

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

1 Purpose of submission

- 1.1 The submission requested a Section 85 (General schedule), Authority required (telephone application for initiation and streamlined approval for the continuation) listing for niraparib for the treatment of platinum-sensitive relapsed (PSR), high grade serous ovarian, fallopian tube or primary peritoneal cancer (HGSOC), who are in response to platinum-based chemotherapy. This is the first submission of niraparib for this indication.
- 1.2 Listing was requested based on a cost-utility analysis of niraparib versus standard medical management in patients without BRCA1/2 pathogenic variants (referred to as BRCA wild type, or non-BRCAm) and cost-minimisation analysis of niraparib versus olaparib in patients with BRCA1/2 pathogenic variants (BRCAm).
- 1.3 The key components of the clinical issue addressed by the submission are presented below.

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

Component	Description	
Population	Platinum-sensitive relapsed HGSOC, who are in response (complete or partial) to platinum-based chemotherapy.	
Intervention	Niraparib (poly ADP ribose polymerase inhibitor)	
Comparator	BRCAm: Olaparib tablet; Non-BRCAm: standard medical management	
Outcomes	PFS, OS, TFST, Safety	
Clinical claim	Efficacy	BRCAm: Niraparib is non-inferior in terms of effectiveness for PFS in comparison to olaparib Non-BRCAm: Niraparib is superior in terms of effectiveness for PFS in comparison to no active treatment
	Safety	Niraparib has a manageable safety profile for the treatment of platinum-sensitive, relapsed HGSOC

Source: Table 2 of the submission, p20

BRCAm = BRCA1/2 pathogenic and likely pathogenic gene variants; HGSOC = high grade serous ovarian, fallopian tube, or primary peritoneal cancer; OS = overall survival; PFS = progression free survival; TFST = time to first subsequent treatment

2 Background

Registration status

- 2.1 Niraparib is TGA registered as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

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- 2.2 The sponsor has applied to the TGA for registration of niraparib in the first-line (1L) maintenance setting for patients with platinum-sensitive HGSOC. The application is still under consideration.
- 2.3 The current TGA approved starting dose of niraparib is 300mg daily. The submission indicated that the sponsor has submitted to the TGA the following amendment:
- For patients who weigh less than 77 kg or have a baseline platelet count <150,000/ μ L; the recommended starting dose of niraparib is 200 mg taken orally once daily. For all other patients, the recommended starting dose is 300 mg.
- 2.4 Both the FDA and EMA have approved niraparib in the first-line maintenance setting and have recommended a starting dose of 200 mg (depending on weight and platelets) as per the protocol change in PRIMA, but neither have changed the dosing instructions in the second-line maintenance setting (i.e., the starting dose in the second-line setting remains 300 mg). In the Pre-Sub-Committee Response (PSCR), the sponsor confirmed their request for the TGA to consider ISD for maintenance treatment using an exploratory analysis of the NOVA trial (2L+ setting) and evidence from PRIMA (1L setting). The PSCR noted that the delegate’s overview for this evaluation is not expected until 6th July 2021). The ESC considered the efficacy and safety of niraparib using the ISD has not been sufficiently established in the relevant population for this submission.

3 Requested listing

Name, restriction, manner of administration, form	Maximum amount (units)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Niraparib 100 mg (as tosilate monohydrate), Capsules	1	84	2 (initial)	\$12,673.34(published);	Zejula, GlaxoSmithKline Australia Pty Ltd
			5 (continuing)	\$██████ (effective)	
	1	56	2 (initial)	\$8507.88 (published);	
			5 (continuing)	\$██████ (effective)	

Category/Program:	General Schedule
Prescriber type	Medical practitioner
Condition:	High grade serous ovarian, fallopian tube, or primary peritoneal cancer
PBS Indication:	High grade serous ovarian, fallopian tube, or primary peritoneal cancer
Treatment phase:	Initial treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required – telephone/online
Clinical criteria:	The condition must be platinum-sensitive. AND Patient must have received at least two previous platinum-containing regimens, AND Patient must have relapsed following a previous platinum-containing regimen,

