R0-1 non-BRCAM patients (HR 0.52, 95% CI: 0.38, 0.72)<sup>7</sup>. However, BRCAM status was not a stratification factor at randomisation and the subgroup analysis for Stage III R0-1 non-BRCAM patients was post-hoc and exploratory. Although niraparib may be more effective than placebo in terms of reduction in the risk of progression, the magnitude of the treatment benefit cannot be reliably assessed based on the subgroup analysis. The ESC noted that insufficient information regarding this subgroup was provided in the submission to allow a comprehensive evaluation of the clinical effectiveness reported. Importantly, baseline demographic information was not provided, particularly with regard to HRD status. Therefore, the ESC agreed with the Commentary that there was a high degree of uncertainty associated with this post-hoc subgroup analysis and noted that this subgroup was modelled in a scenario analysis in the economic model.

- 6.21 The PBAC noted that the PFS results for niraparib compared with placebo differed substantially for patient subgroups based on BRCA and HRD status and this was consistent with trials for other PARP inhibitors in the first line setting (olaparib + bevacizumab PAOLA-1 trial, and veliparib VELIA trial).
- 6.22 The relevance of the ITT results of PRIMA to Australian clinical practice was limited as a considerable proportion of patients in the control arm (BRCAM, sub-optimally debulked Stage IIIB/IIIC and Stage IV) were treated with placebo, while there are active treatments (olaparib and bevacizumab) available in current clinical practice. The ESC noted that approximately one quarter of the proposed patient population would be expected to be BRCAM and therefore eligible for PBS olaparib, consistent with the estimate of 25.3% recognised by the PBAC previously (olaparib PSD, July 2020 PBAC meeting), thereby supporting the importance of olaparib as a relevant comparator in Australian clinical practice.
- 6.23 An anchored indirect comparison (performed during the evaluation) between niraparib and olaparib (in terms of PFS) was numerically in favour of olaparib and did not rule out inferiority of niraparib to olaparib (HR = 1.43, 95% CI: 0.83, 2.45 for niraparib versus olaparib in the overall BRCAM patient population, and HR = 1.11, 95% CI: 0.58, 2.12 for niraparib versus olaparib in BRCAM patient population post NACT-

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<sup>7</sup> Note that the non-BRCAM Stage III R0-1 results are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for PRIMA. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

IDS subgroup)<sup>8,9</sup>. The PSCR stated that these analyses have the potential to mislead (due to heterogeneity across the trials that may confound the ITC).

The Commentary suggested that to inform the treatment effect of niraparib compared with its appropriate comparators, a more reasonable approach may have been to pursue an indirect comparison using the Bucher method, or a matched-adjusted indirect comparison (MAIC), and discuss concerns regarding the transitivity of the studies in the context of the results. The PSCR and pre-PBAC maintained that significant issues of heterogeneity across PRIMA and SOLO-1 trials (in terms of disease stage and extent of residual disease) will confound an indirect treatment comparison, and argued that a MAIC between gBRCA cohorts in SOLO-1 and PRIMA is not feasible given the limited overlap in residual disease categories, thereby precluding a clinical conclusion based on niraparib vs olaparib (see also paragraph 6.9).

### ***Comparative harms***

6.24 The key safety data in the PRIMA trial is presented below.

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<sup>8</sup> Note that the anchored indirect comparisons were conducted by the evaluation specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

<sup>9</sup> Note that the results for niraparib vs placebo in the BRCAm NACT-IDS subgroup included in the indirect comparison are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for PRIMA.

Table 5: Summary of key adverse events in the trial

PRIMA (DCO May 2019)	Niraparib	Placebo	Risk difference (95% CI)*	Relative risk (95% CI)*
<b>Overall population (SAF)</b>				
<b>N</b>	<b>484</b>	<b>244</b>	-	-
Mean treatment duration months (SD)	10.3 (6.6)	9.5 (5.9)	-	-
Any TEAE	478 (98.8)	224 (91.8)	7.0 (3.4, 10.5)	1.08 (1.04, 1.12)
Grade ≥ 3 TEAE	341 (70.5)	46 (18.9)	51.6 (45.2, 58.0)	3.74 (2.86, 4.88)
SAE	156 (32.2)	32 (13.1)	19.1 (13.2, 25.1)	2.46 (1.74, 3.48)
Any TEAE leading drug interruption	385 (79.5)	44 (18.0)	61.5 (55.5, 67.5)	4.41 (3.36, 5.79)
Any TEAE leading drug dose reduction	343 (70.9)	20 (8.2)	62.7 (57.4, 68.0)	8.65 (5.66, 13.21)
Any TEAE leading drug withdrawal	58 (12.0)	6 (2.5)	9.5 (6.0, 13.0)	4.87 (2.13, 11.13)
Any TEAE leading to death	2 (0.4)	1 (0.4)	0.003 (-0.98, 0.99)	1.01 (0.09, 11.07)
<b>Fixed starting dose</b>				
<b>N</b>	<b>315</b>	<b>158</b>	-	-
Mean treatment duration months (SD)	11.3 (7.3)	10.0 (6.6)	-	-
Any TEAE	313 (99.4)	148 (93.7)	5.7 (1.8, 9.6)	1.06 (1.02, 1.11)
Grade ≥ 3 TEAE	239 (75.9)	30 (19.0)	56.9 (49.2, 64.6)	4.00 (2.88, 5.55)
SAE	111 (35.2)	18 (11.4)	23.8 (16.6, 31.1)	3.09 (1.95, 4.90)
Any TEAE leading drug interruption	264 (83.8)	30 (19.0)	64.8 (57.5, 72.2)	4.41 (3.19, 6.11)
Any TEAE leading drug dose reduction	239 (75.9)	15 (9.5)	66.4 (59.8, 73.0)	8.00 (4.92, 13.0)
Any TEAE leading drug withdrawal	35 (11.1)	4 (2.5)	8.6 (4.3, 12.8)	4.39 (1.59, 12.13)
Any TEAE leading to death	2 (0.6)	0	NA	NA
<b>Individualised starting dose**</b>				
<b>N</b>	<b>169</b>	<b>86</b>	-	-
Mean treatment duration months (SD)	8.6 (4.8)	8.6 (4.4)	-	-
Any TEAE	165 (97.6)	76 (88.4)	9.3 (2.1, 16.4)	1.11 (1.02, 1.20)
Grade ≥ 3 TEAE	102 (60.4)	16 (18.6)	41.8 (30.7, 52.8)	3.24 (2.05, 5.13)
SAE	45 (26.6)	14 (16.3)	10.3 (0.09, 20.6)	1.64 (0.95, 2.81)
Any TEAE leading drug interruption	121 (71.6)	14 (16.3)	55.3 (45.0, 65.7)	4.40 (2.70, 7.17)
Any TEAE leading drug dose reduction	104 (61.5)	5 (5.8)	55.7 (46.9, 64.6)	10.6 (4.5, 25.0)
Any TEAE leading drug withdrawal	23 (13.6)	2 (2.3)	11.3 (5.2, 17.4)	5.85 (1.41, 24.25)
Any TEAE leading to death	0	1 (1.2)	NA	NA

Source: Table 36 of the submission, p65 and Table 14.3.1.1A and 14.3.1.1B, PRIMA CSR

DCO = data cut-off; SAF = safety population; TEAE = treatment emergent adverse event, SAE= serious adverse events; SD= standard deviation; NA = not applicable.

\*Calculated during the evaluation using R software

\*\* 44 patients received 300mg starting dose, 125 patients received 200mg starting dose

Note that the results denoted by (\*) presented in Table 5 are derived from post-hoc analyses conducted by the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for PRIMA. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.25 Overall, there were higher rates of treatment emergent adverse events (TEAEs), grade ≥3 TEAEs, serious adverse events (SAE), TEAEs leading to drug interruption, drug reduction and drug withdrawal in the niraparib arm compared to placebo arm. This was observed in the overall population, in the FSD population and the ISD population. Two deaths due to TEAEs were reported in the niraparib arm (with the FSD). The rate of grade ≥3 TEAEs, serious adverse events (SAE), TEAEs leading to drug interruption, or drug reduction were lower with the use of ISD compared to the FSD, however, TEAEs leading to drug withdrawal were almost the same (albeit slightly higher with the ISD).

- 6.26 The ESC noted that, as discussed in the TGA clinical evaluation report, there remains a clinical concern about the rates of myelodysplastic syndromes (MDS) and/or acute myeloid leukaemia (AML) for patients treated with PARP inhibitors. The rate of MDS/AML based on review of niraparib trials was 15/1785 patients (0.8%) in December 2019 but further follow-up data would provide a more accurate estimate of risk.
- 6.27 Olaparib and bevacizumab safety data were presented in the submission, however no formal comparison of safety outcomes were provided. Overall, olaparib seems to have a better safety profile compared to niraparib:
- The rate of dose reduction in the SOLO-1 trial was much lower than that in the PRIMA trial (28.5% in olaparib arm, compared to 70.9% in the niraparib arm (ITT) and 61.5% in the niraparib ISD arm) despite the longer duration of treatment exposure in the SOLO-1 trial (20 months versus 10 months respectively).
  - An indirect comparison performed during the evaluation between olaparib and niraparib (ISD), although underpowered, showed that the rate of TEAEs, TEAEs of  $\geq$  Grade 3 and discontinuation due to TEAEs were consistently in favour of olaparib, with statistical significance reached for Grade  $\geq$ 3 TEAEs.
- 6.28 Given the lack of head-to-head trials of niraparib versus olaparib in the BRCAm population, and versus bevacizumab in the sub-optimally debulked Stage IIIB/IIIC and Stage IV patients, conclusions regarding the safety of niraparib relative to appropriate comparators are limited.
- 6.29 The PBAC noted that for niraparib, the rates of some adverse events were reduced in the ISD cohort compared with the FSD cohort, and the ISD would be most applicable to the PBS population if used as proposed in the draft PI.

### ***Benefits/harms***

- 6.30 A summary of the comparative benefits and harms for niraparib versus placebo is presented in the table below.

