

**7.07 NIRAPARIB,
Capsule 100 mg,
Zejula[®],
GlaxoSmithKline Australia Pty Ltd**

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 85 (General schedule), Authority required (streamlined) listing for niraparib as maintenance therapy for the treatment of newly diagnosed advanced (NDA), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (HGEOC), in patients who are in response to platinum-based chemotherapy. This was unchanged from the previous submission.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis (CMA) of niraparib versus olaparib for patients with BRCA pathological variants (BRCAm), and on the basis of a cost-utility analysis (CUA) of niraparib versus no active treatment (also referred to as standard medical management (SMM)) among patients without BRCAm. The two separate analyses by BRCA status were updated from the previous submission, where a CUA was presented for niraparib versus no active treatment for the overall requested population, irrespective of BRCA status. The PBAC previously noted that the incremental clinical and economic effectiveness of niraparib was unable to be assessed as the evidence presented in the original submission did not include the relevant comparator for patients with BRCA1/2 pathogenic gene variants who would usually be treated with olaparib, or for patients who would otherwise be treated with bevacizumab (Paragraph 7.1, Niraparib Public Summary Document (PSD), July 2021 PBAC meeting).
- 1.3 The updated analyses by BRCA status in the resubmission were consistent with the nominated comparators for these populations and in line with the advice from the PBAC (Paragraph 7.17, Niraparib PSD, July 2021 PBAC meeting). The key components of the clinical issue addressed by the resubmission are summarised below.

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

Component	Description
Population	Patients with NDA (FIGO stage III-IV) HGOEC who are in response (CR/PR) to PBC
Intervention	Niraparib
Comparator	Primary treatment with chemotherapy only: BRCAm: Olaparib Non-BRCAm: no active treatment (also referred to as SMM) Qualitative comparator: bevacizumab ^a
Outcomes	PFS, OS, TFST, Safety
Clinical claim	Non-BRCAm: Niraparib is superior in terms of effectiveness for PFS in comparison to no active treatment. Niraparib is inferior to no active treatment with respect to safety. BRCAm: Niraparib is non-inferior in terms of effectiveness for PFS in comparison to olaparib. Niraparib has comparable safety to olaparib, with no difference in clinically significant SAEs or treatment discontinuations due to TEAEs ^b .

Source: Table 3, p21 of the main resubmission.

AEs = adverse events; BRCAm = BRCA gene mutation; CR = complete response; FIGO = International Federation of Gynaecology and Obstetrics; HGOEC = high grade epithelial ovarian cancer; NDA = newly diagnosed advanced; PBC = platinum-based chemotherapy; PFS = progression-free survival; PR = partial response; OS = overall survival; SAEs = serious adverse events; SMM = standard medical management; TEAEs = treatment-emergent adverse events; TFST = time to first subsequent treatment.

^a No clinical claim was made in the resubmission regarding niraparib vs. bevacizumab.

^b Differences in event rates for key AEs are accounted for in the cost-minimisation analysis.

2 Background

Registration status

2.1 During the evaluation of the resubmission, niraparib as maintenance therapy in the first-line setting was approved by the TGA. The approved indication for niraparib 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.

2.2 Of note, in the final TGA Delegate's overview, the Delegate proposed to impose the following additional condition of registration: submit the final analysis for OS and updated analyses for time to first subsequent therapy (TFST), PFS-2¹ and outcomes for next anticancer therapy from the PRIMA study for evaluation. These recommendations were adopted as conditions of registration (TGA Approval letter dated 17 November 2021).

2.3 Niraparib is also TGA approved as a monotherapy 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.

Previous PBAC consideration

2.4 The previous submission was considered by the PBAC in July 2021 and the key matters

¹ PFS-2 is defined as the time from randomisation to objective tumour progression on next-line treatment or death from any cause.

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of concern are summarised below.

Table 2: Summary of key matters of concern

Component	Matter of concern (niraparib PSD, July 2021 PBAC meeting)	How the resubmission addresses it
Clinical		
Evidentiary basis	The PBAC was unable to assess the incremental effectiveness of niraparib in BRCAm patients and in non-BRCAm patients, compared with its relevant comparators. 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, and that these potential differences were not adequately addressed in the submission (para 7.1). The submission did not present clinical evidence for niraparib versus olaparib or bevacizumab in the relevant populations. Therefore, the comparative clinical effectiveness of niraparib in the proposed PBS population could not be assessed (para 7.4).	Addressed by presenting separate clinical and economic evaluations for niraparib: - vs. olaparib in BRCAm patients, via a common reference-based ITC* of PRIMA (BRCAm subgroup, BRCAm and NACT-IDS subgroup) with SOLO-1 (overall population excluding Stage III R0 PDS subgroup, and NACT-IDS subgroup). - vs. SMM in non-BRCAm patients using relevant subgroup analysis from PRIMA In addition, a qualitative (unanchored) comparison was performed for niraparib vs. bevacizumab.
Maximum treatment duration of niraparib	The PBAC considered 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 (para 3.4 and para 7.17).	Addressed - the requested listing specified a maximum treatment duration of 3 years in patients with complete response as requested. The economic evaluation and financial estimates also applied this circumstance in the respective base cases as requested. However, due to the short follow-up in PRIMA, there is a lack of evidence demonstrating the safety and effectiveness of long-term niraparib use.
Comparative effectiveness of niraparib vs. olaparib	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. (para 7.8). The PBAC noted that an anchored indirect comparison 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 (para 7.11).	Addressed. The ITC* of the BRCAm subgroup of PRIMA and the subgroup excluding Stage III, R0 PDS from SOLO-1 suggested an increased risk of PFS events and a reduction in median PFS in patients receiving niraparib when compared with those treated with olaparib though differences were not statistically significant. The PFS gain seen with olaparib compared to niraparib cannot be fully explained by the modest heterogeneity across the trials.
Comparative safety of niraparib vs. olaparib	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 (para 7.13).	Addressed. Clinically meaningful worsening in safety of niraparib relative to olaparib could not be ruled out, based on the 95% CIs from indirect comparison of AE outcomes, especially ≥ Grade 3 TEAEs and TEAEs leading to treatment discontinuation. Of note, the ITC* results of AE outcomes might have been biased in favour of niraparib, given the shorter treatment duration of niraparib in PRIMA than that of olaparib in SOLO-1.
Treatment	The PBAC noted that evidence of benefit varied	Not addressed. No additional PRIMA trial data by

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Component	Matter of concern (niraparib PSD, July 2021 PBAC meeting)	How the resubmission addresses it
effect of niraparib by HRD status	by patient subgroup on the basis of BRCA and HRD status. The PBAC noted that the PFS benefit for niraparib in the BRCAm subgroup was greater than in the non-BRCAm subgroup and PFS benefit was greater for patients with HRDpos tumours compared to patients in the HRDneg subgroup or HRDnd subgroup (para 7.9). Given the uncertain clinical benefit for niraparib in patients with HRDneg 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 (para 7.17).	HRD status was provided.
OS benefits	The PBAC considered that the PFS benefit may not translate into an OS benefit (para 7.10)	Not addressed. OS data in PRIMA was not mature enough for a reliable assessment of the survival benefits of niraparib. Further reporting of OS from PRIMA is not expected until 2025.
Economic		
Economic model	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 target PBS population. 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 (para 7.14)	Partially addressed. The resubmission presented two economic evaluations: • A CUA comparing niraparib with SMM for the maintenance treatment of non-BRCAm NDA HGEOC; and • A CMA comparing niraparib with olaparib for the maintenance treatment of BRCAm NDA HGEOC. Bevacizumab use in non-BRCAm patients was not included in the model base case but tested in a sensitivity analysis. No discussion for HRD status in economics section was presented.

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Component	Matter of concern (niraparib PSD, July 2021 PBAC meeting)	How the resubmission addresses it
Uncertainty areas	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 poly (ADP-ribose) polymerase inhibitor (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. (para 7.15)	- Not addressed. The model presented for the non-BRCAm cohort also assumed a continued treatment effect beyond the end of trial (97% of the OS benefit modelled for niraparib compared with SMM was accrued in the extrapolated period). - Addressed. The resubmission used independent parametric functions for extrapolation of survival curves (PFS and OS) and time horizon was revised to 15 years. However, due to immature OS data, uncertainties remain. - Addressed. 2L olaparib use removed from CUA to align with non-BRCAm population.
Economic model approach	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 (para 7.16).	Partially addressed. For bevacizumab use, the economic evaluations only presented a sensitivity analysis assuming a 7% use in non-BRCAm cohort, however it was estimated as 27.4% use in the financials. There is a lack of evidence to accurately inform the correct estimate.
Financial		
Uptake of niraparib	The PBAC considered that the financial estimates were uncertain because the uptake assumptions, and rates of substitution of alternative therapies were not well justified. The PBAC considered that the submission's estimate of up to 50% substitution of olaparib with niraparib 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 (para 7.16).	The resubmission assumed a lower uptake rate of niraparib in BRCAm patients who would otherwise receive olaparib and in patients discontinuing olaparib due to AEs. However, the submission still assumed niraparib utilisation would stabilise at 25% BRCAm and 75% non-BRCAm from year three onwards which the ESC considered may be unreasonable.

Source: Compiled during the evaluation.

2L = second-line; AEs = adverse events; BRCAm = BRCA gene mutation; CI = confidence interval; CMA = cost-minimisation analysis; CUA = cost-utility analysis; HGEOC = high-grade epithelial ovarian cancer; HRD = homologous recombination deficiency; HRDnd = homologous recombination deficiency test status not determined; HRDneg = homologous recombination deficiency test negative; HRDpos=homologous recombination deficiency test positive; ITC = indirect treatment comparison; OS = overall survival; PARP = poly (ADP-ribose) polymerase; PDS = primary debulking surgery; PFS = progression-free survival; SMM = standard medical management; TEAEs = treatment-emergent

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adverse events

* Note that the indirect comparisons of niraparib vs. olaparib in the BRCAm population were conducted by the applicant 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.

2.5 Niraparib was also previously 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

Name, restriction, manner of administration, form	Max quantity (packs)	Max quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
NIRAPARIB 100 mg (as tosilate monohydrate), Capsules	1	84	2 (initial)	\$12,657.60 (published); \$ (effective; in resubmission)	Zejula®, GlaxoSmithKline Australia Pty Ltd
			5 (cont.)	\$ (effective; in PSCR) \$ (effective; in pre-PBAC response)	
	1	56	2 (initial)	\$8,492.14 (published); \$ (effective; in resubmission)	
			5 (cont.)	\$ (effective; in PSCR) \$ (effective; in pre-PBAC response)	

Category/Program	General Schedule
Prescriber type	Medical practitioner
Condition	High grade stage III/IV epithelial ovarian, fallopian tube, or primary peritoneal cancer
PBS Indication	High grade stage III/IV epithelial ovarian, fallopian tube, or primary peritoneal cancer
Restriction	☒ Authority Required – STREAMLINED
Administrative Advice	Special Pricing Arrangements apply
Treatment phase	Initial treatment – first line treatment (300 mg/day)
Clinical criteria	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, AND The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition, AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition
Prescriber instructions	Patients treated under this listing should be receiving a dose of 300 mg/day A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer Inter Group (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.
Treatment phase	Initial treatment – first line treatment (200 mg/day)

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Clinical criteria	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, AND The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition, AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition
Prescriber instructions	Patients treated under this listing should be receiving a dose of 200 mg/day A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer Inter Group (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.
Treatment phase	Continuing treatment – first line treatment
Restriction	☒ Authority Required – STREAMLINED
Clinical criteria	The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition, AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND Patient must have previously received PBS-subsidised treatment with this drug as first line maintenance therapy for this condition AND The treatment must not exceed a total of 36 months of combined non-PBS-subsidised and PBS-subsidised treatment for patients who are in complete response

- 3.1 The resubmission proposed a Special Pricing Arrangement (SPA), whereby the effective price for niraparib was derived from a weighting across the BRCAM (28.9%) and non-BRCAM (71.1%) populations. The effective prices in BRCAM and non-BRCAM patients were determined on the basis of a CMA (vs. olaparib) and a CUA (vs. no active treatment), respectively. The resubmission acknowledged that the comparator olaparib has a confidential SPA and the CMA for the BRCAM population was conducted using the published price of olaparib. The weighted price of niraparib would depend on the assumed proportions of non-BRCAM and BRCAM patients who take up niraparib treatment and these proportions may differ from the prevalence of BRCAM in the target population (see paragraph 6.73).
- 3.2 In comparison with the proposed PBS listing in the original submission, the resubmission made the following changes:
- Specifying the disease stage (International Federation of Gynaecology and Obstetrics (FIGO) Stage III/IV) of the target population to be in line with the patient population in the key trial.
 - Proposing separate listings with clinical criteria for patients on a daily dose of 300 mg and those on a daily dose of 200 mg. The Secretariat previously considered that the separate listings will ensure that patients who meet the individualised starting dose (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 (Paragraph 3.9, Niraparib PSD, July 2021 PBAC meeting). The PBAC noted that the separate listing for the smaller pack size may not be required as prescribers can choose the relevant number of repeats depending on the dose required.

- Defining a maximum treatment duration of 3 years for niraparib in patients with complete response. The PBAC previously 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 (Paragraph 3.4, Niraparib PSD, July 2021 PBAC meeting). It was noted that, although the planned duration of treatment in PRIMA was approximately 3 years, the median treatment was only 11.1 months at data cutoff (DCO) 17th May 2019, with a maximum treatment duration of 2.4 years. Therefore, there is a lack of clinical evidence demonstrating the safety and effectiveness of long-term niraparib use. Overall, the PBAC considered that it was reasonable to include a maximum duration of treatment of 3 years for patients with full response in line with the circumstances of use in the PRIMA trial and consistent with the cost-minimisation analysis of niraparib vs olaparib.

- 3.3 The requested PBS restriction was broader than the PRIMA selection criteria by including patients with poor Eastern Cooperative Oncology Group (ECOG) performance status of 2 or above and by including patients with Stage III, R0² after primary debulking surgery (PDS). The PBAC previously considered that, in clinical practice, it would be reasonable for all stage III/IV (including Stage III, R0 post PDS) patients be treated with a poly (ADP-ribose) polymerase inhibitor (PARPi) (Paragraph 3.5, Niraparib PSD, July 2021 PBAC meeting). Nevertheless, the additional clinical benefit of using maintenance niraparib in these two subpopulations was not captured in the PRIMA trial.

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

4 Population and disease

- 4.1 The description of the population and disease in the resubmission is consistent with the previous submission. HGEOC is the most common and aggressive histological subtype of ovarian cancer (OC). Most patients (>75%) are diagnosed at an advanced stage (FIGO Stage III and IV), and have limited long-term survival (7-year survival for Stage III and IV: 26% and 9% respectively).
- 4.2 Although primary treatment with cytoreductive surgery and platinum-based chemotherapy usually leads to an initial response, the majority of patients relapse within the first 3 years. Post-progression treatment is usually associated with reduced

² Cytoreduction outcome: R0: defined as no visible residual disease; R1: defined as macroscopic residual disease with a maximal diameter of ≤1 cm; R2: defined as macroscopic residual disease with a maximal diameter of >1 cm.

efficacy and prolonged exposure to chemotherapeutic agents is associated with long-term toxicities and attenuation in quality of life.

- 4.3 Olaparib is currently available on the PBS as a first-line maintenance therapy for BRCAm NDA HGEOC patients who are in response to platinum-based chemotherapy. Bevacizumab has an unrestricted PBS listing; and its TGA approved indication as first-line therapy is: bevacizumab, in combination with carboplatin and paclitaxel, for the treatment of patients with Stages IIIB, IIIC or IV epithelial ovarian cancer. The current clinical management algorithm for first-line treatment of NDA HGEOC presented in the resubmission was largely consistent with the one in the original submission, with a change in the eligible population for bevacizumab from Stage III R2 or Stage IV to all advanced or metastatic disease. This revision reflects the change to an unrestricted PBS listing for bevacizumab.
- 4.4 The resubmission requested that niraparib be listed as a first-line maintenance therapy for those who have complete or partial response to platinum-based chemotherapy, irrespective of BRCA status or surgical outcomes.
- 4.5 At the July 2021 meeting, 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 deficiency (HRD) 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 (Paragraph 5.5, Niraparib PSD, July 2021 PBAC meeting). An MSAC Application (1658) has been received for the July 2022 MSAC meeting requesting the listing of testing of tumour tissue to determine a positive HRD status in patients NDA HGEOC for access to PBS olaparib.