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Category/Program:	General Schedule
<p>AND Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen, AND The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition, AND The treatment must be maintenance therapy, AND Patients who have progressive disease on PBS subsidised olaparib as maintenance therapy are not eligible to receive PBS subsidised niraparib for this condition</p>	
<p>Prescriber instructions: Patients who have developed intolerance to olaparib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised niraparib Platinum sensitivity is defined as disease progression greater than 6 months after completion of the penultimate platinum regimen. A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer Inter Group (GCIg) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.</p>	
<p>Administrative advice: Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Special Pricing Arrangements apply.</p>	

Category/Program:	General schedule
Prescriber type:	Medical practitioner
Condition:	High grade serous ovarian, fallopian tube, or primary peritoneal cancer
PBS Indication:	High grade serous ovarian, fallopian tube, or primary peritoneal cancer
Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Streamlined
<p>Clinical criteria: Patient must have previously perceived PBS-subsidised treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised PARP inhibitor therapy for this condition AND The treatment must be maintenance therapy AND Patient must not have developed disease progression while receiving treatment with this drug for this condition</p>	

- 3.1 The proposed listing provides two pack sizes to permit 28 days' supply for either a 200mg or 300mg dose.
- 3.2 The proposed effective price was derived from a weighting across the BRCAm (28.9%) and non-BRCAm (71.1%) populations. The submission requested a special pricing arrangement (SPA) with a ■■■% reduction in the published price. The sponsor acknowledged that the cost minimisation analyses in the BRCAm population are contingent on the effective price of olaparib, to which a confidential SPA is currently applicable. The sponsor noted re-specification of the weighted effective price for niraparib would be required following a positive recommendation and disclosure of

the effective price for olaparib. The impact of the recent listing of olaparib in the 1L setting for patients with platinum-sensitive HGSOc on the suggested weighted price is discussed below (see paragraph 6.44).

- 3.3 The PBAC considered that treatment with poly ADP ribose polymerase (PARP) inhibitors should be limited to one course per lifetime and noted American Society of Clinical Oncology (ASCO) PARP inhibitor (PARPi) guidelines recommend against using more than one PARP inhibitor given the lack of evidence.
- 3.4 The sponsor requested the option of treatment switching from olaparib to niraparib for patients who develop olaparib intolerance necessitating permanent treatment withdrawal. The PBAC considered there is likely to be little impetus for treatment switching between PARP inhibitors in practice, particularly from olaparib to niraparib, given that olaparib may have a better safety profile.
- 3.5 The requested restriction did not limit the use of niraparib to patients with a performance status of 0-1 on the Eastern Cooperative Oncology Group (ECOG) scale. The NOVA trial included only patients with a performance status of 0-1, and no clinical data are available regarding the use of niraparib in patients with poorer performance status (TGA niraparib PI, p3). As niraparib efficacy and toxicity are unknown in patients with poor performance status, the commentary suggested restricting the use of niraparib among patients with a performance status of 0-1 on the ECOG scale. The PSCR argued that the olaparib listings are not limited to patients with ECOG 0-1 despite the pivotal evidence for olaparib being limited to patients with ECOG 0-1. The ESC considered that it would be preferable to not limit the listing based on ECOG performance status as clinicians would be best placed to determine whether a patient's level of functioning is likely to be adequate for treatment with niraparib to be beneficial and appropriate.

4 Population and disease

- 4.1 HGSOc is the most common and aggressive histological subtype of ovarian cancer (OC). Most patients (>75%) are diagnosed at an advanced stage (stage III and IV), with a limited long-term survival (7-year survival: serous subtype: 28%, Stage III/IV: 9-15%; High grade: 30-38%).
- 4.2 Although initial treatment with cytoreductive surgery and platinum-based chemotherapy usually leads to initial response, 70% of patients usually relapse within the first three years. Post-progression treatment is usually associated with reduced efficacy and prolonged exposure to chemotherapeutic agents (mainly platinum-based chemotherapy) is associated with long term toxicities and attenuation in quality of life. In July 2020 the PBAC recommended listing of olaparib as maintenance treatment after an initial response to platinum-based chemotherapy in the 1L setting for patients with a BRCA1/2 pathogenic variant. In the PSCR the sponsor noted that a submission to PBAC for listing of niraparib in the 1L setting is planned, for consideration at the July 2021 PBAC meeting. As such the treatment algorithm in ovarian cancer is evolving.

The PBAC considered that the preferred place for PARP inhibitors is in 1L maintenance treatment, and therefore the submission was of limited relevance, particularly for the BRCAm population where olaparib is currently available on the PBS as 1L maintenance.