**Table 6: Summary of comparative benefits and harms for niraparib versus placebo in the PRIMA ITT population**

<b>Benefits</b>						
<b>Progression-free survival (PFS) (DCO May 2019) according to BICR</b>						
<b>Event</b>	<b>Niraparib</b>	<b>Placebo</b>	<b>Absolute difference</b>		<b>HR (95% CI)</b>	
Progressed or died, n (%)	232/487 (47.6%)	155/246 (63.0%)	15.4%		0.62 (0.50, 0.76)	
Median PFS (95% CI), months	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)	5.6 months			
PFS at 12 months <sup>^</sup> (95 % CI)	0.53 (0.48, 0.58)	0.35 (0.29, 0.42)	18%*			
PFS at 24 months <sup>^</sup> (95 % CI)	0.32 (0.25, 0.39)	0.23 (0.14, 0.32)	9%*			
<b>Overall survival (OS) (DCO May 2019)</b>						
Deaths, n/N (%)	48/487 (9.9%)	31/246 (12.6%)	2.7%		0.70 (0.44, 1.11)	
Median OS (95% CI) months	NR	NR	NA			
OS at 12 months <sup>^</sup> (95 % CI)	0.94 (0.91, 0.96)	0.92 (0.88, 0.95)	2%#			
OS at 24 months <sup>^</sup> (95 % CI)	0.84 (0.78, 0.89)	0.77 (0.63, 0.86)	7%#			
<b>Harms</b>						
	<b>Niraparib n/N</b>	<b>Placebo n/N</b>	<b>Relative risk (95% CI)<sup>§</sup></b>	<b>Event rate/100 patients</b>		<b>Risk difference (95% CI)<sup>§</sup></b>
				<b>Niraparib</b>	<b>Placebo</b>	
TEAEs of grade 3-4	341/484	46/244	3.74 (2.86, 4.88)	70.5	18.9	51.6% (45.2%, 58.0%)
SAEs	156/484	32/244	2.46 (1.74, 3.48)	32.2	13.1	19.1% (13.2%, 25.1%)
TEAEs leading to treatment discontinuation	58/484	6/244	4.87 (2.13, 11.13)	12.0	2.5	9.5% (6.0%, 13.0%)

Source: Table 48, p81, Table 49, p84, and Table 58, p97 of the submission.

BICR = blinded independent central review; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NA= not applicable; NR= not reported; OS= overall survival; PFS= progression free survival; TEAE = treatment emergent adverse event, SAE= serious adverse events.

\*Absolute difference in risk of progression or death at each time point (calculated during the evaluation)

#Absolute difference in risk of death at each time point (calculated during the evaluation)

<sup>^</sup> Results were presented in the submission as survival distribution function with estimates calculated from product-limit (Kaplan-Meier) method. Confidence intervals constructed using log-log transformation

<sup>§</sup> Calculated during the evaluation using R software

Note that the results denoted by (\*,#,\$) presented in Table 6 are derived from post-hoc analyses conducted by the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for PRIMA. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.31 Based on the direct evidence presented in the submission for the newly diagnosed advanced high-grade ovarian cancer who are in partial or complete response to platinum-based chemotherapy, irrespective of BRCA status or surgical outcomes, for every 100 patients treated with niraparib in comparison to no active treatment, and followed over a median duration of 15 months:

- Approximately 9 more patients would remain progression-free at 24 months;
- Approximately 52 more patients would experience a grade 3-4 treatment emergent adverse event;
- Approximately 19 more patients would experience a serious adverse event;
- Approximately 10 more patients would experience a treatment-related adverse event that leads to treatment discontinuation.

### **Clinical claim**

- 6.32 The submission described niraparib as superior to “no active treatment” (placebo) in terms of PFS. OS results were immature and no statistical difference was observed in terms of OS between niraparib and placebo.
- 6.33 The submission described niraparib as having a manageable safety profile. Niraparib was inferior to placebo in terms of safety, with more grade  $\geq 3$  TEAEs, SAEs, and TEAEs leading to drug discontinuation being observed in the niraparib arm compared to placebo arm.
- 6.34 Although the claim of superiority in terms of PFS may be adequately supported by the PRIMA trial, its relevance to Australian clinical practice was limited as placebo was not an appropriate comparator for a considerable proportion of patients in the ITT population of PRIMA (BRCAm, sub-optimally debulked Stage IIIB/IIIC and Stage IV), where active treatments (olaparib and bevacizumab) are available in current clinical practice. The PBAC noted that the subgroup analysis for Stage III R0-1 non-BRCAM patients was post-hoc and exploratory and agreed with the ESC that the magnitude of the treatment benefit cannot be reliably assessed based on this subgroup analysis.
- 6.35 The pre-PBAC response stated that an ITC would not adequately inform a clinical claim for niraparib vs olaparib, due to heterogeneity between the SOLO-1 and PRIMA trials. The PSCR argued “given the available evidence (PRIMA, SOLO-1, ICON-7), the comparative effectiveness and safety of niraparib vs olaparib or bevacizumab is unable to be reliably quantified; mandating a corresponding clinical conclusion is unwarranted. In such circumstances, it is reasonable that the clinical conclusion and subsequent economic evaluation be informed by the comparison of niraparib vs SMM”. The ESC noted that the PSCR had not addressed the fundamental clinical issue raised by the Commentary that a clinical claim based purely on the PRIMA trial is not relevant to current Australian clinical practice for the population requested for PBS listing.
- 6.36 The PBAC considered that the claim of superior comparative effectiveness compared to placebo, as proposed by the submission, was adequately supported by the data, noting that the magnitude of PFS benefit varied by patient subgroup on the basis of BRCA and HRD status (paragraph 6.20). The PBAC considered that in the HRD negative or not determined subgroup the PFS benefit was small and may not be clinically meaningful. The PBAC noted that no OS benefit was demonstrated. Further, the PBAC considered that the evidence presented in the submission to support the clinical claim was not fully applicable to the Australian setting because it did not present an adequate comparison versus relevant comparators, olaparib and bevacizumab.
- 6.37 The PBAC considered that niraparib was inferior to placebo in terms of safety, with more grade  $\geq 3$  TEAEs, SAEs, and TEAEs leading to drug discontinuation being observed in the niraparib arm compared to placebo arm. The PBAC noted that no formal comparison of safety between niraparib and olaparib was presented, but considered that overall, olaparib seems to have a better safety profile compared to niraparib

based on the lower rate of dose reduction in the SOLO-1 trial compared to that in the PRIMA trial. The PBAC also noted this was consistent with its previous consideration of comparative safety for niraparib in the 2L maintenance setting (paragraph 7.8, olaparib PSD, March 2021 PBAC Meeting).

### ***Economic analysis***

- 6.38 The submission presented a CUA, based on the PRIMA trial that compared niraparib with no active treatment (SMM) for the first line maintenance treatment in patients with newly diagnosed advanced HGEOC who are in response to platinum based chemotherapy. While the presentation of a CUA based on the PRIMA trial was consistent with the clinical claim presented in the submission, neither the clinical claim nor the model are applicable to Australian clinical practice, as no active treatment was not the only appropriate comparator in the proposed population. The PBAC agreed with the ESC that this limitation is likely to mean that the economic evaluation presented is not an accurate representation of the cost-effectiveness of niraparib in clinical practice.
- 6.39 The submission did not present an economic evaluation of niraparib compared with olaparib for patients with BRCAm, or compared with bevacizumab for patients with non-BRCAm who are treated with bevacizumab.
- 6.40 The model presented in the submission may be reasonable only for the subgroup of patients in whom there are no alternate first-line maintenance treatment options, i.e. Stage III R0-1 non-BRCAm patients, which represented 57% (271/473) of non-BRCAm patients in the PRIMA trial, or 37% (271/733) of the ITT population. Although the results based on the subgroup analysis were presented in the submission, the subgroup analysis was post-hoc and exploratory, and so the magnitude of the treatment effect of niraparib in the subgroup was uncertain.
- 6.41 The PSCR stated that to proceed with an economic evaluation vs olaparib or bevacizumab in the absence of sufficient clinical evidence to determine comparative efficacy/safety is inappropriate and would result in a highly uncertain economic analysis. The PSCR contended that the current approach provides an appropriate model for decision making, and which CADTH and NICE have adopted in their determination of the cost effectiveness of niraparib in the NDA HGEOC setting. The PSCR stated that providing a like for like comparison in a cost utility analyses (i.e., cost per QALY), alignment of the ICER of the current economic evaluation for niraparib with that recommended for olaparib in 1L BRCAm NDA HGEOC (July 2020) will act as an indirect economic comparison. The ESC noted that the sponsor's submission to CADTH presented an additional analysis comparing niraparib with active surveillance and olaparib in the BRCAm population and assumed olaparib would have equivalent

efficacy (i.e., PFS and OS) and time-to-treatment discontinuation as niraparib (p13, pCODR expert review committee final recommendation<sup>10</sup>).

6.42 The model structure, key inputs and rationale are summarised in the table below.

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

Component	Summary
Treatments	Niraparib vs no active treatment
Time horizon	20 years in the model base case versus 15.3 months OS median follow-up in PRIMA
Outcomes	LYG, QALYs
Methods used to generate results	Partitioned survival model (i.e. area under the curve)
Health states	PF (incorporating a 'cured' fraction), PD and death states.
Cycle length	One month
Allocation to health states	Progression-free survival and overall survival curves, which were adjusted using life tables to account for the proportion of 'cured' patients that prior to initiation of 1L maintenance treatment, were used to estimate the proportion of patients in PF, PD and death states.
Extrapolation method	Observed PFS and OS KM data from the PRIMA trial were applied until median follow-up, after which, dependent parametric models, fitted to the KM data, were used to extrapolate survival to the model time horizon. The niraparib TTD KM curve from PRIMA, extrapolated beyond median follow-up, was used to inform niraparib treatment duration. Approximately 98% of the undiscounted incremental life-years gained for niraparib over no active treatment were accrued over the extrapolated period.
Health related quality of life	EQ-5D-5L data from PRIMA ITT cohort translated to utility values via an Australian algorithm (Norman 2013) (PF=0.777; PD=0.689).

Source: Table 70, p112 of the submission.

1L = first-line; EQ-5D-5L = European Quality of Life Scale 5-dimension 5-level; ITT = intention to treat; KM = Kaplan-Meier; LYG = life years gained; OS = overall survival; PD = progressed disease; PF = progression free; QALYs = quality-adjusted life years; TTD = time to treatment discontinuation.