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

5 Comparator

- 5.1 The comparators were nominated on the basis of the primary treatment (chemotherapy only or bevacizumab + chemotherapy) and BRCA status (BRCAm or non-BRCAm):
 - Primary treatment with chemotherapy only:
 - Non-BRCAm subgroup: no active treatment (referred to as SMM)
 - BRCAm subgroup: olaparib
 - Primary treatment with bevacizumab + chemotherapy: bevacizumab

The original submission nominated olaparib, bevacizumab and SMM as the comparators, on the basis of patient BRCA status only. PBAC has previously accepted that olaparib is the appropriate comparator for patients with BRCA1/2 pathological variants; and the appropriate comparator for non-BRCAm patients is either

bevacizumab or SMM (Paragraph 7.4, Niraparib PSD, July 2021 PBAC meeting). The additional consideration of primary treatment (with or without bevacizumab) would not affect the selection of the main comparator in BRCAm patients, given the availability of first-line olaparib maintenance therapy in this patient group and the increased risk of bleeding and surgical wound healing complications associated with bevacizumab; it is expected that the vast majority of patients with BRCAm will opt for first-line chemotherapy followed by olaparib, rather than first-line bevacizumab + chemotherapy. For non-BRCAm patients, bevacizumab maintenance therapy, following front-line bevacizumab + chemotherapy, is the only active maintenance treatment available. However, not all eligible patients would be treated with bevacizumab due to its benefit: risk profile. If niraparib is PBS listed, some patients who would otherwise receive bevacizumab + chemotherapy followed by bevacizumab maintenance therapy, might choose primary treatment with chemotherapy only followed by niraparib maintenance therapy to avoid potential perioperative complications and/or treatment interruption relating to bevacizumab. The ESC noted that few HGEOC patients (BRCAm or non-BRCAm) are currently treated with bevacizumab as maintenance therapy due to its poor tolerability and limited effectiveness.

- 5.2 The resubmission noted that olaparib + bevacizumab combination therapy was TGA approved in March 2021 for the maintenance treatment of patients with advanced HGEOC who are in complete or partial response to platinum-based chemotherapy and whose cancer is associated with HRD positive status.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor provided a written statement from a clinician involved in the treatment of ovarian cancer. The clinician commented on the clinical utility of niraparib for the non-BRCAm cohort and the patient relevance of PFS benefits, highlighting that modest improvements in outcomes were meaningful to patients with ovarian cancer. The clinician also commented on the comparability of niraparib and olaparib in the BRCAm cohort, and considered the outcomes similar for the two drugs, noting that eligibility criteria differed for the PRIMA and SOLO-1 trials. The clinician described that individualised dosing minimises the risk of adverse events with niraparib. Additional noted benefits of niraparib included that it may have less risk of drug interactions, and that it may be taken once-daily.

Consumer comments

- 6.2 The PBAC noted and welcomed input from individuals (55), health care professionals (15), and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with niraparib including

improved progression free survival, a manageable toxicity profile and a delay to subsequent lines of chemotherapy. The comments from individuals who have used the medicine described benefits including improved quality of life, the ability to return to work and spend extended time with family and friends and reduced anxiety. The comments also discussed the significant fear of recurrence that is experienced by patients and their families. Several of the comments described an unmet clinical need for additional treatment options for women with ovarian cancer, especially for non-BRCa patients. Another commonly expressed concern related to the cost of treatment without PBS listing.

- 6.3 The PBAC noted the submission received from Ovarian Cancer Australia, which supported the proposed listing. The submission included a summary of personal experiences from a survey of patients living with an ovarian cancer diagnosis, in which fear of recurrence was the most common concern reported. The also submission described the main advantages of niraparib are that it may extend progression free survival and increase quality of life, and that it would expand the current treatment options and provide hope for patients with ovarian cancer, including non-BRCa patients.
- 6.4 The Medical Oncology Group of Australia (MOGA) 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)^[1], based on a comparison with placebo.³

Clinical studies

- 6.5 In the previous submission, clinical evidence from the PRIMA trial formed the evidentiary basis for the claim of superior efficacy of niraparib versus no active treatment (placebo) and manageable safety profile of niraparib in the NDA HGEOC patients irrespective of BRCA status. The submission claimed that indirect comparisons between niraparib and olaparib or bevacizumab could not be performed due to significant heterogeneity between the trials. The PBAC previously considered that the evidence presented in the submission to support the clinical and economic claim was not fully applicable to the Australian setting because it did not present an adequate comparison versus relevant comparators in respective patients (Paragraph 6.36, Niraparib PSD, July 2021 PBAC meeting). In addition, the Committee:
- Acknowledged that formal quantitative indirect comparison between niraparib and bevacizumab based on the PRIMA and ICON-7 trials would be difficult because the ICON-7 was a considerably older study and included a substantially different patient population compared with the PRIMA trial.

³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

- 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 the Australian population requested for PBS listing (Paragraph 7.8, Niraparib PSD, July 2021 PBAC meeting).
- 6.6 The resubmission addressed the above issues by presenting clinical and economic evidence comparing niraparib with its nominated comparators in the respective BRCAm and non-BRCAm populations, and a qualitative comparison with bevacizumab. In recognition of the major transitivity issues that prevented reliable quantification of the comparative effectiveness and safety of niraparib relative to bevacizumab, the indirect comparison between niraparib and bevacizumab did not form the basis for assessment of the cost-effectiveness of niraparib in the proposed PBS population. The ESC considered this was reasonable and noted that given the limited use of bevacizumab maintenance therapy in practice, this comparison was of less significance.
- 6.7 In accordance with previous PBAC advice, the resubmission performed separate clinical evaluations for niraparib in the non-BRCAm and BRCAm populations⁴:
- Non-BRCAm patients: based on the subgroup analysis of non-BRCAm patients in the PRIMA trial (niraparib vs. no active treatment (placebo)).
 - BRCAm patients: based on an indirect treatment comparison (ITC) of the BRCAm subgroup from the niraparib trial (PRIMA, niraparib vs. placebo) with one olaparib trial (SOLO-1, olaparib vs. placebo). The ITC was performed using the Bucher (1997) method⁵, via placebo as the common reference⁶.
- 6.8 Details of the studies presented in the submission are provided in the table below.

Table 3: 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	November 2019
	European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) assessment report: Zejula (niraparib).	September 2020

⁴ In PRIMA, a total of 37 (0.5%) patients had their BRCA status not determined. These patients were not included for assessment of the effectiveness and safety of niraparib in the non-BRCAm patients or in the BRCAm patients.

⁵ Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of clinical epidemiology*. 1997;50(6):683-91.

⁶ Note that the indirect comparisons of niraparib vs. olaparib in the BRCAm population were conducted by the applicant 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.

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Trial ID	Protocol title/ Publication title	Publication citation
	González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. González-Martín A, Mirza MR, Vergote I, 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. (abstract) Monk BJ, Mirza MR, Vergote I, 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. (abstract) Valabrega G, Pothuri B, Oaknin A, 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. (abstract) Dahlstrand H, Pothuri B, Graybill W, 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. (abstract) Graybill W, Mirza M, Gonzalez-Martin A, et al. Efficacy on individualized starting dose (ISD) and fixed starting dose (FSD) of niraparib per investigator-assessment (IA) in newly diagnosed advanced ovarian cancer (OC). (abstract) Mirza MR, Martin AG, Graybill W, et al. Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. (abstract) 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. (abstract) Braicu EI, Pothuri B, Perez-Fidalgo JA, et al. Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by BRCAwt status: Prima/engot-OV26/GOG-3012 study. (abstract) Korach J, Graybill W, Redondo A, O'Malley DM, Han S, Cloven N et al. Niraparib in patients with newly diagnosed advanced ovarian BRCAm cancer: a post hoc analysis of the PRIMA/ENGOT-OV26/GOG-3012 trial. (abstract) O'Ceirbhail R, Pérez-Fidalgo JA, Monk B, et al. Efficacy of niraparib by timing of surgery and residual disease: a post-hoc analysis of patients in the PRIMA/ENGOT-OV26/GOG-3012 study. (abstract) Whitney G, Mansoor MR, Antonio GM, et al. Efficacy of individualized starting dose (ISD) and fixed starting dose (FSD) of niraparib per investigator assessment (IA) in newly diagnosed advanced ovarian cancer (OC) patients. (abstract)	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 International Journal of Gynecological Cancer 2020;30(Suppl 4):A69-A70 International Journal of Gynecological Cancer 2020;30 (Suppl 3):A10 Journal of Clinical Oncology 2020;38(15 Suppl) Gynecologic Oncology 2020;159:18-19 International Journal of Gynecological Cancer 2020;30(Suppl 4):A70-A71 International Journal of Gynecological Cancer 2020;30(Suppl 4):A125-A126 Gynecologic Oncology 2021;162:S65 Journal of Obstetrics and Gynaecology Research 2021;47(8):2803-2804
SOLO-1	Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. DiSilvestro P, Colombo N, Scambia G, et al. Efficacy of Maintenance Olaparib for Patients with Newly Diagnosed Advanced Ovarian Cancer with a BRCA Mutation: Subgroup Analysis Findings from the SOLO1 Trial. Wu L, Zhu J, Yin R, Wu X, et al. Olaparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer and a BRCA1 and/or BRCA2 mutation: SOLO1 China cohort. Colombo N, Moore K, Scambia G, et al. Tolerability of maintenance olaparib in newly diagnosed patients with advanced ovarian cancer and a BRCA mutation in the randomized phase III SOLO1 trial.	New England Journal of Medicine 2018;379(26):2495-2505 Journal of Clinical Oncology 2020;38(30):3528-3537 Gynecologic Oncology 2021;160(1):175-181 Gynecologic Oncology 2021;163(1):41-49

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Trial ID	Protocol title/ Publication title	Publication citation
	Friedlander M, Moore KN, Colombo N, et al. Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) assessment report on extension of marketing authorisation grouped with a variation: Lynparza (olaparib). Colombo N, Moore KN, Scambia G, et al. Adverse events (AEs) with maintenance olaparib in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Phase III SOLO1 trial. (abstract) Oaknin A, Moore K, Colombo N, et al. Time to second progression (PFS2) and second subsequent therapy (TSST) for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm) treated with maintenance (mt) olaparib (ola): Phase III SOLO1 trial. (abstract) Mathews CA, Moore KN, Colombo N, et al. Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. (abstract) Moore K, Colombo N, Scambia G, et al. Maintenance olaparib after platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: Efficacy by the timing of surgery and residual tumour status following upfront or interval cytoreductive surgery in the phase III SOLO1 trial. (abstract) Gourley C, Brown JS, Lai Z, et al. Analysis of tumour samples from SOLO1: Frequency of BRCA specific loss of heterozygosity (LOH) and progression-free survival (PFS) according to homologous recombination repair deficiency (HRD)-LOH score. (abstract) Friedlander ML, Hettle R, Parkhomenko E. Impact of radiological disease progression on the health status of patients (pts) with BRCA-mutated advanced ovarian cancer (OC) treated with maintenance olaparib (OL) or placebo (PL) after first-line platinum chemotherapy. (abstract) Friedlander ML, Moore K, Colombo N, et al. Patient-centred outcomes with maintenance olaparib in newly diagnosed patients with advanced ovarian cancer (OC) and a BRCA mutation (BRCAm) in the phase III SOLO1 trial to support the clinical benefit of prolongation of progression-free survival (PFS). (abstract) Banerjee S, Moore KN, Colombo N, et al. Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. (abstract) Friedlander ML, Moore K, Colombo N, Scambia G, Kim BG, Oaknin A et al. Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. (abstract) Colombo N, Bradley W, Moore K, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: Subgroup analysis by risk in the phase iii solo1 study. (abstract) Bradley W, Moore K, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO1. (abstract)	The Lancet Oncology 2021;22:632-642 April 2019 Journal of Clinical Oncology 2019;37:S15 Annals of Oncology 2019;30:v405 Journal of Clinical Oncology 2019;37:Suppl 15 International Journal of Gynecological Cancer 2019;39:A14-A15 Annals of Oncology 2019;30:v407 Annals of Oncology 2019;30:ix77-ix78 Annals of Oncology 2019;30:v405-v406 Annals of Oncology 2020;31:S613 Annals of Oncology 2020;31:S1334 International Journal of Gynecological Cancer 2020;30(Suppl 4):A76 Gynecologic Oncology 2021;162:S25-S26

Source: Table 19, pp49-51 of the resubmission

- 6.9 The PRIMA and SOLO-1 trials have previously been reviewed by the PBAC. The trial information presented herein relates primarily to the assessment of the non-BRCAM subgroup analysis of PRIMA and the ITC of PRIMA and SOLO-1 in the BRCAM population. The key features of the included evidence are summarised in the following table.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
BRCAM						
Niraparib vs. placebo						
PRIMA ^a	223	Subgroup analysis of RCT, DB Niraparib 16.2 mths Placebo 15.0 mths ^b	High ^c	BRCAM patients with NDA, high-grade ovarian cancer who had PR or CR to PBC	PFS, OS, AEs	N/A
Olaparib vs. placebo						
SOLO-1	391	RCT, DB 41 mths	Low	BRCAM patients with NDA, high-grade ovarian cancer who had PR or CR to PBC	PFS, OS, AEs	N/A
Non-BRCAM						
Niraparib vs. placebo						
PRIMA ^a	473	Subgroup analysis of RCT, DB Niraparib 15.0 mths Placebo 15.4 mths ^b	High ^c	Non-BRCAM patients with NDA, high-grade ovarian cancer who had PR or CR to PBC	PFS, OS, AEs	Used

AEs = adverse events; CR = complete response; DB = double blind; mths = months; NDA = newly diagnosed, advanced; OS = overall survival; PBC = platinum-based chemotherapy; PFS = progression-free survival; PR = partial response; RCT = randomised controlled trial

^a 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)

^b Median duration of follow up for OS

^c Subgroup was not pre-specified and there was no stratified randomisation.

- 6.10 As BRCA status was not a stratification factor in the PRIMA trial, the BRCAM and non-BRCA subgroups were effectively non-randomised and therefore at high risk of bias. The subgroup analysis results were likely confounded, given the observed differences in patient baseline characteristics between the two treatment arms in these subgroups.
- 6.11 The indirect comparison between niraparib and olaparib was based on the BRCAM subgroup in PRIMA and intention-to-treatment (ITT) population in SOLO-1, or the subgroup of SOLO-1 (excluding Stage III R0 post PDS patients); therefore, the comparison was at risk of bias.
- 6.12 In comparison with the placebo arm, the niraparib arm of the BRCAM subgroup had more patients with a performance status of 1 (27% vs. 17%), fewer patients had Stage IV disease (34% vs 48%) and fewer patients had visible residual disease (R1 or R2) following prior cytoreductive surgery (32% vs. 39%). As all patients included in the PRIMA trial had a relatively good performance status (0 or 1), it is expected that the

impact of the difference in the proportion of patients with a performance status of 1 on prognosis would be modest. The presence of metastases and presence of residual disease after surgery are poor prognostic factors, the imbalanced distribution of these two characteristics between the niraparib and placebo arms in the BRCAM subgroup of PRIMA likely favoured niraparib. These prognostic differences were in the opposite direction in the non-BRCAM patients, but the differences were smaller due to the relatively larger sample size of this subgroup.

- 6.13 The resubmission noted that patients with Stage III R0 PDS were excluded from PRIMA, while these patients were included in SOLO-1. The resubmission thus performed a sensitivity analysis for the indirect comparison by excluding patients with Stage III R0 post PDS from SOLO-1. In the subgroup analysis that excluded Stage III R0 post PDS patients in SOLO-1, a higher proportion of placebo-treated patients had metastatic disease at baseline than those treated with olaparib (36% vs. 27%). These subgroup results, therefore, may have favoured olaparib.
- 6.14 The resubmission noted that the baseline risk in patients in PRIMA was higher than that of SOLO-1. Such differences were largely attributable to the exclusion of Stage III R0 PDS patients from PRIMA. The inter-trial differences in disease stage, response to front-line treatment, type of debulking surgery and outcome of cytoreductive surgery became less evident or even disappeared when the BRCAM subgroup of PRIMA was compared with the subgroup of SOLO-1 after excluding the Stage III R0 PDS patients (Stage IV: 34-48% vs. 27%-36%; CR to primary treatment with chemotherapy: 74%-75% vs. 73%-74%; PDS: 31% vs. 33%-37%; residual R1/R2 disease: 32%-39% vs. 38%-40%).
- 6.15 The Pre-Sub-Committee Response (PSCR) disagreed with the evaluation's interpretation of potential imbalances in prognostic factors, including cytoreductive surgery and surgical outcome, stating that it remains unknown whether the ITC is confounded by imbalances.
- The PSCR stated that baseline information regarding cytoreductive surgery (NACT-IDS and no surgery) and surgical outcome (R0, R1, R2 and unknown/missing) was not reported for SOLO-1 for the Stage III R0 PDS excluded subgroup. These values were calculated in the evaluation by subtracting the Stage III R0 PDS patients (by definition, patients with R0 who underwent PDS).
 - The ESC noted that there was also some inconsistency with regard to the reporting of surgical outcomes between the SOLO-1 and PRIMA trials. The PSCR noted that the UICC (8th Edition) classifies residual disease as: R0 = no residual tumour, R1 = microscopic residual tumour, R2 = macroscopic residual tumour. In the resubmission residual disease was defined as: R0 = nil visible residual disease, R1 = >0cm - ≤1cm residual disease and R2 = >1 cm disease. The SOLO-1 trial publication reported results for patients with or without presence of macroscopic disease after debulking surgery. The evaluation interpreted the presence of macroscopic disease to include both R1 and R2, whereas the resubmission interpreted the presence of macroscopic disease

to include only R2. Based on this assumption, the resubmission noted 4% of BRCAm patients in PRIMA had R2, compared with 21-22% in SOLO-2 (38-40% excluding stage III R0 PDS). This suggests that baseline risk may have been higher in SOLO-1 on the basis of surgical outcomes.