- 4.3 In Australia, olaparib is the only drug PBS listed for maintenance treatment after an initial response in the 2L setting for patients with a BRCA pathogenic variant (although the TGA indication in 2L is not restricted to patients with BRCA pathogenic variants). Patients who receive olaparib as 1L maintenance would not be eligible for retreatment in the 2L setting. Patients with BRCA1/2 pathogenic variants represent less than 30% of all ovarian cancer patients. For the remaining 70% of ovarian cancer patients (BRCA wild type), there is no standard maintenance treatment, with follow-up (standard medical management) as the standard of care for patients who achieve a response to 2L treatment.
- 4.4 Niraparib is a selective PARPi which has shown clinical benefit when used as a maintenance treatment for patients with platinum-sensitive relapsed HGSOc who have achieved a partial (PR) or complete response (CR) to platinum-based chemotherapy in the 2L setting.

5 Comparator

- 5.1 As the proposed patient population was all patients with relapsed HGSOc, irrespective of their BRCA status, the submission nominated two comparators: olaparib for patients with BRCAm; and standard medical management (SMM) (follow-up or no active treatment), as the standard of care for patients with BRCA wild type (non-BRCAm).
- 5.2 **For patients with BRCAm**, the submission nominated olaparib as the comparator on the basis that it is PBS listed for this patient population (recommended November 2016 and expanded to include patients with both somatic BRCAm (sBRCAm) and germline BRCAm (gBRCAm) in March 2020). The nomination of olaparib as a comparator to niraparib in patients with BRCAm (irrespective of having somatic or germline mutation) was appropriate. However, the relevance of the BRCAm population to the submission was limited because of the recent listing of olaparib for the treatment of patients with BRCAm in the 1L setting. The proportion of patients who would not receive 1L maintenance with olaparib and fall into this group is uncertain, and likely to be small and decreasing.
- 5.3 **For patients with BRCA wild type (non-BRCAm)**, the submission provided the following evidence to support SMM (follow-up or no active treatment) as a comparator:
- Currently, there are no PBS listed therapies for maintenance treatment for this patient population;
 - Although bevacizumab is TGA registered for the treatment of recurrent, platinum-sensitive OC, the submission did not consider it as a comparator, given

the cost-effectiveness of this indication has not been considered by the PBAC, with the PBS listing restricting its utilisation to the 1L setting.

The ESC considered that the nominated comparator for patients with BRCA wild type was appropriate.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (14), and organisations (4) via the Consumer Comments facility on the PBS website. The comments noted that patients with ovarian cancer without a BRCA pathogenic variant are not currently able to access PARP inhibitors, nor any kind of immunotherapy. The comments reported that patients often require neoadjuvant chemotherapy before a biopsy can be performed and this can prevent the confirmation of the presence of BRCA pathogenic variants, which is required for access to treatment with PARP inhibitors. One patient reported self-funding additional pathology tests following an initial “unknown” BRCA outcome (as no viable tumour tissue was harvested during biopsy) with a view to accessing PBS funded olaparib if BRCA status could be shown to be positive. Individuals reported that self-funding PARP inhibitors was not possible for most patients due to their high cost. Individuals considered that maintenance with niraparib may increase survival and extend time until progression for patients without BRCA pathogenic variants. Patients also noted the impact on quality of life of chemotherapy which can be poorly tolerated.
- 6.3 The PBAC noted the advice received from the Ovarian Cancer Research Foundation (OCRF), Ovarian Cancer Australia (OCA) and Rare Cancers Australia (RCA) in support of the niraparib submission. The comments from these organisations focussed on the impact of ovarian cancer on patients’ mental health and quality of life and the hope of new treatments that prevent or delay relapse and extend survival. RCA and OCA reported that issues impacting patients with ovarian cancer included: the burden of indignity, impacts on fertility, the fear of recurrence, and the impact on families. In addition, patients felt there was a lack of equity of access, with PARP inhibitors PBS currently subsidised only for patients with BRCA pathogenic variants. OCRF also noted the lack of effective screening strategies to detect ovarian cancer in its earlier stages.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the niraparib submission. 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.