6.43 The PRIMA trial was used to inform a number of inputs in the economic model, including clinical outcomes for PFS and OS, treatment exposure (time to treatment discontinuation [TTD] and dose intensity), health state utility values and adverse event rates. While this is reasonable, data from different cohorts from PRIMA were used to inform different inputs. The ITT cohort was used to inform the clinical outcomes and niraparib treatment duration in uncured patients, but niraparib dosing and incidence of AEs was based on the ISD cohort. PFS, OS and TTD data for the ISD cohort of the PRIMA trial were not included in the submission's model, and so cannot be tested in a sensitivity analysis. The ESC considered that the ISD approach is unlikely to have had a major impact on efficacy outcomes or duration of treatment (see also paragraph 6.19).

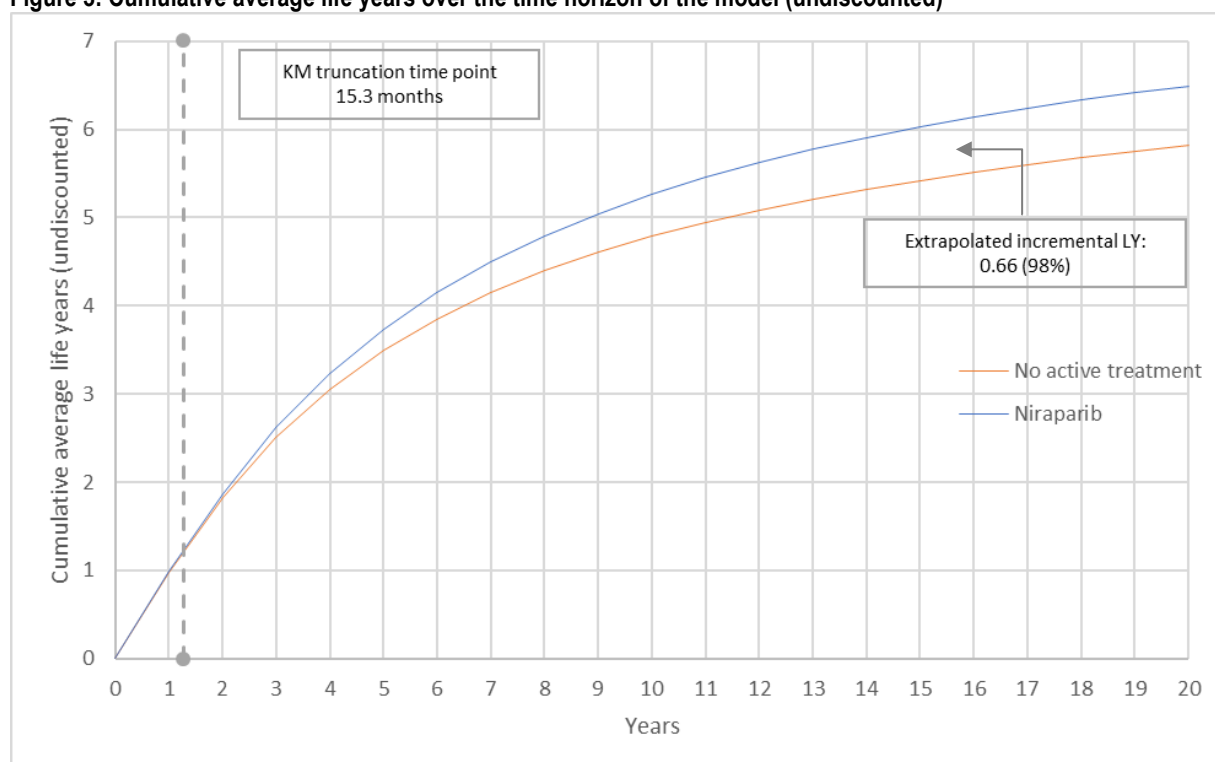
6.44 As noted above, the OS data were immature in PRIMA. The model assumed a continued treatment effect beyond the end of the trial, which was not adequately justified in the submission, and introduced substantial uncertainty to the modelled results. The OS benefit modelled for niraparib compared with no active treatment was

<sup>10</sup> pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

[https://www.cadth.ca/sites/default/files/pcodr/Reviews2021/10224NiraparibOC\\_fnRec\\_pERC%20Chair%20Approved\\_Post29Apr2021\\_final.pdf](https://www.cadth.ca/sites/default/files/pcodr/Reviews2021/10224NiraparibOC_fnRec_pERC%20Chair%20Approved_Post29Apr2021_final.pdf)

accrued primarily (98%) in the extrapolated period beyond trial observation (see Figure 3). The base case analysis predicted that approximately 8% of patients treated with niraparib and about 6% of patients receiving no active treatment would remain alive at the nominated model time horizon of 20 years. The PBAC noted that it previously accepted a model time horizon of 20 years for olaparib (paragraph 7.13, olaparib PSD, July 2020 PBAC meeting). However the PBAC noted that 20 years may be too long for the non-BRCAM population and introduced additional uncertainty due to the immaturity of the OS data from PRIMA.

Figure 3: Cumulative average life years over the time horizon of the model (undiscounted)



Source: Figure constructed during the evaluation, based on data from the 'Zejula (niraparib) 1L ITT CEA.xlsx' workbook  
LY = life-years.

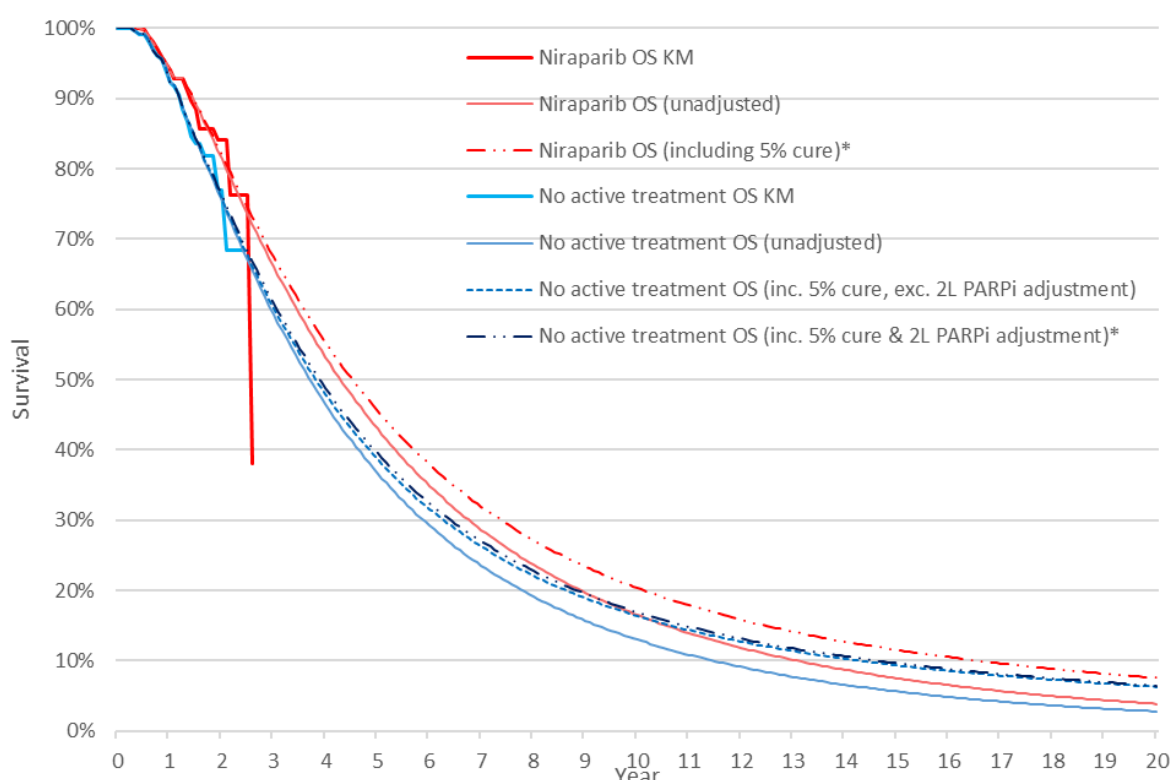
6.45 The model used observed Kaplan-Meier data from the PRIMA trial until median follow-up for both PFS and OS, and then extrapolated the curves using dependent parametric functions. The assumption of proportional hazards may not be reasonable for either PFS<sup>11</sup> or OS (due to immature data). The log-normal model was used in the base case analysis for PFS extrapolation. The incremental cost effectiveness ratio (ICER) is not sensitive to the truncation time point for PFS extrapolation or the parametric model chosen to extrapolate PFS. The log-normal model was also used in the base case analysis for OS extrapolation. The ICER was sensitive to changes in both the model chosen for OS extrapolation and the truncation time point. The Gamma and Weibull

<sup>11</sup> National Institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy - Technology appraisal guidance. 2021.

models were also a reasonable fit to the observed Kaplan-Meier data and the ICER was sensitive to the use of these alternate models (21% and 38% increase in the ICER, respectively). Modelled survival in the SMM arm at 10 years, including the cured fraction, is 5% using the Weibull model, 6% with Gamma and 11% with the log-logistic model.

- 6.46 A comparison of the OS curves with and without the adjustment for the cured fraction and after applying the adjustment for subsequent PARPi (applicable only to the no active treatment arm) is presented below.

Figure 4: Extrapolated OS curves, with and without adjustment for a ‘cured’ fraction and subsequent PARPi use



Source: Adapted from Figure 43, p134, Figure 44, p135, Figure 54-56, p 143 and Figure 58, p145 of the submission

KM = Kaplan-Meier; OS = overall survival; PARPi = poly ADP ribose polymerase inhibitor.

\* The base case of the economic model includes 5% cure fraction in niraparib arm, whereas in the no active treatment arm both the 5% cure fraction and the adjustment for subsequent 2L PARPi use are applied.