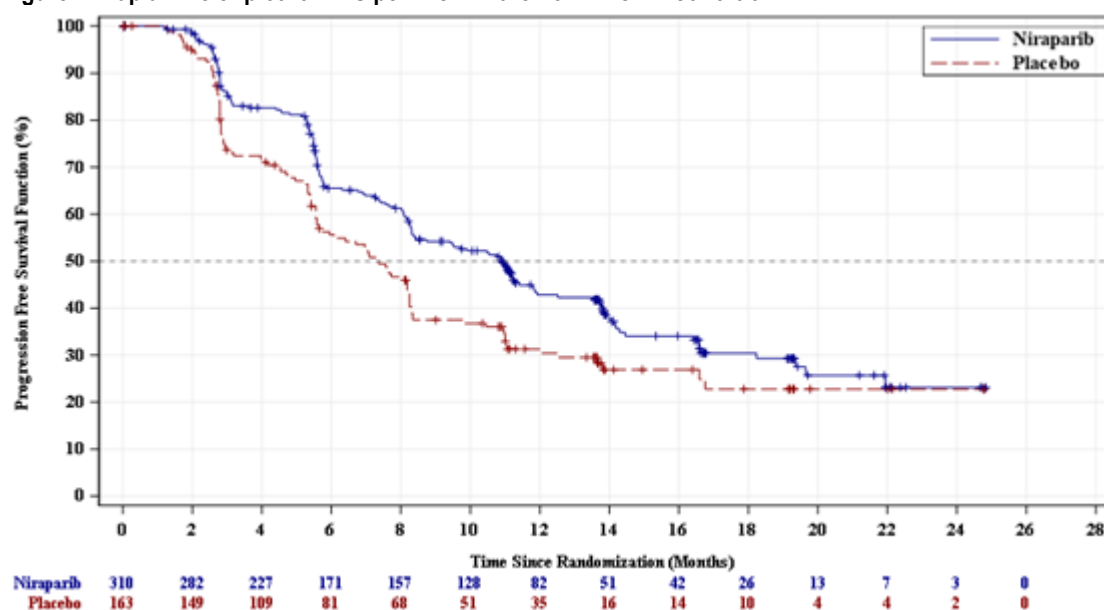
- 6.16 The PSCR also disagreed with the evaluation's interpretation in relation to the observed imbalance in Stage IV patients between the trials. The PSCR noted that there was an increased representation of Stage IV patients in the PRIMA BRCAm subgroup even after Stage III R0 PDS patients were excluded (38% vs. 30%), which may bias the comparison in favour of olaparib. However, in both trials the placebo arms had more patients with metastatic disease than the respective PARPi arms, with a larger difference reported in the PRIMA trial (34% vs. 48% compared with 27% vs. 36% in SOLO-1 excluding the Stage III R0 PDS subgroup). As disease stage is a known prognostic factor, there is a greater risk of bias in favour of PARPi therapy in the PRIMA trial than in the SOLO-1 trial.
- 6.17 The ESC considered that overall it was uncertain whether differences in the patient populations in the subgroups of the PRIMA and SOLO-1 trials included in the ITC had a meaningful impact on the outcome of the ITC. It was also difficult to ascertain the overall direction of potential bias based on these differences.

Comparative effectiveness

Subgroup analyses of non-BRCAm patients for niraparib versus no active treatment (placebo)

- 6.18 The PFS results (per blinded independent central review (BICR)) in the non-BRCAm patients enrolled in PRIMA are presented below.

Figure 1: Kaplan-Meier plot for PFS per BICR in the non-BRCAm cohort of PRIMA



Source: Figure 15, p74 of the resubmission

BICR = blinded independent central review; BRCAm = BRCA gene mutation; PFS = progression-free survival

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Note: Data cut-off 17/05/2019

Table 5: Results of PFS per BICR in the non-BRCAm cohort of PRIMA

		NIRA (n=310)	PBO (n=163)	Absolute Difference (NIRA vs. PBO) #
Events, n (%)		170 (54.8)	108 (66.3)	-11.5%
Probability of PFS (95% CI)*	6 months	0.65 (0.60, 0.71)	0.56 (0.47, 0.63)	9%
	12 months	0.43 (0.37, 0.49)	0.31 (0.24, 0.39)	12%
	18 months	0.30 (0.24, 0.37)	0.23 (0.15, 0.32)	7%
Median, months (95% CI)		10.9 (8.3, 11.8)	7.4 (5.6, 8.2)	3.5 months
HR (95% CI), p-value		0.69 (0.54, 0.88), p=0.0029		
In the BRCAm subgroup, included for reference		Difference in median PFS: 11.2 months (22.1 months vs. 10.9 months) HR: 0.40 (0.27, 0.62), p<0.0001		

Source: Table 37, p73 of the resubmission

BICR=blinded independent central review; BRCAm = BRCA gene mutation; CI=confidence interval; HR = hazard ratio; NE = not evaluable; NIRA = niraparib; PBO = placebo; PFS=progression-free survival

Note: Blue shading indicates data previously seen by the PBAC.

Data cut-off 17/05/2019

Note that the results denoted by (#) are derived from post-hoc analyses 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.

* Note that the results denoted by (*) are derived from post-hoc analyses conducted by the applicant 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

- 6.19 Treatment with niraparib increased the median PFS by a modest 3.5 months, compared with placebo, among non-BRCAm patients. The PBAC previously raised concerns that a magnitude of PFS benefit of 2.7 months (in the HRD-negative and not determined subgroups) was small and may not be clinically meaningful (Paragraph 7.10, Niraparib PSD, July 2021 PBAC meeting). The clinical importance of 3.5 months gained in PFS for non-BRCAm patients should be considered together with the increased toxicity observed with niraparib compared with placebo (see the “Comparative harms” subsection below). The PBAC considered that although the results indicated a small PFS benefit for the non-BRCA subgroup, there would be patients in this subgroup for whom there was no benefit from treatment with niraparib.
- 6.20 The PFS results by HRD status in the non-BRCAm and HRDnd patients of PRIMA are presented in the table below. The PSCR noted that the non-BRCAm HRD and not determined population (n=71 niraparib, n=40 placebo) included 28-30% of patients for whom BRCA status was also not determined, therefore results in this subgroup may not be representative of BRCAwt patients.

Table 6: Results of PFS per BICR by HRD status in the non-BRCAm and HRDnd cohort of PRIMA

		Events n (%)	Survival Distribution (95% CI)			Median, months (95% CI)	HR (95% CI), p value
			6 months	12 months	18 months		
Non-BRCAm ^a	NIRA (N=310)	170 (54.8)	0.65* (0.60, 0.71)	0.43* (0.37, 0.49)	0.30* (0.24, 0.37)	10.9 (8.3, 11.8)	0.69 (0.54, 0.88) p=0.0029
	PBO (N=163)	108 (66.3)	0.56* (0.47, 0.63)	0.31* (0.24, 0.39)	0.23* (0.15, 0.32)	7.4 (5.6, 8.2)	
Non-BRCAm, HRDpos ^{b*}	NIRA (N=95)	32 (33.7)	0.79 (0.69, 0.87)	0.66 (0.53, 0.75)	0.53 (0.39, 0.66)	19.6 (13.6, NE)	0.50 (0.31, 0.83), p=0.0064
	PBO (N=55)	33 (60.0)	0.68 (0.54, 0.79)	0.40 (0.26, 0.53)	0.31 (0.16, 0.47)	8.2 (6.7, 16.8)	
Non-BRCAm HRDneg ^{b*}	NIRA (N=169)	111 (65.7)	0.56 (0.47,0.63)	0.30 (0.23,0.38)	0.22 (0.14,0.30)	8.1 (5.7,9.4)	0.68 (0.49,0.94) p=0.0203
	PBO (N=80)	56 (70.0)	0.43 (0.31,0.54)	0.24 (0.15,0.35)	0.20 (0.11,0.31)	5.4 (4.0,7.3)	
HRDnd ^{c*}	NIRA (N=71)	40 (56.3)	0.70 (0.56,0.79)	0.43 (0.30,0.55)	0.28 (0.16,0.42)	11.0 (7.4,13.9)	0.85 (0.51,1.43) P=0.5577
	PBO (N=40)	26 (65.0)	0.66 (0.49,0.79)	0.37 (0.22,0.52)	0.17 (0.02,0.45)	8.3 (5.7,12.5)	

Source: Table 37, p73 of the resubmission; Table 14.2.1.9m, PRIMA clinical study report

BICR=blinded independent central review; BRCAm = BRCA gene mutation; CI=confidence interval; HR = hazard ratio; HRDnd = homologous recombination deficiency test status not determined; HRDneg=homologous recombination deficiency test negative, referring to homologous recombination proficient (HR-proficient) tumours; HRDpos = homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumours; NE=not estimated; NIRA = niraparib; PBO = placebo; PFS=progression-free survival

Note: Blue shading indicates data previously seen by the PBAC.

Data cut-off 17/05/2019

^a Not including patients whose BRCA status was not determined.

^b Inclusive of patients whose BRCA status was not determined (0-2% of patients in each arm). Results for PFS per BICR excluding patients with unknown BRCA status from the analyses were:

Non-BRCAm HRDpos: (NIRA = 94, PBO = 55): HR = 0.51 [0.31, 0.85], p=0.0085, median PFS: 19.6 (13.6, NE) vs 8.2 (6.7, 16.8) months

Non-BRCAm HRDneg: (NIRA = 166, PBO = 79): HR = 0.64 [0.46, 0.89], p=0.0079, median PFS: 8.2 (5.7, 9.5) vs 5.4 (4.0, 7.3) months

^c Data on the HRDnd subgroup were not provided by the submission, and were extracted from the PRIMA clinical study report. The PSCR indicated that for the HRDnd subgroup 21 (29.6%) of patients in the niraparib arm and 11 (27.5%) of patients in the placebo arm had unknown BRCA status.

Note that the results denoted by () are derived from post-hoc analyses conducted by the applicant 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

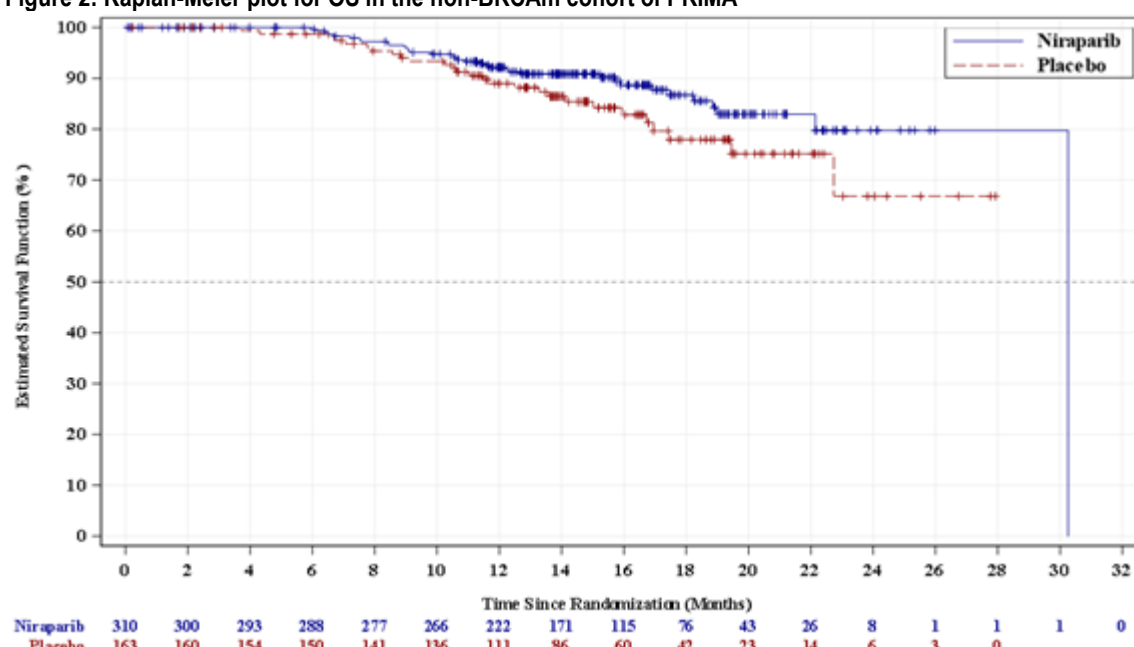
6.21 The PBAC previously noted the uncertain clinical benefit for niraparib in patients with HRD negative HGEOC (Paragraph 7.17, Niraparib PSD, July 2021 PBAC meeting). No further clinical evidence was presented by the resubmission to address this issue. Of note, the stratification factors in PRIMA included HRD status (HRD positive vs. HRD negative/HRD not determined), but not BRCA status. Therefore, randomisation was not preserved in any of the above HRD subgroups in the non-BRCAm cohort. There was a lack of data on patient baseline characteristics in these subgroups to assess whether there was a risk of bias/confounding.

6.22 In the PRIMA trial, the majority of patients (65%) received a fixed (300 mg) starting dose (FSD) of niraparib, with the remaining patients initiating niraparib according to

an ISD protocol as recommended by the TGA-approved Product information. The hazard ratio (HR) for PFS was numerically lower (more favourable) in the FSD subgroup of non-BRCAM patients than in the non-BRCAM, ISD subgroup (0.62 [0.46, 0.85] vs. 0.84 [0.55, 1.28])⁷. These results, however, should be interpreted with caution given the post hoc nature of the analysis and the small sample size of the subgroup (e.g. N=57 in the placebo arm of the non-BRCAM, ISD subgroup). Previously, on the basis of data from the intention-to-treat (ITT) population (including both non-BRCAM and BRCAM), the PBAC considered 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 (Paragraph 6.19, Niraparib PSD, July 2021 PBAC meeting).

6.23 A summary of OS results is presented below.

Figure 2: Kaplan-Meier plot for OS in the non-BRCAM cohort of PRIMA*



Source: Figure 18, p76 of the resubmission

BRCAM = BRCA gene mutation; OS = overall survival

Note: Data cut-off 17/05/2019

*Note that the Figure 2 depicts results that are derived from a post-hoc analysis conducted by the applicant 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

⁷ Braicu EI, Pothuri B, *et al.* Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by BRCAwt status: Prima/engot-OV26/GOG-3012 study (abstract). *International Journal of Gynecologic Cancer*. 2020;30(Suppl 4):A125-A6.

Table 7: Results of OS in the non-BRCAm cohort of PRIMA*

		NIRA (n=310)	PBO (n=163)	Absolute Difference (NIRA vs. PBO)#
Events, n (%)		35 (11.3)	27 (16.6)	-5.3%
Probability of being event-free* (95 % CI)	6 months	1.00 (0.98, 1.00)	0.99 (0.95, 1.00)	1%
	12 months	0.92 (0.88, 0.95)	0.89 (0.83, 0.93)	3%
	18 months	0.87 (0.81, 0.91)	0.78 (0.68, 0.85)	9%
	24 months	0.80 (0.69, 0.87)	0.67 (0.46, 0.81)	13%
Median*, months (95% CI)		NR	NR	–
HR* (95% CI), p value		0.62 (0.37, 1.03), p=0.0629		

Source: Table 38-p76 of the resubmission.

BRCAm = BRCA gene mutation; CI = confidence interval; HR = hazard ratio; NIRA = niraparib; NR = not reached; OS = overall survival; PBO = placebo

Note: Data cut-off 17/05/2019

* Note that the results denoted by (*) are derived from post-hoc analyses conducted by the applicant 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

Note that the results denoted by (#) are derived from post-hoc analyses 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.