Clinical trials

6.5 The submission was based on two randomised placebo-controlled trials:

- **NOVA trial:** A phase III, multicentre, double-blind, randomised, placebo-controlled trial (N= 553), comparing niraparib to placebo in patients with PSR, HGSOc who received at least two prior lines of platinum-based therapies and have developed CR or PR to the last platinum-based therapy;
 - There were two patient cohorts in the NOVA trial: patients with germline BRCAm (gBRCAm), and patients without evidence of these germline variants (non-gBRCAm). Randomisation was conducted separately for each cohort. Germline BRCAm was identified using Myriad Integrated BRCA analysis.
 - The non-gBRCAm cohort is comprised of 3 groups of patients: tumours with homologous recombination deficiency (HRD) (HRDpos), HRD negative (HRDneg), and a group whose tumour HRD status could not be determined (HRDnd). HRD status (including somatic BRCAm) was identified using the myChoice HRD test.
 - Within the HRDpos group there are women with somatic BRCAm and those with HRDpos tumours due to non-BRCA related defects in the homologous recombination pathway (HRDpos/BRCAwt).
- **SOLO-2 trial:** A phase III, multicentre, double-blind, randomised, placebo-controlled trial (N=295), comparing olaparib tablets to placebo in patients with gBRCAm and PSR, HGSOc who received at least two prior lines of platinum-based therapies and have developed CR or PR to the last platinum-based therapy.

6.6 The evidence presented in the submission was based on:

- A direct comparison of niraparib versus placebo (NOVA trial) in patients with non-gBRCAm;
- A one-step indirect comparison between niraparib (NOVA trial) versus olaparib (SOLO-2 trial) in patients with gBRCAm (with placebo as a common comparator).

6.7 The clinical claim for patients with BRCAm was based on evidence from the cohort in the NOVA trial with gBRCAm. The clinical claim for the non-BRCAm group was based on patients in the NOVA trial without gBRCAm, which included 47 patients (~13%) who had a somatic BRCA1/2 pathogenic or likely pathogenic variant (sBRCAm). As patients with germline or somatic BRCAm had a better response to treatment than patients in the non-gBRCAm cohort, inclusion of sBRCAm patients in this group is likely to

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

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overestimate the clinical benefit for the true non-BRCAM group. See also paragraph 6.23-6.24.

6.8 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NOVA	PR-30-5011-C: A phase 3, randomised, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer.	24th September 2016
	PR-30-5011-C: Quality of life analysis in platinum-sensitive ovarian cancer: a phase 3 clinical study analysis – patient reported outcomes report.	27 September 2016
	Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer.	New England Journal of Medicine. 2016; 375(22):2154-64.
	Mirza MR, Dørum A, Benigno B, Mahner S, Bessette P, Bover Barcelo IM, et al. Long-term safety assessment of niraparib in patients with recurrent ovarian cancer: Results from the ENGOT-OV16/NOVA trial.	International Journal of Gynecological Cancer. 2019;29:A15-A6.
SOLO-2	Pujade-Lauraine E, Ledermann JA, Selle F, GebSKI V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO-2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial.	The Lancet Oncology. 2017;18(9):1274-84.
	Poveda A, Floquet A, Ledermann JA, Asher R, Penson T, Oza A et al. Final overall survival (OS) results from SOLO-2/ENGOT-ov21: A phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation.	J Clin Oncol 38: 2020 (suppl; abstr 6002). doi: 10.1200/JCO.2020.38.15_suppl.6002

Source: Table 19 of the submission, p41

6.9 The key features of the pivotal evidence are presented in the below table.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
For patients with non-BRCAm						
NOVA	553	MC, DB, R, PC, Phase III; 15.7 months	Low	Recurrent platinum-sensitive HGSOC who received ≥ 2 lines of platinum-based therapies and have developed CR or PR to the last platinum-based therapy	PFS, OS, TFST, PFS2, TSST, safety	Used
For patients with BRCAm						
NOVA	553	MC, DB, R, PC, Phase III; 15.7 months	Low	Recurrent platinum-sensitive HGSOC who received ≥ 2 lines of platinum-based therapies and have developed CR or PR to the last platinum-based therapy	PFS, OS, TFST, PFS2, TSST, safety	Used
SOLO-2	295	MC, DB, R, PC, Phase III; 22 months	Low	patients with gBRCAm and recurrent platinum-sensitive HGSOC who received ≥ 2 lines of platinum-based therapies and have developed CR or PR to the last platinum-based therapy	PFS, OS, TFST, PFS2, TSST, safety	Used