- 6.47 In the extrapolated period, the PFS, OS and TTD curves were adjusted to take into account a proportion of patients who were ‘cured’ prior to receiving first-line maintenance treatment. The submission claimed that this adjustment was made for consistency with previous PBAC considerations (paragraph 7.20, olaparib PSD, November 2019 PBAC meeting). This proportion was assumed to be 5% based on literature reporting long-term PFS in ovarian cancer cohorts (Irodi 2020, Oliver 2017

and Vergote 2018)<sup>12</sup>, and was assumed to be the same in both model arms. Therefore, ‘cured’ patients in the niraparib arm of the model received no benefit from treatment, although incurred a cost. The ICER was moderately sensitive to the proportion of cured patients modelled (13% increase in the ICER when the cured fraction increased to 10%). Cured patients were assumed to remain on treatment unless they died due to other causes, up to a maximum treatment duration of three years. The proposed restriction did not specify a maximum treatment duration, therefore, the assumption that all cured patients would cease treatment at three years may underestimate the cost of niraparib. Further, it may not be reasonable to model different stopping rules by cured status as, in practice, clinicians may not be able to distinguish a cured from an uncured patient who remains progression-free.

- 6.48 The model also applied an adjustment to the OS curve in the no active treatment arm to account for PARPi use in the later-line maintenance setting for BRCAm patients. The adjustment assumed that a proportion of patients with BRCAm tumours would receive second-line olaparib and that their survival would be the same as the ITT observed in the niraparib arm. The Commentary considered this method of adjustment inappropriate and underestimates the effect in the comparator arm, as BRCAm patients in the comparator arm will receive a superior treatment response than the ITT population receiving niraparib. The ESC considered that it was unclear whether this assumption would favour niraparib or the comparator as patients may respond better to treatment in the first-line setting than the second-line setting, but BRCAm patients would be expected to have a superior treatment response than the ITT population.
- 6.49 Although the proportion of patients in the no active treatment arm that received second line olaparib in the model was relatively small (15.6%<sup>13</sup>, 51.3% of BRCAm patients based on the prevalence of BRCAm in PRIMA) it was higher than the proportion of progressed patients who received second-line PARPi in the PRIMA trial, 10.4%. The PSCR argued this was consistent with the input accepted for olaparib in the 1L setting (51%; para 6.49, olaparib PSD, July 2020), however the value accepted in the olaparib submission was the proportion of progressed BRCAm patients. The cost of second-line PARPi use is the main source of cost-offsets modelled and has a high

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<sup>12</sup> Irodi A, Rye T, et al. Patterns of clinicopathological features and outcome in epithelial ovarian cancer patients: 35 years of prospectively collected data. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2020;127(11):1409-20.

Oliver KE, Brady WE, et al. An evaluation of progression free survival and overall survival of ovarian cancer patients with clear cell carcinoma versus serous carcinoma treated with platinum therapy: An NRG Oncology/Gynecologic Oncology Group experience. *Gynecol Oncol*. 2017;147(2):243-9.

Vergote I, Coens C, et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. *The Lancet Oncology*. 2018;19(12):1680-7.

<sup>13</sup> Calculated by multiplying 73% (the number of patients who progress from cycle four onwards, to reflect response to 1L platinum-based chemotherapy) x 28.9% (proportion of BRCAm) x 82% (response rate to 2L platinum-based chemotherapy) x 90% (uptake rate of 2L PARPi).

impact on the ICER. In the context of the availability of olaparib in the first-line setting, where treatment duration is limited to 24 months, modelling second-line use of olaparib (which is not restricted in duration on the PBS) will overstate the cost-offsets realised in the Australian setting.

- 6.50 The evaluation noted that 21.5 months was previously accepted by the PBAC for olaparib in 2L BRCAm PSR HGEOC based on Study 19 (para 7.16, olaparib PSD July 2020), whereas the current economic model applies 29.1 months based on SOLO-2 (compared with 16 months for first-line niraparib). The PSCR argued that SOLO-2 represents the best available evidence for currently utilised olaparib in the 2L BRCAm PSR HGEOC setting. The ESC noted that this assumption favoured niraparib and considered that Study 19 was a reasonable source of treatment duration and was consistent with previous considerations of olaparib.
- 6.51 The pre-PBAC response maintained that cost offsets associated with use of 2L olaparib were appropriate because the intention of the model was to reflect the treatment pathway for 1L SMM BRCAm patients who had progressed (by definition these patients had not received 1L olaparib). The pre-PBAC response maintained that a treatment duration of 29.1 months is most applicable to olaparib in the 2L setting because it is based on the currently available tablet formulation of olaparib, whereas the 21.5 month duration was based on a trial of a capsule formulation of olaparib which will be delisted in January 2022.
- 6.52 The Commentary noted that as olaparib has been listed on the PBS in the first-line maintenance setting for BRCAm patients, use of olaparib in the later-line setting is unlikely. The PBAC considered that the majority of BRCAm patients are currently treated with olaparib as a first-line maintenance therapy in clinical practice, and therefore the model did not reflect clinical practice. The PBAC agreed with the ESC that it would have been more appropriate to adjust the comparator arm of the model for olaparib use in the first-line setting based on a matched adjusted indirect comparison with the SOLO1 study. The ESC considered that overall, assumptions around second line use of olaparib appear to overestimate the cost offsets for second-line PARP inhibitors in the model.
- 6.53 In the base case analysis, the submission used the progression free (PF) and progressed disease (PD) health states 5 level EuroQol 5-dimension Questionnaire (EQ-5D-5L) data from the PRIMA trial, and translated these to utilities using an Australian based mapping algorithm (Norman 2013)<sup>14</sup>, irrespective of treatment. The utilities from the PRIMA study with UK based preferences were applied in sensitivity analyses. The ICER is not sensitive to the use of these alternate values. The submission did not apply a disutility associated with niraparib treatment compared with no active treatment, which is not appropriate and biased the results in favour of niraparib.

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<sup>14</sup> Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. *Appl Health Econ Health Policy*. 2013;11(3):287-98.

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6.54 The key drivers of the niraparib vs no active treatment model are summarised below.

Table 8: Key drivers of the model

Description	Method/Value	Impact Base case ICER \$ ██████ <sup>1</sup> /QALY
Extrapolation	Treatment effect continued beyond 15 month trial period for up to 20 years; and the choice of log-normal parametric functions used for OS extrapolation	High, favours niraparib Use of Weibull model to extrapolate OS data increased the ICER to \$ ██████ <sup>2</sup> /QALY gained, use of Gamma model increased the ICER to \$ ██████ <sup>1</sup> /QALY gained.
Dose intensity of niraparib	Based on ISD cohort of PRIMA	Moderate, favours niraparib When using data from ITT cohort, the ICER increased to \$ ██████ <sup>1</sup> /QALY.
Proportion of patients that receive 2L olaparib	15.6% <sup>a</sup> compared to 10.4% (13/125) patients in the PRIMA trial who had received any subsequent therapy	High, favours niraparib. When the proportion is reduced to 10.4%, the ICER increases to \$ ██████ <sup>2</sup> /QALY. When no 2L olaparib use is assumed, the ICER increases to \$ ██████ <sup>3</sup> /QALY.
Duration of 2L olaparib treatment	29.1 months, based on the final analysis of the SOLO-2 trial	High, favours niraparib. When the duration is reduced to 21.5 months, as previously considered by the PBAC, the ICER increases to \$ ██████ <sup>2</sup> /QALY.

Source: Compiled during the evaluation based on Table 118, pp182-183 of the submission.

2L = second-line; ICER = incremental cost effectiveness ratio; ISD = individualised starting dose; ITT = intention to treat; OS = overall survival; QALY = quality-adjusted life year.

<sup>a</sup> This was estimated assuming that 73% of patients would progress after month 4 (those that progressed prior to month 4 were assumed not to be eligible for subsequent PARPi as they were not considered to have responded to first-line platinum-based chemotherapy), of which 28.9% were BRCAm, with 82% responding to 2L platinum-based chemotherapy and 90% uptake 2L PARPi.

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$115,000 to < \$135,000

6.55 The results of the model are summarised in the table below.

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Table 9: Results of the stepped economic evaluation

Step and component	Niraparib	No active treatment	Increment
<b>Step 1: Trial-based analysis (24-month analysis)</b>			
Costs	\$ [redacted]	\$0	\$ [redacted]
PFLY	1.17	0.92	0.25
Incremental cost/extra PFLY gained			\$ [redacted] <sup>1</sup>
<b>Step 2: Extrapolation of trial data from median follow-up to 20-year time horizon</b>			
Costs	\$ [redacted]	\$0	\$ [redacted]
PFLY	1.73	1.12	0.60
LYG	4.83	4.27	0.56
Incremental cost/extra PFLY gained			\$ [redacted] <sup>2</sup>
Incremental cost/extra LYG gained			\$ [redacted] <sup>2</sup>
<b>Step 3: Translation of trial outcomes to QALYs</b>			
Costs	\$ [redacted]	\$0	\$ [redacted]
QALYs	3.48	3.04	0.44
Incremental cost/extra QALY gained			\$ [redacted] <sup>3</sup>
<b>Step 4: Inclusion of 'cured' patients into extrapolated survival curves (PFS, OS and TTD)</b>			
Costs	\$ [redacted]	\$0	\$ [redacted]
QALYs	3.77	3.34	0.43
Incremental cost/extra QALY gained			\$ [redacted] <sup>3</sup>
<b>Step 5: Application of health care resource costs and OS adjustment to reflect subsequent 2L PARPi use in comparator arm (OS HR=1 for patients who receive no active treatment followed by olaparib relative to patients who receive niraparib followed by no active treatment)</b>			
Costs	\$ [redacted]	\$74,413	\$ [redacted]
QALYs	3.77	3.38	0.39
Incremental cost/extra QALY gained			\$ [redacted] <sup>4</sup>
<b>Step 6: Translation of exposure to an Australian setting (PRIMA ITT cohort to ISD cohort)</b>			
Costs	\$ [redacted]	\$74,409	\$ [redacted]
QALYs	3.77	3.38	0.39
<b>Incremental cost/extra QALY gained (base case)</b>			<b>\$ [redacted]<sup>4</sup></b>

Source: Compiled during evaluation based on Table 113, p178 of the submission and 'Results' worksheet of the 'Zejula (niraparib) 1L ITT CEA.xlsx' workbook

LYG = life-years gained; PFLY = progression-free life year; QALY = quality-adjusted life-year.