6.24 The OS data⁸ were immature (62 (13.1%) deaths to date) and so the OS benefit from niraparib cannot be reliably assessed in the non-BRCAm cohort. The PBAC noted that there appeared to be a trend toward improved survival for the non-BRCAm subgroup HR 0.62 (95%CI: 0.37, 1.03) with a difference in survival of 13% at 24 months. However, the PBAC considered as the data were immature the OS benefit remained uncertain and its previous concern that the PFS benefit may not translate into an OS benefit (Paragraph 7.10, Niraparib PSD, July 2021 PBAC meeting) remained outstanding. The PSCR confirmed that updated OS data from PRIMA is not expected until 2025.

Indirect comparison of niraparib versus olaparib in BRCAm patients

6.25 The resubmission presented indirect comparisons of niraparib and olaparib using data from the BRCAm cohort of PRIMA and that from the SOLO-1 overall population, or that from the subgroup of SOLO-1 excluding Stage III R0 post PDS⁹. The results of the indirect comparisons are presented below.

⁸ Note that these results are derived from post-hoc analyses conducted by the applicant 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

⁹ Note that the indirect comparisons of niraparib vs. olaparib in the BRCAm population were conducted by the applicant 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.

Table 8: Results of the indirect comparison of niraparib versus olaparib for PFS in BRCAm patients

		PRIMA BRCAm subgroup ^a		SOLO-1 ^b			
				Overall population		Excl Stage III R0 PDS	
		NIRA (n=152)	PBO (n=71)	OLA (n=260)	PBO (n=131)	OLA (n=146)	PBO (n=73)
PFS per BICR							
Events, n (%) [*]		49 (32.2)	40 (56.3)	75 (28.8)	75 (57.3)	Not reported	Not reported
Probability of PFS (95 % CI) [*]	6 months	0.90 (0.84, 0.94)	0.69 (0.56, 0.78)	Not reported	Not reported	Not reported	Not reported
	12 months	0.75 (0.67, 0.82)	0.44 (0.31, 0.56)			0.85	0.47
	18 months	0.59 (0.50,0.66)	0.35 (0.25,0.45)			Not reported	Not reported
Median, months [*] (95% CI)		22.1 (19.3, NE)	10.9 (8.0, 19.4)	Not reached	14.1	Not reached	11.3
HR (95% CI), p-value		0.40 (0.27, 0.62) p<0.0001		0.28 (0.20, 0.39) p<0.0001		0.32 (0.22, 0.49)	
ITC: NIRA vs. OLA		1.43 (0.83, 2.45)				1.25 (0.71, 2.21)	
PFS per investigator [*]							
Events, n (%)		53 (34.9)	45 (63.4)	102 (39.2)	96 (73.3)	Not reported	Not reported
Probability of PFS (95 % CI)	6 months	0.90 (0.84,0.94)	0.75 (0.63,0.84)	0.94	0.81	Not reported	Not reported
	12 months	0.74 (0.66,0.80)	0.49 (0.36,0.60)	0.88	0.51	0.85	0.40
	18 months	0.61 (0.51,0.70)	0.34 (0.22,0.47)	Not reported	Not reported	Not reported	Not reported
Median, months (95% CI)		24.2 (18.7, NE)	11.5 (8.4, 16.7)	Not reached ^c	13.8	39.0	11.1
HR (95% CI), p-value		0.40 (0.27, 0.60) p<0.0001		0.30 (0.23, 0.41) p<0.0001		0.34 (0.24, 0.48)	
ITC: NIRA vs. OLA		1.33 (0.81, 2.19)				1.18 (0.63, 2.20)	

Source: Tables 31 and 32, p65 of the resubmission; Table 30, p134 of the PRIMA clinical study report; Moore et al 2018

BICR=blinded independent central review; CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; NE = not evaluable; NIRA = niraparib; OLA = olaparib; PBO = placebo; PDS = primary debulking surgery; PFS = progression-free survival; R0 = no visible residual disease.

Note: Blue shading indicates data previously seen by the PBAC

^a Median follow-up for PFS of 15.7 months for niraparib and 13.9 months for placebo.

^b Median follow-up of 40.7 months for olaparib and 41.2 months for placebo in the overall population of SOLO-1 at data cutoff 17/05/2018.

Relevant data in the excluding Stage III, R0 PDS subgroup were not available.

^c Updated PFS per investigator data in SOLO-1 were reported by Banerjee et al 2021¹⁰. At data cutoff 05/02/2020, the median follow-up was 4.8 years for olaparib and 5.0 years for placebo. The median PFS was 56.0 months (95% CI: 41.9, not reached) in the olaparib group compared with 13.8 months (95% CI: 11.1, 18.2) in the placebo group, with an HR of 0.33 (95% CI: 0.25, 0.43). No relevant updated data were available for the excluding Stage III R0 PDS subgroup SOLO-1.

Note that the results denoted by () are derived from post-hoc analyses conducted by the applicant 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

6.26 The indirect HRs numerically favoured olaparib over niraparib for both PFS per BICR (1.43 [0.83, 2.45]) and PFS per investigator (1.33 [0.81, 2.19]). The point estimates of HRs indicated slightly diminished PFS benefits of olaparib in comparison with niraparib when the subjects of the niraparib and olaparib trials were more comparable (i.e. excluding Stage III R0 post PDS patients from the SOLO-1 trial) (PFS per BICR: 1.25 [0.71, 2.21]; PFS per investigator: 1.18 [0.63, 2.20]). The 95% CIs of HRs contained clinically relevant worsening of PFS. The median PFS per investigator for olaparib in the subgroup excluding Stage III R0 post PDS of SOLO-1 was 14.8 months longer than

¹⁰ Banerjee S, Moore KN, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2021;22(12):1721-31.

that for niraparib in the BRCam subgroup of PRIMA (39.0 months vs. 24.2 months)¹¹.

- 6.27 The resubmission argued that, given the discrepancies in trial population between PRIMA and SOLO-1, the indirect comparisons of niraparib versus olaparib were substantially biased in favour of olaparib. The comparison between the BRCam cohort in PRIMA and the subgroup of SOLO-1 by excluding Stage III R0 post PDS patients partially alleviated the concerns regarding the transitivity of the PRIMA trial and the SOLO-1 trial. The comparability of the PRIMA BRCam patients and the SOLO-1 subgroup excluding Stage III R0 post PDS patients was supported by the similar results in the common reference (i.e. placebo) arms of the ITC: median PFS per BICR: 10.9 months versus 11.3 months and median PFS per investigator: 11.5 months versus 11.1 months. In addition, there is no convincing evidence indicating the observed heterogeneity in patient age (57 years vs. 54 years), disease stage (Stage IV: 34% for niraparib vs. 27% for olaparib) and the duration of follow-up (median: 16 months for niraparib vs. 41 months for olaparib) would fundamentally invalidate or greatly alter the interpretation of the ITC results for PFS.
- 6.28 No formal common reference-based ITC for OS was possible given the immaturity of the OS data in both trials, and the discrepancy in the use of subsequent PARPi therapy in the later-line setting among patients in the placebo arms between PRIMA and SOLO-1 (9% in PRIMA vs. 37% in SOLO-1).
- 6.29 The ESC noted that the results of the ITC included point estimates favourable to olaparib, though results of the comparison were not statistically significant. Noting the concerns regarding the transitivity of the studies, the ESC considered that the similar outcomes in the placebo arms (excluding Stage III R0 PSD) suggested that the heterogeneity between the patient populations was limited and the comparison was meaningful.

Comparative harms

Subgroup analyses of non-BRCam patients for niraparib versus no active treatment (placebo)

- 6.30 The key safety data of niraparib compared with placebo in the non-BRCam patients in PRIMA are summarised below.

¹¹ Note that the indirect comparisons of niraparib vs. olaparib in the BRCam population were conducted by the applicant 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.

Table 9: Overall summary of TEAEs in the non-BRCaM cohort of PRIMA

	Niraparib (N=307)	Placebo (N=162)	Risk difference (95% CI)^a	Relative risk (95% CI)^a	Odds ratio (95% CI)^a
Any TEAE	304 (99.0)	147 (90.7)	8.3% (3.7%, 12.9%)	1.09 (1.04, 1.15)	10.34 (2.95, 36.28)
≥ Grade 3 TEAE	223 (72.6)	31 (19.1)	53.5% (45.7%, 61.3%)	3.80 (2.75, 5.25)	11.22 (7.05, 17.86)
SAE	105 (34.2)	22 (13.6)	20.6% (13.1%, 28.1%)	2.52 (1.66, 3.83)	3.31 (1.99, 5.50)
TEAEs leading to treatment discontinuation	39 (12.7)	4 (2.5)	10.2% (5.8%, 14.7%)	5.14 (1.87, 14.14)	5.75 (2.02, 16.39)
TEAEs leading to dose reduction	222 (72.3)	12 (7.4)	64.9% (58.5%, 71.3%)	9.76 (5.64, 16.9)	32.65 (17.23, 61.85)
TEAEs leading to dose interruption	249 (81.1)	30 (18.5)	62.6% (55.2%, 70%)	4.38 (3.16, 6.08)	18.89 (11.59, 30.79)
On treatment deaths	0	0	0%	Not calculable	Not calculable

Source: Table 41, p81 of the resubmission

BRCaM = BRCA gene mutation; CI = confidence interval; SAE = serious adverse event; TEAE = treatment-emergent adverse event

^a Risk differences, relative risks and odds ratios were calculated during the evaluation. Note that the results denoted by (^a) are derived from post-hoc analyses 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.

- 6.31 The incidence of treatment emergent adverse events (TEAEs), ≥ Grade 3 TEAEs, serious TEAEs, and TEAEs leading to drug interruption, dose reduction and drug withdrawal were statistically significantly higher in non-BRCaM patients receiving niraparib than in the placebo arm. Risks of these AEs ranged from 2.5 to 10 times higher with niraparib.
- 6.32 The use of niraparib as an ISD regimen reduced the risk of haematological AEs of Grade 3 or above, although was still worse than placebo. Overall, no noticeable difference in the safety profile of niraparib was observed in the non-BRCaM patients compared with that in overall population, as reported in the previous submission.

Indirect comparison of niraparib versus olaparib in BRCaM patients

- 6.33 The results of the indirect comparison for TEAEs between niraparib, at its proposed ISD regimen, and olaparib, are presented below¹².

¹² the anchored indirect comparisons were presented in the re-submission 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

Table 10: Comparison of TEAEs in PRIMA ISD cohort^a and SOLO-1^b

	Trial	PARPi n/N (%)	Placebo n/N (%)	Odds ratio (95% CI) ^c	Relative risk (95% CI) ^c	Risk difference (95% CI) ^c
Any TEAEs						
NIRA vs. PBO	PRIMA ISD cohort	165/169 (97.6%)	76/86 (88.4%)	5.43 (1.65, 17.86)	1.10 (1.02, 1.20)	0.09 (0.02, 0.16)
OLA vs. PBO	SOLO-1	256/260 (98.5%)	120/130 (92.3%)	5.33 (1.64, 17.35)	1.07 (1.01, 1.12)	0.06 (0.01, 0.11)
ITC: NIRA vs. OLA				1.02 (0.19, 5.44)	1.04 (0.94, 1.14)	0.03 (-0.06, 0.12)
≥ Grade 3 TEAEs						
NIRA vs. PBO	PRIMA ISD cohort	102/169 (60.4%)	16/86 (18.6%)	6.66 (3.57, 12.44)	3.24 (2.05, 5.13)	0.42 (0.31, 0.53)
OLA vs. PBO	SOLO-1	102/260 (39.2%)	24/130 (18.5%)	2.85 (1.72, 4.74)	2.13 (1.44, 3.14)	0.21 (0.12, 0.30)
ITC: NIRA vs. OLA				2.34 (1.04, 5.23)	1.53 (0.84, 2.79)	0.21 (0.07, 0.36)
Serious TEAEs						
NIRA vs. PBO	PRIMA ISD cohort	45/169 (26.6%)	14/86 (16.3%)	1.87 (0.96, 3.63)	1.64 (0.95, 2.81)	0.10 (0.00, 0.21)
OLA vs. PBO	SOLO-1	54/260 (20.8%)	16/130 (12.3%)	1.87 (1.02, 3.41)	1.69 (1.01, 2.83)	0.08 (0.01, 0.16)
ITC: NIRA vs. OLA				1.00 (0.41, 2.45)	0.97 (0.46, 2.05)	0.02 (-0.11, 0.15)
TEAEs leading to treatment discontinuation						
NIRA vs. PBO	PRIMA ISD cohort	23/169 (13.6%)	2/86 (2.3%)	6.62 (1.52, 28.77)	5.85 (1.41, 24.25)	0.11 (0.05, 0.17)
OLA vs. PBO	SOLO-1	30/260 (11.5%)	3/130 (2.3%)	5.52 (1.65, 18.45)	5.00 (1.55, 16.08)	0.09 (0.05, 0.14)
ITC: NIRA vs. OLA				1.20 (0.18, 8.02)	1.17 (0.19, 7.37)	0.02 (-0.06, 0.10)

Source: Table 40, p80 and Table 26, p60 of the resubmission.

CI = confidence interval; ISD = individualised starting dose; NIRA = niraparib; OLA = olaparib; PARPi = poly (ADP-ribose) polymerase inhibitor; PBO = placebo; TEAEs = treatment-emergent adverse events

Note: Blue shading indicates data previously seen by the PBAC.

^a Median treatment duration of 11.0 months for niraparib and 8.3 months for placebo in the ISD cohort of PRIMA at data cutoff 17/05/2019.

^b Median treatment duration of 24.6 months for olaparib and 13.9 months for placebo follow-up of 40.7 months for olaparib and 41.2 months for placebo in the overall population of SOLO-1 at data cutoff 17/05/2018.

^c Risk differences, relative risks and odds ratios were calculated during the evaluation. Note that the results denoted by (a) are derived from post-hoc analyses 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

6.34 The proportion of patients experiencing any TEAEs, ≥ Grade 3 TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation was largely comparable across the common reference (placebo) groups from the PRIMA ISD cohort and SOLO-1. The risk of any TEAEs and serious TEAEs was similar between niraparib (ISD regimen) and olaparib. However, the indirect odds ratios for TEAEs of ≥ Grade 3 and discontinuation due to TEAEs were in favour of olaparib, with statistical significance reached for ≥ Grade 3 TEAEs. The wide CIs for most of the indirect estimates of treatment effect suggests that the indirect comparisons were not sufficiently powered. Of note, AEs were collected until 30 days after the treatment last dose in both trials. As patients in the SOLO-1 trial were treated for longer with olaparib compared with those receiving niraparib in PRIMA (median treatment duration: 11.0 months for niraparib in PRIMA vs. 24.6 months for olaparib in SOLO-1), the ITC of safety outcomes could have favoured niraparib, particularly for events that are caused by cumulative exposure.

The PBAC noted that Grade 3-5 thrombocytopenia events were reported in 14.8% of patients receiving ISD niraparib in PRIMA, compared with an incidence of <5% in the olaparib group in SOLO-1 and Grade ≥ 3 neutropenia occurred in 9.5% of patients receiving ISD niraparib in PRIMA, compared with an incidence of for 5.0% patients treated with olaparib in SOLO-1. The pre-PBAC response argued that that insights from the PBAC hearing indicated haematological toxicities are asymptomatic and manageable with dose reductions in practice, and symptomatic TEAEs such as nausea and fatigue that have been reported with olaparib have been less of a concern with niraparib. The PBAC considered it was appropriate that hospitalisation costs for thrombocytopenia and anaemia TEAEs were included in the CMA, accounting for the observed incremental differences in the incidence of these events across PRIMA and SOLO-1.

Benefits/harms

6.35 A summary of the comparative benefits and harms for niraparib versus placebo in the non-BRCam subgroup is presented in the table below.

Table 11: Summary of comparative benefits and harms for niraparib and placebo in the non-BRCam subgroup

Benefits						
Progression free survival (median duration of follow up 14 months)						
Event	Niraparib	Placebo	Absolute Difference#	HR (95% CI)		
Progressed, n (%)	170/310 (54.8%)	108/163 (66.3%)	11.5%	0.69 (0.54, 0.88) p=0.0029		
Median PFS, months (95% CI)*	10.9 (8.3, 11.8)	7.4 (5.6, 8.2)	3.5			
% not progressed at 12 months (95% CI)*	43 (37, 0.49)	31 (24, 39)	12%			
% not progressed at 18 months (95% CI)*	30 (24, 37)	23 (15, 32)	7%			
Overall survival (median duration of follow up 15 months)*						
Deaths, n/N (%)	35/310 (11.3%)	27/163 (16.6%)	5.3%	0.62 (0.37, 1.03) P=0.0629		
Median OS, months (95% CI)	NR	NR	–			
% Alive at 12 months (95% CI)	92 (88, 95)	89 (83, 93)	3%			
% Alive at 24 months (95% CI)	80 (69, 87)	67 (46, 81)	13%			
Harms						
	Niraparib n/N	Placebo n/N	RR (95% CI)# ^a	Event rate/100 patients#		RD (95% CI)#
				Niraparib	Placebo	
Serious TEAEs	105/307	22/162	2.52 (1.66, 3.83)	34	14	20.6% (13.1%, 28.1%)
Grade ≥ 3 TEAEs	223/307	31/162	3.80 (2.75, 5.25)	73	19	53.5% (45.7%, 61.3%)
TEAEs leading to treatment discontinuation	39/307	4/162	5.14 (1.87, 14.14)	13	3	10.2% (5.8%, 14.7%)

Source: Table 37, p73, Table 38, p76 and Table 41, p81 of there submission

OS = overall survival; PFS = progression free survival; HR = hazard ratio; NR = not reached; RD = risk difference; RR = risk ratio; TEAE = treatment emergent adverse event.