Source: Section 2.3 and 2.4 of the submission

CR = complete response; DB= double blind; gBRCAm = germline BRCA1/2 pathogenic and likely pathogenic gene variants; HGSOC = high grade serous ovarian, fallopian tube, or primary peritoneal cancer; MC= multicentre; OS= overall survival; PFS = progression free survival; PFS2= second progression free survival; PR = partial response; PC= placebo controlled; R= randomised, TFST= time to first subsequent treatment; TSST= time to second subsequent treatment

Comparative effectiveness

- 6.10 The submission included results of the NOVA trial at the first data cut-off (DCO) (May 2016). The PSCR provided an update on the NOVA trial which reported that data collection and analysis have been impacted by COVID-19, mainly due to considerable premature study discontinuation and the absence of research staff at participating institutions. The pre-PBAC response provided updated efficacy results for NOVA with a data cut-off of 1/10/2020. In the overall population 28% of patients (155/553) discontinued for reasons other than death and survival status could not be retrieved for 49% (76/155) of these patients. The pre-PBAC response noted that interpretation of the results for overall survival was challenging due to the high rate of subsequent PARP inhibitor use and missing data.
- 6.11 The indirect comparison between NOVA and SOLO-2 trials was conducted based on the SOLO-2 trial results at the first DCO (September 2016). Updated OS data of the SOLO-2 trial were presented but not included in the indirect comparison.
- 6.12 **Regarding the non-BRCAm cohort**, the comparative effectiveness was based on the direct comparison between the niraparib arm and the placebo arm in the NOVA trial (Intention to treat (ITT) analysis = 350 in the non-gBRCAm cohort). The primary outcome (PFS) was based on the blinded independent central review (BICR)

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assessment. Compared to placebo, niraparib resulted in 5.4 months increase in median PFS (HR= 0.45 (0.34, 0.61)). Sensitivity analyses (for PFS), according to per investigator assessment (INV), were consistent with the primary analyses.

- 6.13 At the time of first DCO (May 2016), the median OS was not reached, and there was no statistically significant difference in OS between the niraparib arm and the placebo arm (Table 4). The PBAC noted that at the final data cut (October 2020) a higher proportion of patients had died in the niraparib arm than the placebo arm and the unadjusted OS HR numerically favoured placebo, though there was no statistically significant difference. The pre-PBAC response noted that although cross-over to a PARPi was not permitted within the NOVA trial, receipt could occur following disease progression or withdrawal from the trial and subsequent use of PARPi was extensive in the placebo arm of the gBRCAm cohort (reported as 46% in the text but only 13% as reported in Table 2 of the attachment to the pre-PBAC response). The HR adjusted for post-progression PARPi use in the control group also did not show a difference from placebo: HR=0.97 (0.74, 1.26).

Table 4: PFS and OS results in the non-gBRCAm group, NOVA trial (ITT)

	Niraparib 234/350 (66.9%)	Placebo 116/350 (33.1%)	Absolute difference	HR (95% CI)
Progression-free survival (according to BICR)				
Patients with event	125/234 (53.4%)	88/116 (75.9%)	22.5%	-
Median PFS months (95% CI)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	5.4 months	0.45 (0.338, 0.607)
PFS at [^] (95 % CI)	6 months	0.61 (0.54, 0.68)	0.25	-
	12 months	0.41 (0.33, 0.48)	0.27	-
	18 months	0.30 (0.23, 0.38)	0.18	-
	24 months	0.27 (0.19, 0.35)	0.15	-
Overall survival				
Patients with event	44/234 (18.8%)	27/116 (23.3%)	4.5%	-
Patients with event (final DCO)	160/234 (68.4%)	78/116 (67.2%)	-1.2%	
Median OS months (95% CI)	NR	NR	NA	0.74 (0.452, 1.200)
Median OS months (95% CI) final DCO*	31.1 (27.8, 37.3)	36.5 (27.9, 41.6)	-5.4 months	1.10 (0.831, 1.459)
OS at [^] (95 % CI)	6 months	0.99 (0.96, 1.00)	0.03	-
	12 months	0.93 (0.89, 0.96)	0.03	-
	18 months	0.81 (0.74, 0.86)	0.06	-
	24 months	0.71 (0.61, 0.78)	0.09	-