The redacted values correspond to the following ranges:

<sup>1</sup> \$155,000 to < \$255,000

<sup>2</sup> \$95,000 to < \$115,000

<sup>3</sup> \$115,000 to < \$135,000

<sup>4</sup> \$55,000 to < \$75,000

- 6.56 There is no translation step or capacity in the model to adjust the comparator to active treatment for a proportion of patients as would be expected in Australian clinical practice, therefore the ICER does not directly inform the funding decision relevant to the submission.
- 6.57 The above stepped results table indicates that the extrapolation from the trial period to 20 years, the application of health care resource costs and OS adjustment for increased use of subsequent PARPi post progression in the no active treatment arm had large impacts on the results of the model.
- 6.58 The translation of niraparib dose intensity from the ITT population in PRIMA to the ISD cohort had a moderate impact on the result of the model. Although ISD was consistent with the proposed dose regimen, the health outcomes used in the model remained

based on the ITT population where the majority of patients (65%) received a fixed (300 mg) starting dose of niraparib. In those that initiated treatment according to the ISD protocol, 74% (125/169) received a lower (200 mg) starting dose. PFS, OS and TTD data for the ISD cohort of the PRIMA trial were not included in the submission's model, and so could not be tested in a sensitivity analysis. The ESC noted that use of the ISD for drug exposure may favour niraparib, whereas use of the ITT population for drug exposure was more conservative but raised applicability issues as the ISD is more likely to be used in practice. The ESC noted that dose reductions were more frequent in the FSD cohort compared with the ISD cohort and therefore the dose intensity of the two cohorts was not substantially different (mean dose intensity in FSD 181.4 mg/day in FSD compared with 162.1 mg/day in ISD cohort<sup>15</sup>).

- 6.59 The submission presented a scenario analysis for the subgroup of patients with non-BRCaM Stage III R0+R1 disease. Although the results from the PRIMA trial from this subgroup were more favourable (resulting in an ICER of \$45,000 to < \$55,000/QALY compared to \$55,000 to < \$75,000 /QALY in the base case), this post-hoc analysis was exploratory, and therefore likely to be associated with a high degree of uncertainty. The PBAC agreed with ESC that the ICER for the subgroup was not suitable as a basis for decision-making as the analysis was exploratory in nature, and based on a small sample size with immature data.
- 6.60 The results of key sensitivity analyses are summarised below.

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<sup>15</sup> *Note that the mean dose of treatment was provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

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Table 10: Results of key sensitivity analyses

Model variable	Incremental cost	Incremental QALYs	ICER per QALY	% difference
Base case	\$█████	0.39	\$█████ <sup>1</sup>	-
<b>Time horizon: 20 years</b>				
15 years	\$█████	0.37	\$█████ <sup>1</sup>	6%
10 years	\$█████	0.32	\$█████ <sup>1</sup>	22%
<b>Utility values: PRIMA ITT cohort (Australian dataset)</b>				
Olaparib PSD July 2020 PBAC meeting	\$█████	0.42	\$█████ <sup>1</sup>	-7%
PRIMA, ITT cohort (UK dataset)	\$█████	0.40	\$█████ <sup>1</sup>	-2%
<b>Utility decrements for AEs (not included)</b>				
Utility decrement for AEs included in model (0.03) <sup>b</sup>	\$█████	0.36	\$█████ <sup>1</sup>	8%
Utility decrement for all Grade 3/4 anaemia, thrombocytopenia and neutropenia events included (0.05) <sup>c</sup>	\$█████	0.34	\$█████ <sup>1</sup>	14%
<b>Dose intensity (based on the PRIMA ISD cohort)</b>				
PRIMA ITT cohort	\$█████	0.39	\$█████ <sup>a,1</sup>	18%
<b>OS extrapolation: Log-normal</b>				
Weibull	\$█████	0.29	\$█████ <sup>2</sup>	38%
Log-logistic	\$█████	0.34	\$█████ <sup>1</sup>	15%
Gamma	\$█████	0.33	\$█████ <sup>1</sup>	21%
<b>OS KM truncation time point: 15.3 months</b>				
Niraparib: 13.9 months, no active treatment: 13.8 months (PFS median follow-up time)	\$█████	0.34	\$█████ <sup>1</sup>	17%
<b>TTD extrapolation: Exponential</b>				
Weibull	\$█████	0.39	\$█████ <sup>1</sup>	-10%
Gompertz	\$█████	0.39	\$█████ <sup>1</sup>	-6%
Generalised Gamma	\$█████	0.39	\$█████ <sup>1</sup>	13%
Gamma	\$█████	0.39	\$█████ <sup>3</sup>	-9%
<b>Proportion of cured patients: 5%</b>				
0%	\$█████	0.40	\$█████ <sup>3</sup>	-14%
10%	\$█████	0.39	\$█████ <sup>1</sup>	13%
<b>Proportion of no active treatment patients receiving 2L olaparib: 15.6% (73.8% of platinum-sensitive BRCAm patients)</b>				
14.0% (51% of progressed BRCAm patients)	\$█████	0.40	\$█████ <sup>1</sup>	11%
10.4% (as per the PRIMA trial) (37.9% of progressed BRCAm patients)	\$█████	0.41	\$█████ <sup>2</sup>	38%
0%	\$█████	0.43	\$█████ <sup>4</sup>	109%
25.3% (BRCAm prevalence previously accepted by the PBAC), assuming the modelled treatment course cost of 1L niraparib (i.e. \$54,343) <sup>d</sup>	\$█████	0.36	\$█████ <sup>5</sup>	86%
<b>Duration of subsequent 2L olaparib use (29.1 months)</b>				
21.5 months (final average treatment duration from Study 19)	\$█████	0.39	\$█████ <sup>2</sup>	34%

Source: Compiled during the evaluation based on Section 3.9 Table 118, pp182-183 of the submission and conducted during the evaluation using the "Zejula (niraparib) 1L CEA.xlsx" workbook.

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2L = second-line; AE = adverse event; BRCAm = breast cancer susceptibility gene mutation; ICER = incremental cost effectiveness ratio; ISD = individualised starting dose; ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; PARPi = poly ADP ribose polymerase inhibitor; PFS = progression free survival; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

<sup>a</sup> This figure is different from the result of Step 5 in Table 9 due to the lower adverse event costs in ISD cohort compared to ITT cohort. During sensitivity analysis for dosing schedule, adverse event profile should be changed from 'ISD cohort' to ITT cohort' (cell 'D210') in the 'Costs' worksheet of the 'Zejula (niraparib) 1L ITT CEA.xlsx' workbook.

<sup>b</sup> This is calculated by applying thrombocytopenia: 14.80%, anaemia: 21.9% and neutropenia: 8.90% of patients, by weighted disutilities identified in the NICE Single Technology Appraisal for Niraparib TA673 [ID1680], (Source: Table 35, p 159 of Document B Company evidence submission, <https://www.nice.org.uk/guidance/ta673/evidence>).

<sup>c</sup> This is calculated by applying thrombocytopenia: 4.1%, and anaemia: 21.9% of patients. Estimation of differential disutility was based on the rates of treatment-related AEs from PRIMA SAF population, with application of AE disutilities as identified in the NICE document mentioned above.

<sup>d</sup> This analysis attempts to replicate 1L olaparib use as best as possible with the data provided in submission's model. This analysis does not adjust PFS with no active treatment and uses the ITT HR for the non-BRCAm population, and so the incremental QALYs gained likely remain an overestimate

*The redacted values correspond to the following ranges:*

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$45,000 to < \$55,000

<sup>4</sup> \$115,000 to < \$135,000

<sup>5</sup> \$95,000 to < \$115,000

- 6.61 The model was sensitive to the parametric functions for OS extrapolation and time horizon. The longer the model time horizon, the more health benefit would be modelled, given the assumed continued treatment benefit of niraparib. Since the OS data from PRIMA were immature, extrapolation based on such data introduced substantial uncertainty. The model was also sensitive to the dose distribution data that were used to estimate the cost/cycle of niraparib.
- 6.62 The PSCR proposed a new base case (as shown in Table 11) to account for the key drivers of the analysis (long term OS, dose intensity) to ensure the cost effectiveness of niraparib is maintained. The revised base case included the following changes:
- re-specification of the OS extrapolation function to the log-logistic model. The ESC noted that the log-logistic model was more conservative than the original log-normal model, however Gamma and Weibull models were also a reasonable fit to the observed Kaplan-Meier data and the ICER was sensitive to the use of these alternate extrapolation functions;
  - revised dose exposure & safety costs based on the ITT population in PRIMA. The PSCR acknowledged that applying exposure and safety costs based on the ISD PRIMA cohort introduces additional uncertainty into the model as clinical outcomes (PFS, OS and TTD) are based on the ITT PRIMA cohort in the economic model. The ESC noted that the exposure applied in the revised base case resulted in a slight increase in drug costs, consistent with the fact that patients treated with the FSD would have dose reductions due to AEs; and
  - a revised effective price of \$ [REDACTED] (100mg x 56) in order to maintain the ICER presented in the submission base case.

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**Table 11: Revised base case cost-effectiveness analysis of niraparib vs SMM in NDA HGEOC**

Model variable	Submission base case	Revised base case (PSCR)
#1. Dosing schedule	ISD	ITT
#2. Safety costs	AE rates in ISD cohort	AE rates in ITT cohort
#3. OS parametric extrapolation	Log-Normal	Log-Logistic
Niraparib effective price (100mg x 56)	\$ [REDACTED]	\$ [REDACTED]
ICER	\$ [REDACTED] <sup>1</sup>	\$ [REDACTED] <sup>1</sup>

Abbreviations: AE = adverse event; ICER = incremental cost effectiveness ratio; ISD = individualised starting dose; ITT = intent to treat; OS = overall survival

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

- 6.63 The pre-PBAC response noted that the ICER would reduce to \$45,000 to < \$55,000/QALY if the model assumed drug costs based on ISD use with no reduction to effectiveness.
- 6.64 The submission did not present an economic evaluation of niraparib compared to the clinically relevant comparators in Australian practice, i.e. compared to olaparib for BRCAm patients, and compared with bevacizumab for relevant non-BRCAm patients. The presentation of a cost utility analysis (CUA) for niraparib compared with no active treatment may be reasonable only for the subgroup of patients in whom there are no alternate first-line maintenance treatment options, non-BRCAm patients who are not treated with bevacizumab. This subgroup represents up to 57% (271/473) of non-BRCAm patients in the PRIMA trial, (37% of the whole study population).
- 6.65 The PBAC considered that the economic model provided in the submission was not reliable for decision making because it failed to present an economic evaluation that reflects the proposed circumstances of use of niraparib in the proposed PBS population. The PBAC considered it was reasonable to expect differences in comparative benefits and harms in the different patient subgroups if niraparib is used in place of olaparib, bevacizumab or SMM. Noting the differences in PFS benefit in the BRCAm and HRD positive subgroups demonstrated in the PRIMA trial, the PBAC considered that the efficacy outcomes were driven by inclusion of the BRCAm patients in the model. The PBAC noted that the approach taken in the economic model was also inconsistent with the proposed place in therapy and the utilisation and financial estimates presented.