Note: Blue shading indicates data previously seen by the PBAC.

Note that the results denoted by (#) are derived from post-hoc analyses 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.

Note that the results denoted by () are derived from post-hoc analyses conducted by the applicant 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

- 6.36 On the basis of subgroup analysis of non-BRCa patients in PRIMA presented by the resubmission, for every 100 patients treated with niraparib in comparison with no active treatment (placebo):
- Approximately 7 additional patients will remain progression-free after 18 months; however, the overall survival gain is unknown as the data are immature and cannot be reliably assessed.
 - Approximately 21 additional patients would experience a serious TEAE over a median follow up of 15 months.
 - Approximately 54 additional patients would experience a Grade ≥ 3 TEAE over a median follow-up of 15 months.
 - Approximately 10 additional patients would experience a TEAE leading to treatment discontinuation.

Clinical claim

Niraparib vs SMM (non-BRCa)

- 6.37 The resubmission described niraparib as superior in terms of PFS and inferior in terms of safety compared to no active treatment for the treatment of non-BRCa NDA HGEOC.
- 6.38 The PBAC considered the claim of superior effectiveness in terms of PFS was supported by the observed statistically significant improvement in PFS associated with niraparib versus no active treatment (placebo) in all non-BRCa patients from PRIMA (HR for PFS: 0.69 [0.54, 0.88]). However, the PBAC considered the clinical importance of a PFS gain of 3.5 months was uncertain, particularly considering the toxicity of niraparib therapy and in the context of uncertain OS benefit. The PBAC considered that the PFS benefit may not translate to OS benefit.
- 6.39 The PBAC considered the claim of inferior safety of niraparib in comparison with no active treatment in the non-BRCa cohort was supported by the safety data presented. The incidence of TEAEs, $\geq$ Grade 3 TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation was statistically significantly higher in non-BRCa patients who received niraparib than those treated with placebo.

Niraparib vs olaparib (BRCa)

- 6.40 The resubmission claimed that niraparib is non-inferior in terms of PFS and has comparable safety in comparison with olaparib for treatment of BRCa NDA HGEOC.
- 6.41 The PBAC considered that on balance, the non-inferior effectiveness conclusion was sufficiently supported by the evidence from the common reference-based ITC of niraparib vs olaparib, despite the limitations of the ITC as discussed in paragraphs 6.10 to 6.17. The PBAC noted that confidence intervals were wide, reflecting the relatively small sample size for the comparison between a subgroup of the PRIMA trial (BRCa)

and in the SOLO-1 trial (excluding Stage III R0 post PDS). The PBAC also considered that there were likely transitivity issues with the indirect comparison due the differences in trial populations between PRIMA and SOLO-1, some of which remained even after exclusion of Stage III R0 post PDS patients from SOLO-1.

- 6.42 The PBAC noted that an anchored ITC of OS for niraparib versus olaparib would not be meaningful due to the immature OS data in both trials and the dissimilar crossover rate from placebo to later-line PARPi in the common reference groups (9% in PRIMA vs. 37% in SOLO-1).
- 6.43 The PBAC noted that there appeared to be significantly worse safety for niraparib compared with olaparib with regard to Grade 3-5 TEAEs including differences in the incidence of thrombocytopenia and anaemia. However, the PBAC noted that treatment discontinuations due to TEAEs were similar between PRIMA (ISD): 13.6% and SOLO-1: 11.5%. In addition, the PBAC noted that the sponsor hearing suggested that gastrointestinal AEs (possibly due to twice daily dosing) and drug interactions may be more common for olaparib. The PBAC noted that the indirect comparison of safety was limited due to differences in the patient population and duration of follow-up. On balance, the PBAC considered that TEAEs for niraparib appeared to be generally manageable with dose interruptions and overall safety likely to be sufficiently similar for niraparib and olaparib such that the claim of non-inferior comparative safety was reasonable. The PBAC noted that hospitalisation costs for thrombocytopenia and anaemia were included in the CMA (see paragraphs 6.34 and 6.65).

Economic analysis

- 6.44 The resubmission presented two economic evaluations in accordance with the PBAC's advice (Paragraph 7.17, Niraparib PSD, July 2021 PBAC meeting):
- A cost-utility analysis comparing niraparib with SMM for the maintenance treatment of non-BRCaM NDA HGEOC; and
 - A cost-minimisation analysis (CMA) comparing niraparib with olaparib for the maintenance treatment of BRCaM NDA HGEOC.

Cost utility analysis of niraparib vs. SMM

- 6.45 The resubmission presented a stepped economic evaluation based on a subgroup of the direct randomised trial (the non-BRCaM cohort of PRIMA). The type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation are presented below.

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Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Niraparib vs SMM; Unchanged from the previous submission, but the population in the resubmission only included non-BRCaM patients.
Time horizon	15 years in the model base case versus 15 months median follow-up in PRIMA. The 15-year time horizon is in line with PBAC advice that 20 years may be too long for non-BRCaM patients (paragraph 7.15, Niraparib PSD, July 2021 PBAC meeting).
Outcomes	QALYs gained; life-years gained; Unchanged from the previous submission
Methods used to generate results	Partitioned survival model (i.e. area under the curve); Unchanged from the previous submission
Health states	Progression-free (incorporating a 'cured' fraction), progressed disease and death states. Unchanged from the previous submission
Cycle length	One month; Unchanged from the previous submission
Allocation to health states	Progression-free survival and overall survival curves from the non-BRCaM patients, which were adjusted using life tables to account for the proportion of 'cured' patients prior to initiation of first-line maintenance treatment, were used to estimate the proportion of patients in progression free, progressed disease and death states. The resubmission revised survival curves based on the PRIMA non-BRCaM cohort (which was based on PRIMA ITT in the previous submission) to align with the modelled non-BRCaM subgroup.
Extrapolation method	Observed PFS and OS KM data from the non-BRCaM cohort of the PRIMA trial were applied until median follow-up, after which independent parametric models, fitted to the KM data, were used to extrapolate survival to the model time horizon. The resubmission updated the extrapolation methods from the previous submission, in which dependent parametric models were applied. The niraparib TTD KM curve from the PRIMA non-BRCaM, extrapolated beyond median follow-up, was used to inform the niraparib treatment duration. Approximately 97% of the undiscounted incremental life-years gained for niraparib over SMM 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). Unchanged from the previous submission. This may not be reasonable since the data were not specific to non-BRCaM cohort and no disutility for treatment related adverse events was applied.

Source: Table 46-7, pp89-90 of the resubmission.

ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; QALYs = quality adjusted life years; SMM = standard medical management (no active treatment); TTD = time to treatment discontinuation.

6.46 The model structure in the resubmission remained unchanged from the previous submission. However, other key changes included:

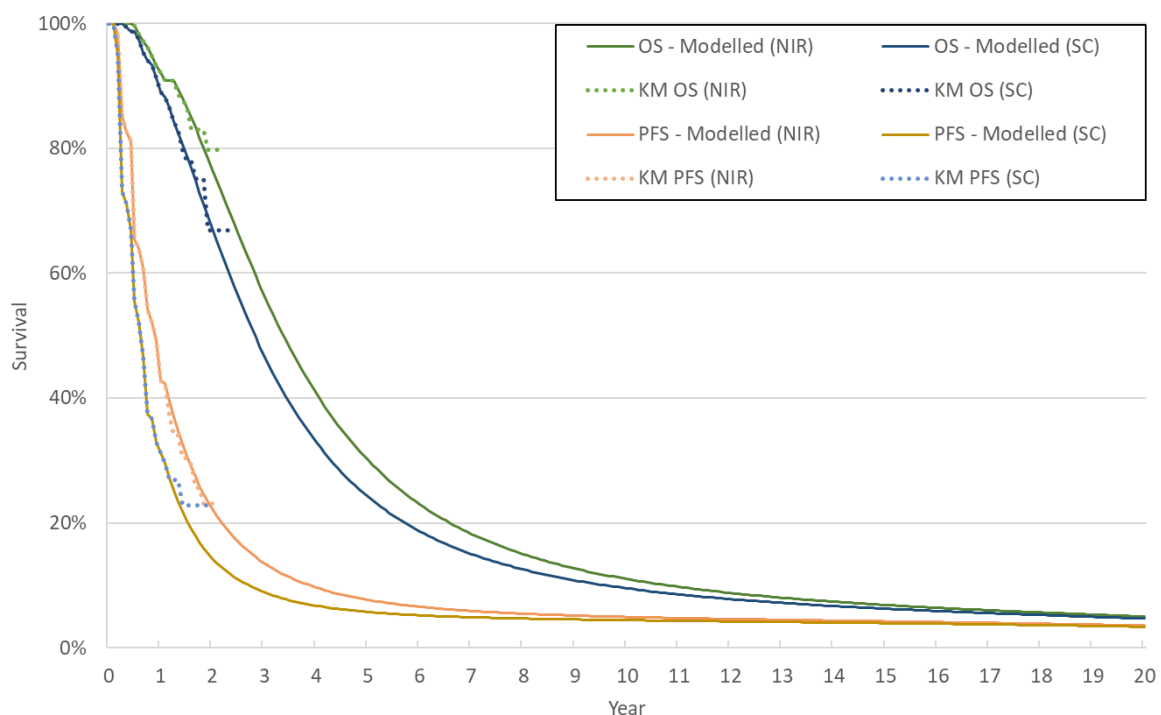
- The time horizon was reduced to 15 years from 20 years in line with PBAC advice.
- Subsequent PARPi use in the second-line setting in the SMM arm was removed. This is reasonable and consistent with previous PBAC advice (Paragraph 7.15, niraparib PSD, July 2021 PBAC Meeting).
- Extrapolation methods were updated by applying independent parametric functions for the extrapolation of PFS, OS and TTD.
- Costs associated with niraparib, subsequent chemotherapies, disease monitoring and management of AEs were also updated.

6.47 In the resubmission economic model, non-BRCaM cohort data from the PRIMA trial was used to inform clinical outcomes for PFS, OS and TTD, whereas health state utility

values were based on the PRIMA ITT cohort. The PRIMA ISD cohort was used to source the dose intensity and adverse event rates. ISD dosing is consistent with the approved PI, and expected to reflect clinical practice in Australia. However, uncertainty may have been introduced by using data from different cohorts as the dosing intensity in the different subgroups may have affected survival outcomes or time on treatment.

- 6.48 The resubmission applied the same approach that was used in the previous submission to extrapolate survival curves for PFS and OS. The KM curves for PFS and OS for PRIMA non-BRCAm cohort are presented below in comparison to the modelled PFS and OS curves.

Figure 3: Trial based and modelled PFS and OS in the non-BRCAm cohort



Source: Figure adapted during the evaluation from the Excel workbook "Survival Traces" 'Zejula (niraparib) 1L nonBRCAm CUA' BRCAm = BRCA gene mutation; KM = Kaplan-Meier; NIR = niraparib; OS = overall survival; PFS = progression-free survival; SC = standard care

- 6.49 The lognormal distribution was chosen for the extrapolation of PFS. The ICER was not sensitive to changes in the truncation time point for PFS or the change of extrapolation approach. In contrast, due to the immature OS data in PRIMA, the ICER was sensitive to the changes in the truncation point of OS and the extrapolation approach applied (log-logistic was chosen for the model base case). The OS benefit modelled for niraparib compared with SMM was still accrued primarily in the extrapolated period (97%, vs 98% in the previous submission). In the base case analysis with a time horizon of 15 years, approximately 3% of niraparib patients and 2% of SMM patients remain alive.
- 6.50 The ESC noted that it was difficult to judge which extrapolation function was the best fit for either niraparib or SMM due to the immaturity of the OS data. The ESC noted

that the extrapolation function (log-logistic) appeared to be fairly conservative for both treatment arms. The PSCR noted that this was conservative relative to the curve of best statistical fit (log-normal), which was associated with a 27% reduction in the ICER.

- 6.51 The ESC also noted that the economic model was sensitive to the OS truncation point. The PSCR and pre-PBAC response argued that the economic model is best informed by an approach that is aligned to the PRIMA trial data such that the KM estimates to median OS follow-up (15 months) is applied followed by the parametric extrapolation (as in the base case). The ESC noted that applying the KM data up to the PFS median follow-up time (niraparib: 13.8 months, SMM: 13.7 months) increased the ICER to \$55,000 to < \$75,000(13%).
- 6.52 Similar to the previous submission, a proportion of patients (5%) who were cured prior to receiving first-line maintenance treatment were incorporated in both arms the model. Cured patients in the niraparib arm did not receive any benefit from the treatment but incurred a cost. The resubmission proposed a restriction that included a maximum treatment duration of three years and the economic model was revised to reflect this. Although this is in line with PBAC's consideration (Paragraphs 3.4 and 7.17, Niraparib PSD, July 2021 PBAC meeting) and consistent with the proposed restriction, the PRIMA trial does not have data at three years and 'the proportion of patients on treatment at three years who are no longer deriving clinical benefit is uncertain' (Section 3A.3 of the submission).
- 6.53 Similar to the previous submission, the resubmission did not apply a disutility associated with niraparib treatment compared with SMM. This was not appropriate given the conclusion of inferior safety, and favours niraparib (Paragraph 6.53, Niraparib PSD, July 2021 PBAC meeting). The PSCR acknowledged that the clinical claim of inferiority for niraparib vs SMM with respect to safety (non-BRCam) should be reflected in the economic analyses and presented a respecified analysis including a total disutility of 0.094 for niraparib applied to the first model cycle (one month) resulting in a total QALY loss of 0.008 [0.094*(1/12)]. The ESC noted that this increased the ICER to \$55,000 to < \$75,000/QALY (see also Table 15 and paragraph 6.60). The ESC considered that this may have been a reasonable approach, however it was unclear whether there may be treatment-related disutility outside the immediate AE period.
- 6.54 The resubmission applied drug exposure (dose intensity) from the PRIMA ISD cohort (including both BRCam and non-BRCam patients), as in the previous submission. The resubmission stated that dose intensity was similar across non-BRCam and BRCam patients in PRIMA and the ISD regimen reflects clinical practice. Although ISD was consistent with the dose regimen in the approved PI, the health outcomes used in the model were based on the non-BRCam population, not both subgroups. The ICER was sensitive to niraparib exposure, however, no dose intensity data for non-BRCam cohort was included in the resubmission, so a revised ICER cannot be estimated.

6.55 The key drivers of the model are summarised below. Extrapolation, and dose intensity of niraparib remained unchanged from the previous submission. The disutility for adverse events is also included below.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: \$1/QALY
Extrapolation	Treatment effect continued beyond 15 month trial period for up to 15 years; and the choice of log-normal parametric functions used for OS extrapolation	High, favours niraparib Use of lognormal model to extrapolate OS data decreased the ICER to \$ ² /QALY gained, whereas use of PFS median follow-up time (13.8 months for the niraparib arm) as the truncation time point increased the ICER to \$ ¹ /QALY.
Utility	Assumed to be equal in both arms	Low, favours niraparib Applying a total disutility of 0.008 (0.094 for the first month) increases the ICER to \$ ¹ /QALY.
Dose intensity of niraparib	Based on ISD cohort of PRIMA	Moderate, favours niraparib When using data from the ITT cohort, the ICER increased to \$ ¹ /QALY.