## Drug cost/patient/course

Table 12: Drug cost per patient for niraparib (requested effective DPMQ)\*, olaparib and bevacizumab (PBS-listed prices)\*\* – 1L maintenance treatment of NDA HGEOC

	Niraparib			Comparators (olaparib and bevacizumab)		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose <sup>1</sup> in Cycle 1	PRIMA ITT cohort dosing <sup>a</sup> 203.7 mg/day	PRIMA ISD cohort dosing <sup>b</sup> 183.8 mg/day	PRIMA ISD cohort dosing <sup>b</sup> 183.8 mg/day	Ola: 300 mg BD <sup>f</sup> Bev: 600 mg Q3W <sup>g</sup>	Not used	Ola: 300mg BD Bev: 600 mg Q3W <sup>g</sup>
Mean duration	10.3 month <sup>c</sup>	16 months <sup>k</sup>	16.8 months	Ola: 20.9 months <sup>h</sup> Bev: not reported	Not used	Ola: 20.9 months <sup>h</sup> Bev: 8.9 months <sup>i</sup>
Cost/patient/course	\$ ██████ <sup>d</sup>	\$ ██████ <sup>e</sup>	\$ ██████	Ola: \$151,014 <sup>j</sup> Bev: –	Not used	Ola: \$151,014 <sup>j</sup> Bev: \$25,323

Source: Compiled during evaluation based on Table 36, p65 and Table 89, p154 of the submission and spreadsheet 'Trace-Niraparib, Zejula (niraparib) 1L ITT CEA.xlsx' workbook; Zejula (niraparib) 1L BIM.xlsx' workbook

1L = First line; Bev = bevacizumab; BD = twice daily; DPMQ = dispensed price for maximum quantity; DPMQ = dispensed price for maximum quantity; ISD = individualised starting dose, ITT = intention-to-treat; NDA HGEOC = newly diagnosed advanced high grade epithelial ovarian, fallopian tube or primary peritoneal cancer; Ola, olaparib; Q3W = every 3 weeks.

<sup>a</sup> Initial dose intensity for ITT cohort was 204 mg/day, decreasing to 160-170 mg/day from Cycle 4 onwards.

<sup>b</sup> Initial dose intensity for ISD cohort was 184 mg/day, decreasing to 150-158 mg/day from Cycle 4 onwards.

<sup>c</sup> Truncated mean treatment exposure for niraparib arm in the PRIMA overall safety population (Table 36, p65 of the submission)

<sup>d</sup> This figure is undiscounted and without half-cycle correction.

<sup>e</sup> This figure is undiscounted and includes the half-cycle correction applied in the model. The cost/patient/course is \$ ██████ without half-cycle correction (undiscounted).

<sup>f</sup> Dosage regimen as specified in the study protocol. Data on mean dose are not available.

<sup>g</sup> Dose regimen of 7.5 mg/kg Q3W and an average weight of 80 mg

<sup>h</sup> Treatment duration of olaparib in SOLO-1, sourced from Table 13, July 2020 olaparib PBAC public summary document

<sup>i</sup> Derived from the 2018 DUSC report on bevacizumab

<sup>j</sup> A factor of 95.3% (=1-1/21.5) was applied in calculating the drug cost per course to account for dose interruptions

<sup>k</sup> This figure is undiscounted and with half-cycle correction (The undiscounted mean duration without half-cycle correction is 16.5 months).

\* Requested effective DPMQ for niraparib: 84-capsule pack \$ ██████, 56-capsule pack \$ ██████.

\*\* Published DPMQ for olaparib: \$6,971.16 for both 100 mg-tablet pack and 150 mg-tablet pack; weighted dispensed price for bevacizumab: \$1,958.52 per administration.

<sup>1</sup> Note that the mean dose of treatment stated in Table 12 was provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose

6.66 The mean undiscounted cost per patient per course was \$ ██████, based on the mean treatment duration (16 months) at the price proposed in the submission. At the revised effective price for niraparib proposed in the PSCR (\$ ██████ per 56 capsules) this was reduced to \$ ██████. This was calculated by adding the cost per patient in each cycle during the treatment duration. The total cost of niraparib per cycle is estimated by multiplying the distribution of patient dosing per cycle, compliance (starting daily dose vs mean daily dose in each cycle) in the PRIMA ISD cohort (ITT population in the PSCR revised model).

### Estimated PBS usage & financial implications

6.67 This submission was not considered by DUSC.

6.68 The submission used an epidemiological approach to estimate the number of patients likely to be treated with niraparib as first-line maintenance therapy in newly

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diagnosed advanced HGEOC. The key inputs for financial estimates are summarised below.

**Table 13: Key inputs for financial estimates**

<b>Data</b>	<b>Value and Source</b>	<b>Comment</b>
Incidence of ovarian, fallopian tube or peritoneal cancer	1,594 in Year 1 to 1,683 in Year 6. AIHW ICD-10 codes C48, C56 and C57 (2000-2016); NZ MoH 4 character ICD code data	The use of AIHW data was appropriate. NZ MoH data was used to determine the proportion of ICD-10 codes that was applicable to the population of interest was of small sample size.
% with epithelial disease	90.9% AIHW 2010	The PBAC previously accepted an estimate of 16% of ovarian cancer with non-epithelial histology (Olaparib PSD, July 2020 PBAC meeting). Consistent with the above, the PSCR submitted a revised model using 83.7% instead of 90.9% (PSCR).
% with high-grade carcinoma	93.6% Analysis of patients in the AOCS (Alsop 2012)	
% advanced (FIGO III/IV) disease in high-grade ovarian cancer	81.8% Analysis of patients in the AOCS (Lindemann 2018)	
% treated with 1L PBC	91.5% Analysis of patients in the AOCS (Alsop 2012)	
Response rate (CR or PR) to 1L PBC	88.6% Analysis of response rates in ICON-8 trial (Morgan 2021)	
% with BRCAm (germline and/or somatic)	gBRCAm: 22.6% sBRCAm: 6.3% Total: 28.9% Alsop 2012; CGARN 2011	The PBAC previously accepted a prevalence of 20.3% for gBRCAm and 5% for sBRCAm (Olaparib PSDs, November 2019, March 2020 and July 2020 PBAC meetings).
% discontinuing olaparib as 1L therapy due to AEs	11.5% SOLO-1 trial	
Uptake of various first-line maintenance therapies without listing of niraparib	<u>BRCAM patients:</u> Bevacizumab: 15% in Year 1 to 5% in Years 3-6 Olaparib: 75% in Year 1 to 90% in Years 3-6 SMM: 10% in Year 1 to 5% in Years 3-6 <u>Non-BRCAM patients:</u> Bevacizumab: 41.4% in Years 1-6 SMM: 58.6% in Years 1-6 Submission's assumptions, 2018 DUSC report on bevacizumab, assumptions in previous olaparib submissions	The uptake rates were largely based on assumptions and were, therefore, uncertain.
Uptake of various first-line maintenance therapies with listing of niraparib	<u>BRCAM patients:</u> Niraparib: 26.3% in Year 1 to 45% in Years 3-6 Bevacizumab: 15% in Year 1 to 5% in Years 3-6 Olaparib: 48.8% in Year 1 to 45% in Years 3-6 SMM: 10% in Year 1 to 5% in Years 3-6 <u>Non-BRCAM patients:</u> Niraparib: 50% in Year 1 to 75% in Years 3-6 Bevacizumab: 30% in Year 1 to 15% in Years 3-6 SMM: 20% in Year 1 to 10% in Years 3-6 Submission's assumptions	As above  The ESC considered that niraparib uptake in BRCAM patients is unlikely to be as high as olaparib as there is less clinical experience with niraparib and no apparent safety advantages over olaparib.

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Data	Value and Source	Comment
Uptake of niraparib in patients discontinuing olaparib due to AEs	80% Submission's assumption	This was a likely overestimate. When the niraparib (later-line) submission was considered, the DUSC commented that the number of patients switching from olaparib to niraparib is likely to be very small and these patients could reasonably be removed from the estimates (Niraparib DUSC Advice, March 2021).
% remaining on niraparib treatment in subsequent treatment years	46% after 1 <sup>st</sup> year of treatment, 23% after 2 <sup>nd</sup> year to 1% after 6 <sup>th</sup> year Modelled TTD from PRIMA ITT	PRIMA ITT population included patients who initiated niraparib at a fixed starting dose. The treatment duration in these patients might not represent the treatment duration of niraparib, at its proposed individualised starting dose regimen.  The ESC also noted this would be impacted by a cap on treatment duration if applied in the niraparib restrictions.
No. of niraparib packs per patient in each treatment year	84-capule pack: 0.99 in the 1 <sup>st</sup> year of treatment, 0.30 in each subsequent years 56-capule pack: 8.79 in the 1 <sup>st</sup> year of treatment, 9.37 in each subsequent years Dose intensity and compliance data from PRIMA, individualised starting dose cohort*	This was the appropriate data source.
Treatment duration of bevacizumab maintenance therapy	12.93 doses 2018 DUSC report on bevacizumab	The ESC considered that the DUSC report was an appropriate source for the bevacizumab treatment duration.
No. of first-line olaparib scripts in each treatment year	10.3 in the 1 <sup>st</sup> year, 8.2 in 2 <sup>nd</sup> year, 1.4 in 3 <sup>rd</sup> year to 0 in 6 <sup>th</sup> year July 2020 olaparib submission, based on TTD curve for olaparib in SOLO-1	The restriction for first-line olaparib specifies a maximum treatment duration of 24 months for patients in complete response who have not experienced relapsed disease. The submission's estimated number of scripts per year was not adjusted to account for treatment interruption and for the difference in days of treatment covered per olaparib script (28 days) and the days in each months (30.4 days).
MBS costs CBC GP consultation IV administration	\$16.95 (MBS item 65070) \$38.75 (MBS item 23) \$111.40 (MBS item 13950)	