Source: Compiled during the evaluation based on Table 92, pp159-160 of the submission

ICER = incremental cost effectiveness ratio; ISD = individualised starting dose; ITT = intention to treat; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$45,000 to < \$55,000

6.56 The results of the stepped economic analysis are presented below.

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Table 14: Results of the stepped economic evaluation

Step and component	Niraparib	SMM	Increment
Step 1: Trial-based analysis (24-month analysis)			
Costs (\$)			
PFLY	1.0121	0.8456	0.1665
Incremental cost/extra PFLY gained (\$)			¹
Step 2: Extrapolation of trial data from median follow-up to 15-year time horizon			
Costs (\$)			
PFLY	1.2977	0.9427	0.3550
LYG	3.6667	3.2199	0.4468
Incremental cost/extra PFLY gained (\$)			²
Incremental cost/extra LYG (\$)			³
Step 3: Translation of trial outcomes to QALYs			
Costs (\$)			
QALYs	2.6406	2.3014	0.3391
Incremental cost/extra QALY gained (\$)			²
Step 4: Inclusion of 'cured' patients into extrapolated survival curves (PFS, OS and TTD)			
Costs (\$)			
QALYs	2.8970	2.5619	0.3352
Incremental cost/extra QALY gained (\$)			²
Step 5: Application of health care resource costs			
Costs (\$)			
QALYs	2.8970	2.5619	0.3352
Incremental cost/extra QALY gained (\$)			²
Step 6: Translation of drug exposure to an Australian setting (PRIMA ITT cohort to ISD cohort)			
Costs (\$)			
QALYs	2.8970	2.5619	0.3352
Incremental cost/extra QALY gained (base case) (\$)			²
July 2021 Submission			
Costs (\$)			
QALYs	3.77	3.38	0.39
Incremental cost/extra QALY gained (base case) (\$)			²

Source: Table 87, p55 of the submission and 'CUA Results' worksheet of the Excel workbook 'Zejula (niraparib) 1L nonBRCAm CUA'
 ISD = individualised starting dose; ITT = intent-to-treat; LY = life-year; OS = overall survival; PFLY = progression-free life year; PFS = progression free survival; QALY = quality-adjusted life-year; TTD = time to treatment discontinuation

Note: Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$55,000 to < \$75,000

³ \$45,000 to < \$55,000

6.57 The results of key sensitivity analyses are summarised below.

Table 15: Results of key sensitivity analyses

Model variable	Incremental cost (\$)	Incremental QALYs	ICER per QALY (\$)	% difference
Base case		0.3352	¹	-
Time horizon: 15 years				
20 years		0.3423	¹	-1.8%
10 years		0.3156	¹	5.1%
Terminal care costs: \$38,443				
Goldsbury 2018 (\$63,760)		0.3352	¹	-2.9%
Excluded (\$0)		0.3352	¹	4.4%
Utility values: PRIMA ITT cohort (Australian dataset)				
Olaparib July 2020 PSD		0.3375	¹	-0.7%
PRIMA, ITT cohort (UK dataset)		0.3475	¹	-3.5%
Assuming a total QALY loss of 0.008 (PSCR)		0.3274	¹	2.4%
Exposure: PRIMA ISD cohort				
PRIMA ITT cohort		0.3352	¹	7.6%
OS KM truncation time point: Niraparib 15.0 months, SMM: 15.4 months				
Niraparib: 13.8 months, SMM: 13.7 months (PFS median follow-up time)		0.2981	¹	13.0%
OS extrapolation: Loglogistic				
Lognormal		0.4489	²	-27.1%
TTD KM truncation time point: Niraparib 13.8 months				
Niraparib median PFS: 10.9 months		0.3352	¹	2.6%
TTD extrapolation: Weibull				
Exponential		0.3352	¹	4.9%
Generalised Gamma		0.3352	¹	7.1%
Proportion of cured patients: 5%				
10%		0.3351	¹	3.5%
Bevacizumab use in the comparator arm (active treatment option for non-BRCa patients (none))				
7% of patients receive bevacizumab in the comparator arm		0.2817	¹	0.5%

Source: Table 92, p159-160 of the submission and analyses in *italics* were conducted during the evaluation using the Excel workbook 'Zejula (niraparib) 1L nonBRCa CUA'

2L = second-line; BICR=blinded independent central review; BRCa = BRCA gene mutation; ICER = incremental cost effectiveness ratio; ISD = individualised starting dose; ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; TTD = time to treatment discontinuation

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$45,000 to < \$55,000

- 6.58 The model was sensitive to OS extrapolation and niraparib exposure, which remained unchanged from the previous submission. OS extrapolation and also truncation time point were the drivers of uncertainty in the model, due to the use of immature OS data.
- 6.59 The resubmission conducted a sensitivity analysis for the inclusion of bevacizumab in the comparator arm for the active treatment of non-BRCa patients. As the resubmission presented bevacizumab as a qualitative comparator, with no clinical claim in terms of efficacy or safety or an economic evaluation, this analysis addresses the uncertainty in the resubmission's model and the result shows that the ICER is not sensitive to incorporating bevacizumab as a comparator (see Table 15).

- 6.60 The PSCR proposed a revised price for niraparib (\$████ per 56 capsules, in the non-BRCAM setting) in order to maintain the ICER at \$55,000 to < \$75,000/QALY (equal to the resubmission base case) after accounting for disutility due to treatment-related AEs (see paragraph 6.53).

Cost minimisation analysis of niraparib vs. olaparib

- 6.61 The equi-effective doses were estimated as niraparib 162.1 mg/day for 25 months and a fixed daily cost of any olaparib daily dose (600 mg/day, 500 mg/day or 400 mg/day) for 20.9 months. The mean dose of niraparib per day was derived from the ISD cohort of the PRIMA ITT/overall population, which includes both BRCAM and non-BRCAM patients. It is unclear whether the mean dose differs between patients with BRCAM and those without BRCAM. The ESC considered any differences are likely to be modest.
- 6.62 The PBAC had previously considered the average duration of treatment per patient in the first six years of listing of olaparib in the first line setting based on the SOLO-1 trial (Table 13, olaparib PSD, July 2020 PBAC meeting). The resubmission assumed the same average treatment duration per year for niraparib as previously considered by PBAC for olaparib, except for Year 3, which was estimated to be 5.4 months, higher than treatment duration with olaparib in Year 3 (1.4 months) due to the stopping rule at 36 months for niraparib compared with 24 months for olaparib. The estimated average treatment duration of niraparib in Year 3 (5.4 months) was based on SOLO-1 and olaparib first line EPAR reports. The average treatment duration per patient per year for both olaparib and niraparib are presented below. The modelled treatment durations for niraparib and olaparib were 25.0 months and 20.9 months, in comparison with the trial based mean treatment duration of 10.3 months vs 20.65 months, respectively. These treatment durations were unlikely to be comparable due to the difference in follow-up between the PRIMA and SOLO-1 trials (approximately 15 months and 41 months, respectively).

Table 16: Average treatment duration per patient per year

Year of treatment	Olaparib (Based on SOLO-1) ^a	Niraparib (estimated)
Year 1	10.3	10.3
Year 2	8.2	8.2
Year 3	1.4	5.4
Year 4	0.6	0.6
Year 5	0.4	0.4
Year 6	0.0	0.0
Total	20.9	25.0

Source: Table 101, p168 of the resubmission

^a Table 13, olaparib PSD, July 2020 PBAC meeting

- 6.63 Given the flat price per tablet of olaparib, there is a constant daily cost for olaparib treatment, irrespective of daily dose of 600 mg, 500 mg or 400 mg. The resubmission calculated the olaparib cost per course by multiplying the daily treatment cost (\$243.21) and the treatment duration (20.9 months), which was not reasonable because it did not account for olaparib dose intensity in terms of missed doses.

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- 6.64 In addition to the costs of niraparib and olaparib, the resubmission included in the CMA the costs of managing and monitoring AEs.
- 6.65 The resubmission applied hospitalisation costs to thrombocytopenia and anaemia TEAEs in the CMA, accounting for the observed incremental differences in the incidence of these events across PRIMA and SOLO-1. Weighted average hospitalisation costs per event were calculated based on NHCDC Cost Reports (NHCDC Round 22 Public Sector Cost Weight Tables, 2018-2019).
- 6.66 Based on different requirements in the frequency of complete blood count (CBC) and blood pressure (BP) monitoring in the respective product information documents for niraparib and olaparib, the resubmission assumed that all niraparib patients will need an additional 3.35 CBCs in the first month of treatment and an additional 10.3 GP consultations for BP monitoring in the first year of treatment.
- 6.67 The results of the CMA are presented below.

Table 17: Results of the cost-minimisation analysis (as presented in the resubmission – based on cost per course using published AEMP for olaparib)

	Parameter	Input	Source / calculation
Cost of olaparib			
A	Cost per maximum quantity (112 tablets)	\$6,810.00 ^a	Published AEMP
B	Packs per script	2	By definition
C	Tablets per pack	56	
D	Tablets per day	4	
E	Cost per day	\$243.21	A / (B*C/D)
F	Treatment duration, months	20.9	Table 16 above
G	Cost per course of treatment	\$154,719.25	E * (F/12*365.25)
Additional costs / cost offsets			
H	Net safety costs: niraparib versus olaparib	\$	Table 104, p170 of the resubmission
I	Net monitoring costs: niraparib versus olaparib	\$	Table 107, p172 of the resubmission
J	Total net costs: niraparib versus olaparib	\$	H+I
Niraparib			
K	Cost per course of treatment	\$	G-J
L	Mean dose intensity, mg/day*	162.1	PRIMA ISD (CSR Table 14.3.5.13b)
M	Treatment duration, months	25.0	Table 16 above
N	Amount per course of treatment, mg	123,310	L * (M/12*365.25)
O	Cost per mg	\$	K / N
P	Amount per 84-capsule pack/56-capsule pack ^b	8400 mg/5600 mg	
	Cost-minimising niraparib AEMP per 84-capsule script	\$	O * 8400
	Cost-minimising niraparib AEMP per 56-capsule script	\$	O * 5600

Source: Table 108, p172 of the resubmission.

AEMP = approved ex-manufacturer price; EMP = ex-manufacturer price; ISD = individualised starting dose

^a The AEMP for 28 days' supply of olaparib (112 tablets) is the same for both the 100 mg and the 150 mg tablets.

^b Maximum quantity of one pack per script

*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

- 6.68 The CMA analysis presented in the resubmission was not reasonable as it assumed 100% compliance for olaparib, but used the mean dose intensity of niraparib (162.1 mg/day from PRIMA ISD cohort)¹³.
- 6.69 The following sensitivity analyses were performed during the evaluation.
- Reduced dose intensity for olaparib was tested using the mean dose intensity of olaparib of 93.13% (558.80 mg/day) in SOLO-1 trial, which resulted in 6.9% decrease in the cost-minimised price for niraparib. The PSCR argued that applying the mean dose intensity for olaparib was not appropriate as, due to olaparib's flat pricing structure, patients on a reduced dose would incur the same cost. Applying a compliance rate of 97% (based on SOLO-1) resulted in a 3.0% decrease in the cost-minimised price for niraparib.
 - Equi-effective dosing based on PI dose recommendation was tested using 225.1 mg for niraparib and 600 mg for olaparib, which resulted in 28% decrease in the cost-minimised price for niraparib.
 - When the maximum study follow-up of 29 months in the PRIMA trial was tested, the cost-minimised price of niraparib for the BRCAm subgroup decreased by 14%.
 - The mean dose¹⁴ intensity in the PRIMA ITT cohort (174.7 mg/day) was tested in sensitivity analyses, the cost-minimised price of niraparib for the BRCAm subgroup decreased by 7%.

¹³ 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

¹⁴ 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

Table 18: Results of the sensitivity analyses performed during the evaluation (published AEMP for olaparib)

		Cost-minimised EMP for niraparib (BRCam)		
Base case		84-capsules	56-capsules	
Treatment duration for niraparib 25.0 months, olaparib 20.9 months)				
Niraparib mean dose intensity in ISD cohort (162.1 mg/day)*		\$█	\$█	
Net safety costs: niraparib versus olaparib (\$█)				
Sensitivity analyses				% Change
#1	The same treatment duration applied to niraparib as olaparib (20.9 months)	\$█	\$█	19.6%
#2	Equi-effective dosing based on PI recommendations ^a Niraparib: 225.1 mg once daily ^b Olaparib: 300 mg twice daily Treatment duration (as in the base case)	\$█	\$█	-28.0%
#3	Increased niraparib treatment duration (to 29 months)	\$█	\$█	-13.8%
#4	Increased niraparib mean dose intensity in PRIMA ITT cohort (to 174.7 mg/day)	\$█	\$█	-7.2%
#5	Reduced olaparib dose intensity (558.80 mg/day in SOLO-1)	\$█	\$█	-6.9%

Source: Table compiled during the evaluation using the Excel workbook "Zejula (niraparib) 1L BRCam CMA"

AEMP = approved ex-manufacturer price; BRCam = BRCA gene mutation; EMP = ex-manufacturer price; ISD = individualised starting dose, ITT = intention-to-treat; PI = product information

^a The recommended starting dose of niraparib is 200 mg (two 100 mg capsules) taken once daily. For patients who weigh ≥ 77 kg and have baseline platelet count $\geq 150,000/\mu\text{L}$, the recommended starting dose of niraparib is 300 mg (three 100 mg capsules) taken orally once daily. For olaparib, the recommended dose is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.

^b This is calculated by the weighted PI recommended dose based on the patient numbers weight/platelet high patient numbers in the PRIMA trial (183 out of 728 patients were on 300 mg ISD dosing).

*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

6.70 The PSQR presented a revised base case CMA accounting for 97% compliance for olaparib which resulted in a revised CMA price of \$█ for niraparib in the BRCam cohort. Overall, the ESC considered that the basis for the revised base case CMA of niraparib appeared reasonable and after accounting for reduced compliance for olaparib, the assumptions applied in the CMA calculations were appropriate.

Proposed weighted effective price of niraparib

6.71 The resubmission proposed a different effective price of niraparib for the non-BRCam and BRCam populations, based on the CUA and CMA respectively. The resubmission stated that the price of niraparib for the BRCam population was based on the published price of olaparib, and following a PBAC recommendation, the sponsor expects to be made aware of the appropriate deed of agreement for olaparib to re-specify the cost-minimised price for niraparib. The weighted price of niraparib is presented below.

Table 19: Proposed weighted effective EMP for niraparib presented in the resubmission

Population	Prevalence	Proposed EMP by BRCA status (for maximum quantity)		Proposed weighted effective EMP	
		84-capsule pack	56-capsule pack	84-capsule pack	56-capsule pack
non-BRCAM	71.1%	\$	\$	\$	\$
BRCAM	28.9%	\$	\$		

Source: Table 13, p40 of the submission

EMP = ex-manufacturer price.

- 6.72 The proposed weighted effective price in the resubmission of \$ (100 mg x 56 capsules) was the same as the revised price proposed in the PSCR following the evaluation of the previous submission. This is compared with the price of \$ proposed in the initial submission considered in July in 2021 by the PBAC.
- 6.73 The weighted effective price of niraparib depends on the relative proportion of scripts for patients with BRCAM and non-BRCAM. The resubmission assumed relative proportions of non-BRCAM (71.1%) and BRCAM (28.9%) populations based on the prevalence of germline and somatic BRCA pathological variants (22.6% and 6.3%, respectively) Alsop 2012 CGARN 2011. Of note, the BRCAM prevalence previously considered as reasonable by the PBAC was 25.3% (Paragraph 6.46, Olaparib PSD, July 2020 PBAC meeting). The relative proportions of non-BRCAM and BRCAM patients who use niraparib are likely to differ from the distribution of non-BRCAM and BRCAM patients in the target population, since all eligible non-BRCAM patients may elect to receive niraparib (compared to no active treatment or bevacizumab), but BRCAM patients may choose either niraparib or olaparib. Therefore, the proportion of patients treated with niraparib who have BRCAM will most likely be lower than 28.9%, and the weighted ex-manufacturer price would therefore be lower than that presented in Table 19.
- 6.74 The PSCR noted that weighting should be based on the estimated proportion of drug utilisation for each indication. This is impacted by mean treatment duration which is estimated to be longer for patients with BRCAM (25 months) compared with non-BRCAM (11.9 months). The PSCR provided a revised weighted price calculated based on relative use of niraparib in BRCAM and non-BRCAM patients as projected in the financial estimates. These estimates assumed a prevalence of 25.3% for BRCAM, resulting in a distribution of niraparib utilisation in the BRCAM/non-BRCAM cohort of 22.9%/77.1% over the six-year estimates. From Year 3 onwards, niraparib utilisation is expected to stabilise at a 25% (BRCAM)/75%(non-BRCAM) distribution. Incorporating the revised effective prices applicable to the BRCAM cohort (\$, see paragraph 6.70) and non-BRCAM (\$, see paragraph 6.60) to the re-specified weighting based on utilisation resulted in a weighted AEMP of \$/56 capsules. The pre-PBAC response revised the peak uptake for niraparib to 30%, which resulted in utilisation in the BRCAM/non-BRCAM population of 19.3%/80.7% (respectively) and a weighted AEMP of \$ per 56 capsules.
- 6.75 The ESC considered that uptake in the BRCAM patient population may be as low as 10% of BRCAM patients as very few patients are expected to be treated with niraparib

over olaparib, given the stronger clinical evidence, potentially superior safety and greater clinician experience with olaparib. Assuming a prevalence of 25.3% and an uptake rate of 10% in BRCAM patients vs. 100% of non-BRCAM patients over the first 6 years of listing results in:

- 3.8% of BRCAM patients receiving niraparib; and
- 8.1% of niraparib scripts which will be prescribed to BRCAM patients (due to the longer treatment duration in this subgroup).

6.76 The ESC noted that assuming 10% uptake in patients with BRCAM and 100% uptake in patients with non-BRCAM would result in an AEMP of \$| per 56 capsule pack (based on the published olaparib price), compared with \$| as proposed by the submission. The pre-PBAC response argued that assuming a 10% market share for the BRCAM cohort significantly underestimates utilisation in clinical practice based on: the extent of local experience due to the access program, patient-specific considerations such as once per day dosing and drug interactions, |.

Niraparib cost/patient/course

6.77 As above, the cost of niraparib is based on the requested weighted effective price derived in the CUA (for non-BRCAM NDA HGEOC) and CMA (for BRCAM NDA HGEOC). The estimated cost/patient/course of niraparib for patients with non-BRCAM and BRCAM across the sections of the resubmission are summarised in Table 20 and Table 21, respectively, with revised costs based on the proposed prices in the PSCR also shown.

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Table 20: Drug cost per patient for niraparib - non-BRCaM NDA HGEOC (requested effective DPMQ)*

	Niraparib		
	Trial dose and duration	Model	Financial estimates
Mean dose in Cycle 1	PRIMA ITT cohort dosing ^a 203.7 mg/day	PRIMA ISD cohort dosing ^b 183.8 mg/day	PRIMA ISD cohort dosing ^b 183.8 mg/day
Mean duration	10.89 month ^c	12.4 months ^d	11.9 months ^e
Cost/patient/course	\$ ^f	\$ ^f	\$ ^g
Cost/patient/course (PSCR revised price)	\$ ^f	\$ ^f	\$ ^g

Source: Compiled during evaluation based on Table 26, p60 and Table 65, p134 of the submission and spreadsheet 'Trace-Niraparib of using the Excel workbook "Zejula (niraparib) 1L BRCaM CMA' and "Zejula (niraparib) 1L BIM_Nov21'

BRCaM = BRCA gene mutation; 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

*Requested effective DPMQ for niraparib (non-BRCaM NDA HGEOC): 84 caps = \$[REDACTED]; 56 caps = \$[REDACTED]

^a Initial dose intensity for ITT cohort was 204 mg/day, decreasing to 160-170 mg/day from Cycle 4 onwards. Note that the mean dose of treatment stated in Table 20 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

^b Initial dose intensity for ISD cohort was 184 mg/day, decreasing to 150-158 mg/day from Cycle 4 onwards. Note that the mean dose of treatment stated in Table 20 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

^c The cost is calculated for the truncated mean treatment exposure for niraparib arm (10.89 months) in the model using Step 1 and ITT cohort for the dosing schedule of the Excel workbook "Zejula (niraparib) 1L BRCaM CMA'. The mean duration of treatment in the niraparib arm in the PRIMA overall safety population is 10.3 months (Table 26, p60 of the submission).

^d Undiscounted mean duration without half-cycle correction. The undiscounted mean duration with half-cycle correction is 11.9 months.

^e The duration used in the financial analysis was the undiscounted mean duration with half-cycle correction from the economic evaluation.

^f This figure is undiscounted and without half-cycle correction, using the niraparib price for non-BRCaM.

^g The financial analysis used the weighted price for niraparib.

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Table 21: Drug cost per patient for niraparib and olaparib - BRCaM NDA HGEOC (requested effective DPMQ* for niraparib, and published DPMQ of olaparib)

	Niraparib			Olaparib		
	Trial dose and duration	CMA	Financial estimates	Trial dose and duration	CMA	Financial estimates
Mean dose	PRIMA ITT cohort dosing ^a 174.7 mg/day	PRIMA ISD cohort dosing ^b 162.1 mg/day	PRIMA ISD cohort dosing ^b	558.80 mg/day ^c	600mg/day, 500mg/day or 400mg/day ^d	Not estimated ^d
Mean duration	Not reported	25 months	25 months	20.65 months ^c	20.9 months ^e	20.9 months ^e
Cost/patient/course	–	\$ ^f	\$ ^f	\$149,210 ^g	\$158,382.07 ^h	\$151.017 ^g
Cost/patient/course (PSCR revised price)		\$ ⁱ	\$ ⁱ			

Source: Compiled during evaluation based on Table 26, p60 and Table 108, p172 of the submission and Excel workbook "ZeJula (niraparib) 1L BIM_Nov21"

BRCaM = BRCA gene mutation; CMA = cost-minimisation analysis, DPMQ = dispensed price for maximum quantity; ISD = individualised starting dose; ITT = intention-to-treat

* Requested effective DPMQ for niraparib (BRCaM NDA HGEOC): 84 caps = \$^g; 56 caps = \$^h

^a Initial dose intensity for ITT cohort was 204 mg/day, decreasing to 160-170 mg/day from Cycle 4 onwards. Note that the mean dose of treatment stated in Table 21 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

^b Initial dose intensity for ISD cohort was 184 mg/day, decreasing to 150-158 mg/day from Cycle 4 onwards. Note that the mean dose of treatment stated in Table 21 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

^c In SOLO-1 trial, a mean dose intensity of 558.80 mg/day for a mean treatment duration of 20.65 months was reported for olaparib (Paragraph 6.40, Olaparib PSD, July 2020 PBAC meeting).

^d Olaparib has a flat pricing irrespective of daily dose.

^e The resubmission used the 20.9 months in the CMA based on the average duration of treatment per patient in the first six years of listing olaparib in the 1L setting based on SOLO-1 trial (Table 13, olaparib PSD, July 2020 PBAC meeting).

^f The financial analysis used the weighted price for niraparib.

^g Taking into treatment interruptions, which were estimated to account for 1 month out of a total of 21.5 months of treatment (paragraph 6.48, olaparib PSD, July 2020 PBAC meeting)

^h Based on a constant olaparib daily cost of \$248.97 (= \$6,971.22 / 28) for a treatment duration of 20.9 months.

ⁱ This is calculated by multiplying the proposed DPMQ price for mg in BRCaM cohort (\$^g = \$^h/5600 mg) by the total mg per course (123,310 mg).

Estimated PBS usage & financial implications

6.78 This submission was not considered by DUSC.

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

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Table 22: Key inputs for the updated financial estimates in the resubmission

Data	Value and source	Comment
Eligible population		
Incidence of ovarian, fallopian tube or peritoneal cancer	1,629 in Year 1, increasing to 1,759 in Year 6 AIHW incidence data (2021); NZ MoH data	Data source unchanged from previous submission. Updated AIHW data were used. The NZ MoH data which was used to determine the proportion of ICD-10 Code C48 ^a cases that are peritoneal cancers was of small sample size.
% with epithelial disease	83.7% AIHW 2010	Revised as per previous PBAC consideration
% with high-grade carcinoma	93.6% Analysis of patients in the AOCS (Alsop 2012)	Unchanged from previous submission. Reasonable data sources.
% 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% Morgan 2021	Unchanged from previous submission. Reasonable estimate
% with BRCAm (germline and/or somatic)	gBRCAm: 22.6% sBRCAm: 6.3% Total: 28.9% Alsop 2012; CGARN 2011	Unchanged from previous submission. The prevalence of BRCAm used in the resubmission was higher than the estimate previously accepted by the PBAC (25.3%). Using a lower prevalence would increase the net costs to the PBS/RPBS.
% discontinuing olaparib as 1L therapy due to AEs	11.5% SOLO-1 trial	Unchanged from previous submission. Reasonable.
Treatment utilisation		
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: 27.4% in Years 1-6 SMM: 72.6% in Years 1-6 Resubmission's assumptions, 2018 DUSC report on bevacizumab, PBS utilisation data on bevacizumab (2018-2020), assumptions in previous olaparib submissions	The uptake of treatments in BRCAm patients was unchanged. The proportion of non-BRCAm patients receiving bevacizumab was revised based on the updated PBS statistics on relevant bevacizumab items in 2018-2020, before the change of bevacizumab PBS listing (unrestricted). There is a lack of data on bevacizumab use in the proposed population in current clinical practice. However, a sensitivity analysis performed during the evaluation indicated that a change in this variable would not have a big impact on the net PBS/RPBS costs
Uptake of various first-line maintenance therapies with listing of niraparib	<u>BRCAm patients:</u> Niraparib: 15% in Year 1 to 36% in Years 3-6 Bevacizumab: 15% in Year 1 to 5% in Years 3-6 Olaparib: 60% in Year 1 to 54% 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: 25% in Year 1 to 15% in Years 3-6	In comparison with the previous submission, a lower substitution rate of niraparib for olaparib in BRCAm patients was assumed as per advice from previous review. For non-BRCAm patients, the proportion of patients receiving niraparib remained unchanged; but the extent of use of bevacizumab was adjusted on the basis of the PBS data on bevacizumab in 2018-2020.

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Data	Value and source	Comment
	SMM: 25% in Year 1 to 10% in Years 3-6 Resubmission's assumptions	
Uptake of niraparib in patients discontinuing olaparib due to AEs	20% Resubmission's assumption	This estimate has been reduced from 80% to 20%, as the PBAC previously considered that this group of patients would be "very small" (Paragraph 7.16, Niraparib PSD, July 2021 PBAC meeting).
Average treatment duration of niraparib in subsequent treatment years (years)	<u>BRCaM patients:</u> 0.86 in 1 st year of treatment, 0.68 in 2 nd year, 0.46 in 3 rd year, 0.05 in 4 th year, 0.03 in 5 th year, 0.0 in 6 th year <u>Non-BRCaM patients:</u> 0.65 in 1 st year of treatment, 0.23 in 2 nd year, 0.10 in 3 rd year, 0.02 in 4 th year, 0.0 in 5 th and 6 th years CMA, modelled TTD used in the CUA, based on the PRIMA trial data in the non-BRCaM subgroup.	Unlike the previous submission, the treatment duration for niraparib in non-BRCaM and BRCaM cohorts was estimated separately. The non-BRCaM subgroup of PRIMA included patients who initiated niraparib at a FSD. The treatment duration in these patients might not represent the treatment duration of niraparib, at its proposed ISD regimen.
No. of niraparib packs per patient in each treatment year	84-capsule pack: 0.99 in the 1 st year of treatment, 0.30 in each subsequent year 56-capsule pack: 8.79 in the 1 st year of treatment, 9.37 in each subsequent year Dose intensity and compliance data from PRIMA, ISD cohort*	Unchanged from previous submission. Appropriate.
Treatment duration of bevacizumab maintenance therapy	12.93 doses 2018 DUSC report on bevacizumab	Unchanged from previous submission. The PBS restriction for bevacizumab as in the 2018 DUSC report ^b was not in line with the proposed listing of niraparib. Therefore, the DUSC data might not reflect the treatment duration of bevacizumab in the requested target population.
No. of first-line olaparib scripts in each treatment year	10.7 in the 1 st year, 8.5 in 2 nd year, 1.5 in 3 rd year, 0.6 in 4 th year, 0.4 in 5 th year, 0 in 6 th year July 2020 olaparib submission, based on TTD curve for olaparib in SOLO-1	The treatment duration of olaparib was revised to account for treatment interruption and for the difference in days of treatment covered per olaparib script (28 days) and the days in each month (30.4 days), as per advice from the previous review.
MBS costs CBC GP consultation IV administration	Schedule fee: \$16.95 (MBS item: 65070) \$39.10 (MBS item: 23) \$112.40 (MBS item: 13950)	Updated MBS costs

Source: Table 112, p177 and Section 4.1, pp177-187 of the resubmission; "Zejula (niraparib) 1L BIM_Nov21" Excel workbook
1L = first-line; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; CBC = complete blood count; CGARN = Cancer Genome Atlas Research Network; CMA = cost-minimisation analysis; CR = complete response; CUA = cost-utilisation analysis; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub-Committee; FIGO = International Federation of Gynecology and Obstetrics; FSD = fixed starting dose; gBRCAm = germline BRCA gene mutation; GP = general practitioner; ICD-10 = International Classification of Disease 10th revision; ISD = individualised starting dose; 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

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= somatic BRCA gene mutation; SMM = standard medical management; TTD = time to treatment discontinuation

^a ICD-10 Code C48 refers to malignant neoplasm of retroperitoneum and peritoneum

Note: Blue shading indicates data previously seen by the PBAC.

^b The bevacizumab restriction was suboptimally debulked Stage IIIB/IIIC or Stage IV ovarian, regardless of grade and treatment response to 1L PBC, at the time of the 2018 DUSC report.

*Note that the dose intensity and compliance data from PRIMA used to derive the number of niraparib packs stated in Table 22 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

6.80 Overall, the epidemiological approach taken by the resubmission to estimate the financial impacts of the proposed listing of niraparib was largely consistent with the previous submission. The following amendments were made as per advice from the previous evaluation (Table 13 and Paragraph 7.16, Niraparib PSD, July 2021 meeting):

- The proportion of ovarian cancers with epithelial histology was adjusted by removing tumours with unspecified histology from the estimate.
- The extent of substitution of olaparib with niraparib in BRCAm patients was reduced (from a peak of 50% PARPi use to 40%).
- A lower uptake of niraparib among patients discontinuing olaparib due to intolerance was assumed.
- The niraparib script use per year of treatment was estimated separately for non-BRCAm patients (aligned with CUA vs. SMM) and BRCAm patients (based on CMA vs. olaparib).
- Olaparib script use per year of treatment has been revised to account for treatment interruption and pack size.

6.81 The ESC considered that the changes to the financial estimates applied in the resubmission appeared reasonable, however the extent of substitution of olaparib with niraparib remains higher than is expected (see also paragraph 6.75) which also impacts on the weighted price for niraparib.

6.82 The estimated use and financial implications of listing niraparib as first-line maintenance therapy for NDA HGEOC are summarised below. Revised financial estimates as presented in the PSCR are also shown in the table below. The revised estimates applied the revised PSCR effective price (AEMP: 56 capsules = \$1; 84 capsules = \$1) and reduced the prevalence of BRCAm to 25.3%. The financial estimates were revised again in the pre-PBAC response, as shown below, based on a revised weighting between populations as described paragraph 6.74.

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Table 23: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated ^a	1	2	2	2	2	2
Number of scripts dispensed ^b	2	2	5	5	5	5
Estimated financial implications of niraparib						
Cost to PBS/RPBS less copayments (\$)	3	3	6	6	6	6
Estimated financial implications for other medicines						
Olaparib (\$)	4	4	3	3	3	3
Bevacizumab (\$)	4	4	4	4	4	4
Net financial implications						
Net cost to PBS/RPBS (\$)	4	4	3	3	3	3
Net cost to MBS (\$)	4	4	4	4	4	4
Net cost to PBS/RPBS/MBS (\$)	4	4	3	3	3	3
Net financial implications – revised PSCR						
New listing (\$)	4	3	6	6	6	6
Changed listing (\$)	4	4	3	3	3	3
Net cost to PBS/RPBS (\$)	4	4	4	3	3	3
Net financial implications – revised pre-PBAC response						
New listing (\$)	4	3	6	6	6	6
Changed listing (\$)	4	4	3	3	3	3
Net cost to PBS/RPBS	4	4	3	3	3	3
Previous submission July 2021						
Net cost to PBS/RPBS (\$)	4	4	3	3	3	3

Source: Table 134, p194, Table 141, p200, Table 145, pp201-202, Table 157, p208, Table 158, p209, Table 170, p214 of the resubmission.

Note: Blue shading indicates data previously seen by the PBAC.

^a Only including patients who initiate niraparib therapy in each listing year.

^b The average treatment duration in subsequent treatment years was estimated separately for non-BRCa patients (based on modelled time to treatment discontinuation in the cost-utility analysis) and for BRCa patients (based on the assumed treatment duration in the cost-minimisation analysis). 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.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$10 million to < \$20 million

⁴ \$0 to < \$10 million

⁵ 5,000 to < 10,000

⁶ \$20 million to < \$30 million

6.83 The total cost to the PBS/RPBS of listing niraparib was estimated to be \$10 million to < \$20 million per year in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing, revised to \$50 million to < \$60 million in the PSCR and \$50 million to < \$60 million in the pre-PBAC response.