Source: Table 126, p191 and Section 1, pp188-203 of the submission; "Zejula (niraparib) 1L BIM" Excel workbook

1L = first-line; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; AOCS = Australian Ovarian Cancer Study; CBC = complete blood count; CGARN = Cancer Genome Atlas Research Network; CR = complete response; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub-Committee; FIGO = International Federation of Gynecology and Obstetrics; gBRCAm = germline BRCA mutation; GP = general practitioner; ICD-10 = International Classification of Disease 10<sup>th</sup> revision; ITT = intention-to-treat; IV = intravenous; NZ MoH = New Zealand Ministry of Health; PBC = platinum-based chemotherapy; PR = partial response; PSD = public summary document; sBRCAm = somatic BRCA mutation; SMM = standard medical management; TTD = time to treatment discontinuation

\* Note that the dose intensity and compliance data from PRIMA used to derive the number of niraparib packs stated in Table 13 was provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.69 The financial analysis assumed that the proposed listing of niraparib would reduce the use of existing first-line maintenance therapies, including bevacizumab and olaparib,

but would not affect the extent of use of later-line maintenance therapies. The ESC noted that this assumption was not consistent with the economic model which compared first-line niraparib with placebo (followed by olaparib if BRCAm), though it reflects Australian clinical practice.

- 6.70 The uptake of various first-line maintenance therapies for treatment of newly diagnosed advanced HGEOC in scenarios with and without the listing of niraparib was mainly based on the submission's assumptions and was a major area of uncertainty in the financial analysis. The changes in these uptake variables have large impacts on the net financial implications of the listing of niraparib to the PBS/RPBS. The ESC noted that the submission assumed that, if listed, niraparib would substitute for around one third of BRCAm patients treated with olaparib in year one, increasing to around half in years 3-6. In the non-BRCAm population niraparib was assumed to substitute for around one quarter of patients treated with bevacizumab in year one. The ESC considered that predicted changes in first line therapy were not justified and are uncertain.
- 6.71 The ITT TTD data applied in the economic evaluation and in the financial analysis included 65% (315 out of 484) patients who initiated niraparib therapy at a fixed dose. Therefore, the trial-based ITT TTD might not reflect the treatment duration of niraparib in clinical practice if the proposed ISD regimen is used. The ESC considered that although FSD caused higher TEAE requiring dose reductions, drug withdrawals due to TEAE were similar in both groups of patients (13.6% ISD vs 11.1% FSD vs 12.0% in the full population; Table 5) therefore treatment duration was unlikely to be particularly different to the ITT population.
- 6.72 The estimated use of niraparib as first-line maintenance therapy and financial implications are summarised below.

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Table 14: Estimated use and financial implications (uses proposed effective price from submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated <sup>a</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Number of scripts dispensed <sup>b</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Estimated financial implications of niraparib</b>						
Cost to PBS/RPBS less copayments	\$█ <sup>4</sup>	\$█ <sup>5</sup>	\$█ <sup>5</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>
<b>Estimated financial implications for olaparib and bevacizumab</b>						
Cost of bevacizumab to PBS/RPBS less copayments	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>
Cost of olaparib to PBS/RPBS less copayments	-\$█ <sup>7</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>
Revised <sup>c</sup>	-\$█ <sup>7</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>	-\$█ <sup>4</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS Revised <sup>c</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
Net cost to MBS Revised <sup>c</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>
Net cost to Government health budget Revised <sup>c</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>

Source: Table 152, p215, Table 158, p218, Table 162, p220, and Table 185, p232 of the submission; '4c. Impact - affected (eff)' spreadsheet in the "Zejula (niraparib) 1L BIM" Excel workbook.

<sup>a</sup> Includes patients initiating treatment and patients continuing treatment from previous years.

<sup>b</sup> The number of niraparib scripts was estimated on the basis of the distribution of doses and compliance rates from the individualised starting dose cohort of the PRIMA trial. Dose volumes and compliance rates were translated into an estimated number of niraparib scripts per cycle, by assuming all patients on 300 mg daily receive 84-capsule packs and all patients on 200 mg and 100 mg daily receive 56-capsule packs.

<sup>c</sup> Financial implications were revised during the evaluation by correcting the estimated number of olaparib scripts substituted by niraparib. A factor of 1.087 (=365.25/12/28) was applied to the average number of treatment in months in each treatment year as provided in Table 13 of July 2020 olaparib public summary document (PSD) to calculate the number of olaparib scripts required. In addition, a factor of 95.35% (=1-1/21.5) was applied to the number of scripts to account for dose interruptions (Paragraph 6.48, olaparib PSD, July 2020 PBAC meeting).

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> 5,000 to < 10,000

<sup>4</sup> \$10 million to < \$20 million

<sup>5</sup> \$20 million to < \$30 million

<sup>6</sup> \$30 million to < \$40 million

<sup>7</sup> \$0 to < \$10 million

6.73 The total cost to the PBS/RPBS of listing niraparib was estimated to be \$10 million to < \$20 million in Year 6, and a total of more than \$60 million to < \$70 million in the first 6 years of listing.

6.74 The estimated financial implications for the PBS/RPBS listing of niraparib were sensitive to:

- Niraparib uptake rates. In the non-BRCAM population niraparib is expected to substitute bevacizumab, a lower cost medicine compared with niraparib, or SMM where no cost of medicines was considered. Whereas, in the BRCAM population niraparib is expected to substitute olaparib, a higher published price compared with the proposed effective price for niraparib. Therefore, increasing the uptake

of niraparib in the non-BRCAM cohorts or decreasing the uptake of niraparib in the BRCAM cohorts would result in a proportionally larger financial impact, and vice versa.

- Bevacizumab uptake. Reducing the estimated current bevacizumab uptake rate among newly diagnosed advanced HGEOC patients receiving first-line platinum-based chemotherapy prior to the listing of niraparib from 41.4% to 30%, the net PBS/RPBS implications of niraparib listing would increase by 18%.
- Prevalence of BRCAM. The change of this variable would affect the number of patients currently being treated with first-line olaparib (BRCAM patients only) or bevacizumab (in both BRCAM and non-BRCAM patients) who would otherwise receive niraparib if PBS listed. When a 25.3% prevalence rate as accepted by the PBAC was used (vs. 28.9% in base case), the net PBS/RPBS costs over the 6 years of listing would increase by 19% to \$70 million to < \$80 million.

6.75 The PSCR provided revised estimates of financial implications to the PBS/RPBS, using:

- a revised proportion of patients with epithelial ovarian cancer (83.7% vs. 90.9% in the submission);
- the corrected number of olaparib scripts, adjusting for dose interruptions (adjustment factor of 0.9535) and for the difference in days of treatment covered per olaparib script and the days in each month (adjustment factor of 1.087); and
- an updated effective ex-manufacturer price for niraparib proposed in the PSCR (\$ [REDACTED] vs. \$ [REDACTED] per 100mg x 56 capsules).

Based on these changes to the financial estimates, the estimated net cost to the PBS/RPBS was reduced to \$30 million to < \$40 million over the first 6 years of listing.

### ***Quality Use of Medicines***

6.76 The submission noted additional pharmacovigilance activities outlined in the regulatory dossier, as part of ensuring the quality of use of niraparib: specific adverse reaction follow-up questionnaires to ensure additional follow-up information when cases occur and to monitor outcomes and trends in incidence and evaluation of risk factor for acute myeloid leukaemia/myelodysplastic syndrome and second primary malignancies.

6.77 The submission also outlined activities being developed to support the quality use of medicines, a patient access program, educational activities (e.g. webinars), advisory boards, and health care provider and patient brochures.

### ***Financial Management – Risk Sharing Arrangements***

6.78 The submission did not propose a risk-sharing arrangement (RSA). It is expected that the listing of first-line niraparib would affect the extent of use of olaparib in BRCAM patients.

- 6.79 The PSCR acknowledged that an RSA will be required for the PBS listing of niraparib. The PSCR noted that given the different populations (niraparib = 1L all comers; olaparib = 1L and 2L BRCAm), associated effective prices and the inability to distinguish niraparib utilisation based on BRCA status there are several challenges associated with a joint cap. The sponsor recognised that a joint cap, with expansion of the existing olaparib arrangement (1L & 2L BRCAm) to include the estimated expenditure from the non-BRCAm cohort for niraparib 1L may limit the above challenges.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend niraparib for the treatment of newly diagnosed advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (HGEOC), who are in response to platinum-based chemotherapy. The PBAC was unable to assess the incremental clinical and economic effectiveness based on the submission provided, which did not include the relevant comparator for patients with BRCA1/2 pathogenic gene variants who would be treated with olaparib, or for patients who would otherwise be treated with bevacizumab. The PBAC noted that the progression free survival (PFS) benefit from treatment with niraparib varied depending on the presence of BRCA1/2 pathogenic gene variants and homologous repair deficiency (HRD) status. The PBAC considered there may be differences in benefits and harms in the different patient subgroups, if niraparib is used in place of olaparib, bevacizumab or standard medical management (SMM), and that these potential differences were not adequately addressed in the submission.
- 7.2 The PBAC noted that the NCCN guidelines include niraparib as an alternative to olaparib in BRCAm patients, and as an alternative to observation (SMM) in non-BRCAm patients, especially those patients whose tumours are HRD-positive. The PBAC considered that for patients without BRCAm there is a moderate need for additional PBS therapies, noting that no PARP inhibitors are PBS listed for this population though other treatments, such as bevacizumab, are available. The PBAC also noted that NCCN guidelines state that in the absence of BRCAm, homologous recombination status may provide information on the magnitude of benefit of PARPi therapy. The PBAC noted that HRD testing is not currently part of the standard clinical management of HGEOC in Australia.
- 7.3 The PBAC noted that patients with Stage III HGEOC, R0 after PDS were excluded from the PRIMA trial, however the PBAC considered that it was clinically appropriate that the listing include all patients with Stage III/IV HGEOC. The PBAC considered that it would be appropriate for restrictions to limit access to PARP inhibitors to one course per patient lifetime and the duration of treatment should be consistent with the clinical data, economic model and financial estimates.
- 7.4 The PBAC noted that for patients with BRCA1/2 pathological variants olaparib is the appropriate comparator, while for patients without BRCAm the appropriate

comparator is either bevacizumab or SMM, noting that not all eligible patients would be treated with bevacizumab due to its benefit:risk profile. The PBAC noted that the submission nominated the appropriate comparators but did not present clinical evidence for niraparib versus olaparib or bevacizumab in the relevant populations and did not present an economic model that included these comparators. Therefore, the PBAC considered that the comparative clinical effectiveness and cost-effectiveness of niraparib in the proposed PBS population could not be assessed based on the clinical evidence and economic evaluation presented in the submission. Importantly, the PBAC considered there may be differences in benefits and harms in the different patient subgroups if niraparib is used in place of olaparib, bevacizumab or SMM.