6.84 The main areas of uncertainty in the financial analysis are:

- The prevalence of BRCa. Revised from 28.9 to 25.3% in line with the value previously accepted by the PBAC. BRCa prevalence varied across clinical studies. There is a lack of recent, large-scale, Australian studies of the relevant ovarian cancer population for a reliable estimation of BRCa prevalence in the

proposed NDA HGEOC patients in the current Australian setting. A high estimate of the BRCaM prevalence would favour niraparib, as it would result in greater cost offsets (associated with increased substitution of olaparib with niraparib) in the BRCaM cohort and lower incremental costs (due to the decreased substitution of no active treatment with niraparib) in the non-BRCaM cohort. The application of 25.3% in the financial analysis would increase the net PBS/RPBS cost by 16% over the first 6 years of listing.

- The uptake of niraparib. Although the extent of use of olaparib in BRCaM patients and in patients discontinuing olaparib due to AEs has been revised as per advice in the previous evaluation, the uptake of various first-line maintenance therapies with and without the availability of the niraparib was mainly based on the resubmission's assumptions. Sensitivity analyses indicated the changes in these uptake variables would moderately affect the financial implications to the PBS/RPBS associated with the proposed PBS listing of niraparib. The ESC considered that the uptake estimates remained uncertain and appeared substantially overestimated in the BRCaM population. The ESC also considered that uptake in the non-BRCA population was uncertain as it may be somewhat dependent on HRD testing (where available). The ESC considered that uncertainty was further increased by the lack of clinical consensus on the use of PARPi in patients without evidence of HRD.

- 6.85 The PBAC noted that the financial impact from listing of niraparib in the BRCaM population would be expected to be cost-neutral overall, with a small reduction in the cost to the PBS/RPBS due to cost offsets from AEs and monitoring included in the CMA. The PBAC noted that financial estimates would need to be revised to reflect the population recommended for listing.

Quality Use of Medicines

- 6.86 The resubmission outlined a number of activities to promote the safe and effective use of niraparib in clinical practice, including additional pharmacovigilance activities outlined in the regulatory dossier, a niraparib patient access program, webinars, collaborative medical education, advisory boards, and health care provider and patient brochures.

Financial Management – Risk Sharing Arrangements

- 6.87 The resubmission indicated that the sponsor recognised that a Risk Sharing Arrangement (RSA) would be required for the PBS listing of niraparib.

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

7 PBAC Outcome

- 7.1 The PBAC recommended niraparib for the treatment of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients with BRCA1/2 pathogenic gene variants, who are in response (complete response or partial response) to 1L platinum-based chemotherapy. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of niraparib would be acceptable if it were cost-minimised to olaparib. The PBAC did not recommend niraparib for patients without evidence of a BRCA1/2 pathogenic gene variant. The PBAC considered that in this population the PFS benefit from treatment with niraparib was relatively small (3.5 months) and may not result in an overall survival benefit. The PBAC considered that for a number of patients in this population there may be no clinical benefit from treatment with niraparib, with added toxicity compared to no active treatment. The PBAC considered that the cost-effectiveness of niraparib was uncertain because the economic model relied on gains in overall survival that were not supported by the immature trial data.
- 7.2 The PBAC noted that consumer comments reflected a clinical need for effective alternatives to chemotherapy and bevacizumab for the patients without a confirmed BRCA1/2 pathological variant, noting that no PARP inhibitors are PBS listed for this population. Consumers noted that patients with ovarian cancer value improved PFS and QoL and felt that access to PBS subsidised treatment would reduce the fear of progression and reduce the financial burden for patients who were funding treatment with PARP inhibitors outside the PBS.
- 7.3 The PBAC considered that the clinical place for PARP inhibitors in patients without BRCAm remained somewhat uncertain and is likely to become clearer as additional survival data becomes available. 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 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 but considered that the appropriate clinical place for PARP inhibitors may move toward a more targeted population identified through biomarkers such as HRD testing. The PBAC considered that this would help to identify patients most likely to benefit from treatment.
- 7.4 The PBAC considered that for the BRCAm population the restriction for niraparib should allow up to 3 years of treatment for patients with a complete response, in line with the circumstances of use in the PRIMA trial. The restriction should otherwise be aligned with the current first listings for olaparib in terms of: PBS indication, authority level, ECOG status and other clinical criteria. In addition, the PBAC considered it would be appropriate to include a treatment criterion to enable patients who have

developed intolerance to olaparib of a severity necessitating permanent treatment withdrawal to receive PBS-subsidised niraparib and a flow-on to the olaparib listing that would allow patients with intolerance to niraparib to switch to olaparib. The PBAC also noted that flow on changes to the first and second line olaparib listings would be required to prevent sequential subsidy of olaparib after disease progression following treatment with niraparib.

- 7.5 The PBAC previously noted that for patients with BRCAm, 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 (paragraph 7.4, niraparib PSD, July 2021 PBAC meeting). The PBAC noted that this was appropriately addressed in the resubmission which presented economic models that included olaparib as the comparator for patients with BRCAm and SMM as the comparator for patients without BRCAm and a qualitative comparison with bevacizumab.
- 7.6 The PBAC noted that in the resubmission, the clinical evidence for niraparib in non-BRCAm patients was based on the subgroup analysis of non-BRCAm patients in the PRIMA trial (niraparib vs. no active treatment (placebo)). In BRCAm patients the clinical evidence was based on an indirect treatment comparison of the BRCAm subgroup from the niraparib trial (PRIMA, niraparib vs. placebo) with one olaparib trial (SOLO-1, olaparib vs. placebo) with placebo as the common reference. The resubmission noted that patients with Stage III R0 PDS were excluded from PRIMA, while these patients were included in SOLO-1 and therefore presented an indirect comparison using data from the subgroup of SOLO-1 excluding Stage III R0 post PDS. The PBAC noted that there were some concerns around the assumption of transitivity in this indirect comparison, including differences in the proportion with stage IV disease.
- 7.7 The PBAC noted that there was a statistically significant improvement in PFS associated with niraparib versus no active treatment in non-BRCAm patients from PRIMA (HR for PFS: 0.69 [0.54, 0.88]). However, the PBAC considered that the clinical importance of a PFS gain of 3.5 months was uncertain and this gain may not translate to overall survival benefit. The PBAC noted that overall survival data was immature and although there was a trend toward overall survival benefit, it remained uncertain whether a survival benefit would be realised, especially given the small additional PFS benefit. The PBAC noted the PFS benefit was greater for patients with non-BRCAm HRD positive tumours (HR= 0.50, 95% CI: 0.31, 0.83; medians: 19.6 months versus 8.2 months) compared to patients in the HRD negative subgroup (HR= 0.68, 95% CI: 0.49, 0.94; medians: 8.1 months versus 5.4 months). The PBAC considered that in the non-BRCAm population there may be patients who do not receive any clinically meaningful benefit from treatment with niraparib.
- 7.8 The PBAC noted that in the indirect comparison, in patients with BRCAm, the HR numerically favoured olaparib over niraparib for both for the full SOLO-1 trial population (PFS per BICR: 1.43 [0.83, 2.45]) and excluding Stage III R0 post PDS

patients from the SOLO-1 trial (PFS per BICR: 1.25 [0.71, 2.21])¹⁵, though the results of the comparisons were not statistically significant and the confidence intervals were wide reflecting the relatively small sample sizes for the comparison between a subgroup of the PRIMA trial (BRCam) and in the SOLO-1 trial (excluding Stage III R0 post PDS). The PBAC considered that there were likely transitivity issues with the indirect comparison due the differences in trial populations between PRIMA and SOLO-1, some of which remained even after exclusion of Stage III R0 post PDS patients from SOLO-1. However, the PBAC accepted that based on the available evidence, and noting that niraparib has a similar mechanism of action to olaparib, that the efficacy of niraparib is overall likely to be similar to that for olaparib and therefore considered, on balance, that the claim that niraparib is non-inferior to olaparib in terms of efficacy was sufficiently supported.

- 7.9 The PBAC noted that for non-BRCam patients in the PRIMA trial the incidence of TEAEs, $\geq$ Grade 3 TEAEs, serious TEAEs, and TEAEs leading to drug interruption, dose reduction and drug withdrawal were statistically significantly higher in patients receiving niraparib than in the placebo arm and considered the claim of inferior safety was supported. The PBAC noted that for BRCam patients the submission made a claim of comparable safety for niraparib (ISD) in comparison with olaparib, based on an indirect comparison between the PRIMA and SOLO-1 trials. The PBAC noted that there appeared to be significantly worse safety for niraparib compared with olaparib with regard to Grade 3-5 TEAEs including differences in the incidence of thrombocytopenia and anaemia. However, the PBAC noted that treatment discontinuations due to TEAEs were similar between PRIMA (ISD): 13.6% and SOLO-1: 11.5%. The PBAC noted that the indirect comparison of safety was limited due to differences in the patient populations and duration of follow-up. On balance, the PBAC considered that TEAEs for niraparib appeared to be generally manageable with dose interruptions and likely to be sufficiently similar for niraparib and olaparib, and that reduced likelihood of drug interactions compared to olaparib may improve its safety profile. The PBAC noted that hospitalisation costs for thrombocytopenia and anaemia were included in the CMA (see paragraphs 6.34 and 6.65).
- 7.10 The PBAC noted that the resubmission addressed its previous concerns regarding the approach to comparators for the economic evaluation (paragraph 7.17, niraparib PSD, July 2021 PBAC meeting) by presenting two economic evaluations: a cost-utility analysis comparing niraparib with SMM for the maintenance treatment of non-BRCam NDA HGEOC; and a cost-minimisation analysis comparing niraparib with olaparib for the maintenance treatment of BRCam NDA HGEOC. The PBAC noted that the resubmission did not present separate analyses for the HRD-negative, HRD-positive and HRD not determined populations, which would have required a co-dependent

¹⁵ Note that the indirect comparisons of niraparib vs. olaparib in the BRCam population were performed 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.

submission. The PBAC also noted that the economic evaluation did not include bevacizumab as a comparator but considered that this appeared reasonable as few HGEOC patients (BRCAm or non-BRCAm) are currently treated with bevacizumab as maintenance therapy.

- 7.11 The PBAC noted that for the non-BRCA population the structure of the economic evaluation was similar to that for the original submission. The PBAC noted that the time horizon was reduced to 15 years and subsequent PARPi use in the second line setting in the SMM arm removed, in line with the PBAC's previous advice (paragraph 7.15, niraparib PSD, July 2021 PBAC meeting). In addition, the extrapolation methods were updated by applying independent parametric functions for the extrapolations of PFS, OS and TTD, and costs for treatments, monitoring and AEs were updated. The PBAC noted that the economic evaluations that were presented were inherently uncertain because the OS data from PRIMA were immature and that 97% of the incremental benefit occurred in the extrapolated modelling. The PBAC considered that the ICER was uncertain as it relied on gains in overall survival that were not supported by the immature trial data.
- 7.12 The PBAC noted that the cost-minimisation analysis with olaparib in the BRCAm population presented in the resubmission assumed the same average treatment duration per year for niraparib as previously considered by PBAC for olaparib, except for Year 3, which was estimated to be 5.4 months, higher than treatment duration with olaparib in Year 3 (1.4 months) due to the stopping rule at 36 months for patients who are in complete response with niraparib compared with 24 months for olaparib. The PBAC noted that trial-based treatment durations are unlikely to be comparable due to the difference in follow-up between the PRIMA and SOLO-1 trials (approximately 15 months and 41 months, respectively). The PBAC considered that the resubmission's approach to the treatment durations appeared reasonable. The PBAC also noted that in addition to the costs of niraparib and olaparib, the resubmission included in the CMA the costs of managing and monitoring AEs. The PBAC considered this was appropriate. The PBAC noted that the PSCR presented a revised base case CMA accounting for 97% compliance for olaparib which the PBAC considered was reasonable.
- 7.13 The PBAC recommended niraparib for use in the BRCAm population on a cost-minimisation basis to olaparib, with cost offsets for hospitalisations due to thrombocytopenia and anaemia and monitoring of CBC and BP. The equi-effective doses were estimated as niraparib 162.1 mg/day for 25 months and a fixed daily cost of any olaparib daily dose (600 mg/day, 500 mg/day or 400 mg/day) for 20.9 months at 97% compliance (see paragraph 6.70).
- 7.14 The PBAC noted that the resubmission calculated a weighted price based on the estimated proportion of drug utilisation for each indication (BRCAm and non-BRCAm), however as the PBAC recommended listing of niraparib in the BRCAm population only, calculation of the weighted price is not required.

- 7.15 The PBAC noted that the financial impact from listing niraparib in the BRCAM population was expected to be cost-neutral overall, with a small reduction in the cost to the PBS/RPBS due to inclusion of AE and monitoring costs in the CMA. The PBAC noted that financial estimates would need to be revised to reflect the population recommended for listing.
- 7.16 The resubmission indicated that the sponsor recognised that an RSA would be required for the PBS listing of niraparib. The PBAC considered it would be appropriate for niraparib to join the existing arrangements for olaparib. The PBAC considered that no increase to the caps was justified as the listing of niraparib for the BRCAM population is not expected to grow the market.
- 7.17 The PBAC considered that any resubmission for the non-BRCAM population should be supported with additional overall survival data to support a clinically meaningful benefit. The PBAC considered that it may be reasonable for a resubmission to include a more targeted population to identify patients most likely to benefit from treatment, noting that this is likely to require a codependent submission.
- 7.18 The PBAC recommended that niraparib should not be treated as interchangeable with any other drugs.
- 7.19 The PBAC advised that niraparib is not suitable for prescribing by nurse practitioners.
- 7.20 The PBAC recommended that the Early Supply Rule should apply.
- 7.21 The PBAC noted the flow-on restriction changes as described in paragraph 7.4.
- 7.22 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because niraparib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over olaparib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.23 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new medicinal product as follows:

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
Restriction Summary [NEW 1]					

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Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
	Episodicity: [blank] Severity: High grade stage III/IV Condition: epithelial ovarian, fallopian tube, or primary peritoneal cancer
26510	Indication: High grade stage III/IV epithelial ovarian, fallopian tube, or primary peritoneal cancer
	Treatment Phase: Initial treatment – first line treatment
26522	Clinical criteria:
26521	The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation
25620	Clinical criteria:
26519	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.
	AND
7890	Clinical criteria:
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
14393	Clinical criteria:
14392	Patient must not have previously received PBS-subsidised treatment with this drug for this condition.
	Treatment criteria:
New TC1	Patient must be undergoing treatment with this drug class for the first time; or
New TC2	Patient must be undergoing treatment with this drug class on a subsequent occasion, but only because there was an intolerance/contraindication to another drug in the same class that required permanent treatment withdrawal
20142	Prescribing Instructions: A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.
26232	Prescribing Instructions: Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline or somatic mutation testing.
25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
New AA1	Administrative Advice: This drug belongs to the poly ADP ribose polymerase (PARP) inhibitor drug class. The restriction refers to the following PARP inhibitors: olaparib, niraparib
7608	Administrative Advice: Special Pricing Arrangements apply

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	5	Zejula
Restriction Summary [NEW 2]					
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒ Medical Practitioners				

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(for internal Dept. use)	Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
26510	Indication: High grade stage III/IV epithelial ovarian, fallopian tube, or primary peritoneal cancer
	Treatment Phase: Continuing treatment – first line treatment
26516	Clinical criteria:
26515	Patient must have previously received PBS-subsidised treatment with this drug as first line maintenance therapy for this condition
	AND
7890	Clinical criteria:
7889	The treatment must be the sole PBS-subsidised therapy for this condition,
	AND
21513	Clinical criteria:
21512	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	AND
	Clinical criteria:
NEW CC1	The treatment must not exceed a total of 36 months of combined non-PBS-subsidised/PBS-subsidised treatment for patients who are in complete response
25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
7608	Administrative Advice: Special Pricing Arrangements apply

8.2 Flow-on changes to first line olaparib initial listings (item numbers 12157W (150 mg tablet) and 12170M (100 mg tablet)) add new Treatment criteria and a NOTE to the existing text as follows:

	Treatment criteria:
New TC1	Patient must be undergoing treatment with this drug class for the first time; or
New TC2	Patient must be undergoing treatment with this drug class on a subsequent occasion, but only because there was an intolerance/contraindication to another drug in the same class that required permanent treatment withdrawal
Insert New AA1	Administrative Advice: This drug belongs to the poly ADP ribose polymerase (PARP) inhibitor drug class. The restriction refers to the following PARP inhibitors: olaparib, niraparib

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

9 Context for Decision

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

in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

GSK welcomes the recommendation of niraparib for the treatment of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients with BRCA1/2 pathogenic gene variants, who are in response (complete response or partial response) to 1L platinum-based chemotherapy. GSK thanks the organisations and many individuals who provided their experience and support for the submission for women regardless of their genetic status. Your contributions are a key part of the PBAC process.