- 7.5 The PBAC noted that the evidence presented in the submission was based on a direct comparison of niraparib versus placebo (SMM) from the PRIMA trial, a phase 3, randomised, double-blind, placebo-controlled, multicentre study of niraparib maintenance treatment in patients with advanced ovarian cancer following response to front-line platinum-based chemotherapy.
- 7.6 The PBAC noted that the sponsor also presented results of the SOLO-1 trial (olaparib versus placebo) and the ICON-7 trial (bevacizumab versus placebo). The submission claimed that indirect comparisons between niraparib and olaparib or bevacizumab using these trials could not be performed due to significant heterogeneity between trials. Consequently, the clinical claim and economic model were primarily informed by the head-to-head comparison of niraparib versus placebo in the ITT population of the PRIMA trial.
- 7.7 The PBAC acknowledged that a formal quantitative indirect comparison between niraparib and bevacizumab based on the PRIMA and ICON-7 trials would be difficult because the ICON-7 study was a considerably older study and included a substantially different patient population than the PRIMA trial. However the PBAC also recalled that it had previously recognised bevacizumab as a relevant comparator to olaparib in a subgroup of patients in the 1L setting during its consideration of olaparib in July 2020 and that the sponsor of olaparib provided a qualitative analysis using data from trials comparing efficacy of bevacizumab to olaparib (from SOLO-1) (paragraph 2.4, olaparib PSD, July 2020 PBAC Meeting).
- 7.8 The PBAC noted that olaparib was the relevant comparator for the BRCAm population however the sponsor maintained that an adjusted indirect comparison using the SOLO-1 and PRIMA trials was inappropriate due to differences in baseline demographics between patients in the SOLO-1 trial and the BRCAm patient population in the PRIMA trial and the population in PRIMA may have poorer prognosis than the population in SOLO-1. The sponsor also argued that conducting a MAIC would not be informative as matching would result in a considerably reduced sample size available for comparison. The PBAC noted that the ESC considered a comparison between niraparib and olaparib may have been achievable with the PRIMA and SOLO-1 trials, noting that concerns regarding the transitivity of the studies would need to be considered in interpretation of the results. The PBAC considered that a comparison

with olaparib would provide important evidence applicable to Australian population requested for PBS listing.

- 7.9 The PBAC noted that the PRIMA trial demonstrated a PFS benefit for niraparib compared to placebo in the ITT population of 13.8mo vs 8.2mo (HR 0.62,  $p < 0.001$ ), however the OS data was immature and a statistical difference had not been demonstrated. The PBAC noted that evidence of benefit varied by patient subgroup on the basis of BRCA and HRD status. The PBAC noted that the PFS benefit for niraparib in the BRCAm subgroup (HR= 0.40, 95% CI: 0.27, 0.62) was greater than in the non-BRCAm subgroup (HR= 0.69, 95% CI: 0.54, 0.88 in non-BRCAm); and PFS benefit was greater for patients with HRD positive tumours (HR= 0.43, 95% CI: 0.31, 0.59) compared to patients in the HRD negative subgroup (HR= 0.68, 95% CI: 0.49, 0.94) or HRD not determined subgroup (HR= 0.85, 95% CI: 0.51, 1.43). The PBAC noted that about 30% of patients in PRIMA had BRCAm and 51% had HRD positive tumours (which included BRCAm patients). As such, the PBAC considered that the PFS benefit was driven by patients who were BRCAm or HRD positive.
- 7.10 The PBAC considered that while the PRIMA trial supported the clinical claim of superior efficacy versus placebo in the ITT population, in the HRD-negative and not determined subgroups the magnitude of benefit was small and may not be clinically meaningful. Further, the PBAC considered that the PFS benefit may not translate into an OS benefit. Importantly, the PBAC considered that the evidence presented in the submission to support the clinical claim was not fully applicable to the Australian setting because it did not present an adequate comparison versus relevant comparators, olaparib and bevacizumab.
- 7.11 The PBAC noted that an anchored indirect comparison<sup>16</sup> of PFS of niraparib vs olaparib in the BRCAm population was conducted during the evaluation. Acknowledging the limitations of this comparison, the PBAC noted that the result was numerically in favour of olaparib and did not rule out inferiority of niraparib to olaparib (HR = 1.43, 95% CI: 0.83, 2.45 for niraparib versus olaparib in the overall BRCAm patient population, and HR = 1.11, 95% CI: 0.58, 2.12 for niraparib versus olaparib in BRCAm patient population post NACT-IDS subgroup<sup>17</sup>).
- 7.12 The PBAC noted that the PRIMA trial protocol was changed to include an ISD regimen based on baseline body weight and platelet count, which the sponsor indicated would be used in clinical practice. The PBAC considered that efficacy is likely to be similar for

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<sup>16</sup> Note that the indirect comparisons of niraparib vs olaparib were conducted by the evaluation specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

<sup>17</sup> Results for niraparib vs placebo in the BRCAm NACT-IDS subgroup included in the indirect comparison are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for PRIMA.

ISD and FSD approaches because a high rate of dose reductions would be expected for the latter approach, as seen in PRIMA.

- 7.13 Based on the PRIMA trial the PBAC considered that niraparib was inferior to placebo in terms of safety, with more grade  $\geq 3$  TEAEs, SAEs, and TEAEs leading to drug discontinuation being observed in the niraparib arm compared to placebo arm. The PBAC noted that no formal comparison of safety between niraparib and olaparib was presented, but considered that overall, olaparib seems to have a better safety profile compared to niraparib based on the lower rate of dose reduction in the SOLO-1 trial compared to that in the PRIMA trial. The PBAC also noted this was consistent with its previous consideration of comparative safety for niraparib in the 2L maintenance setting (paragraph 7.8, olaparib PSD, March 2021 PBAC Meeting).
- 7.14 The PBAC considered that the economic model provided in the submission was not reliable for decision making because it failed to present an economic evaluation that reflects the proposed circumstances of use of niraparib in the proposed PBS population. The PBAC considered it was reasonable to expect differences in comparative benefits and harms in the different patient subgroups if niraparib is used in place of olaparib, bevacizumab or SMM. Noting the differences in PFS benefit in the BRCAm and HRD positive subgroups demonstrated in the PRIMA trial, the PBAC considered that the efficacy outcomes were driven by inclusion of the BRCAm patients in the model.
- 7.15 In addition, the PBAC considered that the ICER presented was uncertain and likely to be underestimated for the following reasons:
- The model assumed a continued treatment effect beyond the end of the trial, which was not adequately justified in the submission, and introduced substantial uncertainty to the modelled results;
  - The model was sensitive to the parametric functions for OS extrapolation and time horizon. The PBAC considered that 20 years may be too long for the non-BRCAm population and introduced additional uncertainty due to the immaturity of the OS data from PRIMA.
  - The cost of second-line PARPi use is the main source of cost-offsets modelled and has a high impact on the ICER and assumptions around second line use of olaparib appear to overestimate the cost offsets for second-line PARP inhibitors in the model.
- 7.16 The PBAC noted that the approach taken in the economic model was inconsistent with the proposed place in therapy and the utilisation and financial estimates presented, which assumed that the proposed listing of niraparib would reduce the use of existing first-line maintenance therapies, including bevacizumab and olaparib, but would not affect the extent of use of later-line maintenance therapies. The PBAC considered that the financial estimates were uncertain because the uptake assumptions, and rates of substitution of alternative therapies were not well justified. Furthermore, the PBAC

noted that the current submission had assumed that niraparib would substitute for olaparib in up to one half of olaparib-eligible patients. The PBAC considered this proportion was overestimated as clinicians are familiar with the use of olaparib and its safety profile appears superior to niraparib. The PBAC also considered that the number of patients switching from olaparib to niraparib is likely to be very small and these patients could reasonably be removed from the estimates.

7.17 Given the uncertain clinical benefit for niraparib in patients with HRD negative HGEOC, the PBAC considered that a resubmission for niraparib may need to identify and target the patients who are most likely to benefit from treatment. The PBAC noted that HRD testing is not currently part of the clinical management of HGEOC in Australia, and therefore a codependent submission would be required if the sponsor was to seek a PBS listing that relied on HRD status. The PBAC considered a resubmission for niraparib should also address the following:

- Present a clinical and economic evaluation including relevant comparators (olaparib and bevacizumab) for the proposed population.
- Address uncertainty in the clinical claims by providing separate clinical evaluations for the BRCAm population and nonBRCAm populations; and possibly the HRD-positive, HRD-negative, and HRD-not-determined populations.
- Quantify any differences between niraparib and olaparib in terms of safety profile, noting that a CMA (if pursued) would require adjustment for higher rates of AEs with niraparib, unless it can be shown that this is mitigated by the ISD.
- Address areas of uncertainty in the economic model as outlined in paragraph 7.15.
- Justify the duration of treatment proposed and ensure consistency between the proposed restrictions, economic model and financial estimates.
- Revise the financial estimates as outlined in paragraph 7.16.

7.18 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

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

**Outcome:**

Not recommended

## **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**

GSK is disappointed by the PBAC's decision not to recommend niraparib (Zejula), for newly diagnosed advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (HGEOC), who are in response to platinum-based chemotherapy. However, we remain committed to working with the PBAC to ensure Australian women with ovarian cancer have timely access to Zejula.