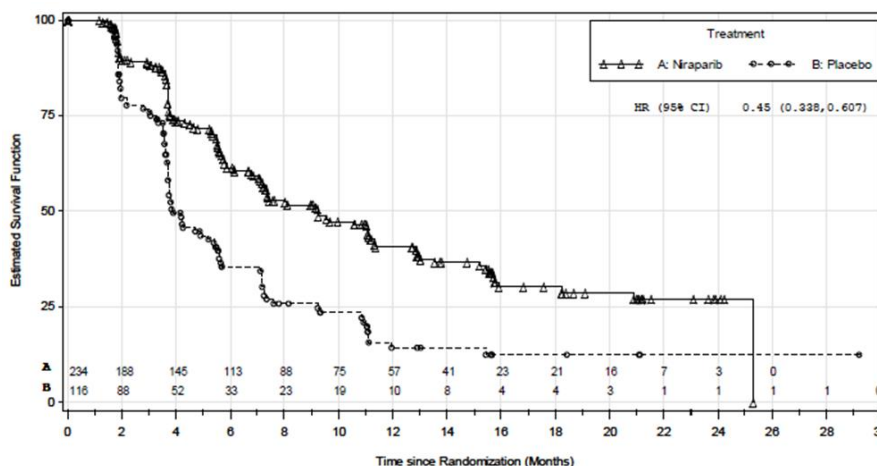
Source: Table 44 of the submission, p71 and table 45 of the submission, p74

BICR = blinded independent central review; CI = confidence interval; gBRCAm = germline BRCA1/2 pathogenic and likely pathogenic gene variants; HR = hazard ratio; INV = investigator; ITT = intent to treat; NA= not applicable; NR= not reported; OS= overall survival; PFS= progression free survival

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

* Unadjusted for subsequent use of PARP inhibitors in the placebo group

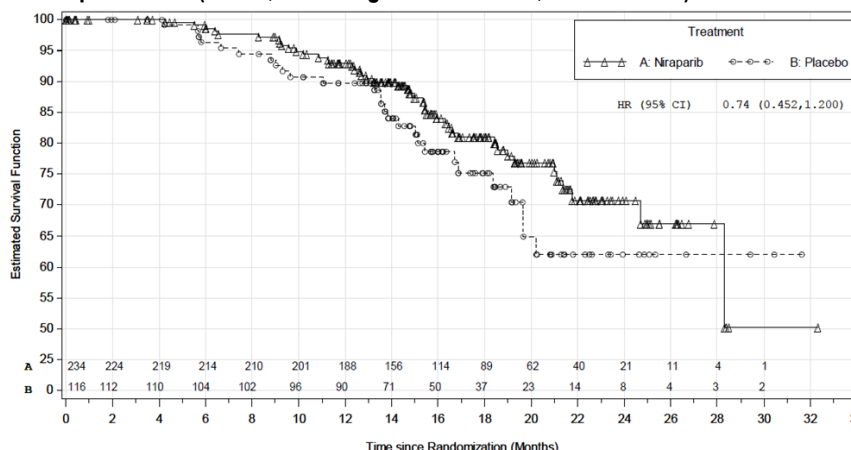
Figure 1: Kaplan-Meier plot for PFS per BICR assessment – primary analyses (NOVA, ITT non-gBRCAm cohort, DCO: 30/5/16)



Source: Figure 9 of the submission, p72

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

Figure 2: Kaplan-Meier plot for OS (NOVA, ITT non-gBRCAm cohort, DCO: 30/5/16)



Source: Figure 12 of the submission, p74

ITT= intention to treat; OS= overall survival; DCO= data cut-off

- 6.14 Regarding the secondary outcomes, there was an improvement in time to first subsequent treatment (TFST: 4.6 months, HR= 0.55 (0.41, 0.72)) and second PFS (3 months, HR = 0.69 (0.49, 0.96)) in the niraparib arm compared to the placebo arm.
- 6.15 Throughout the maintenance treatment period (cycles 2, 4 and 6) and at post-progression, no significant differences were observed in the quality of life assessment using the Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O) Symptom Index (FOSI) score LS mean changes from baseline as well as the EQ-5D-5L.
- 6.16 **Regarding the BRCAm cohort**, the clinical efficacy of niraparib was based on a one-step indirect comparison between niraparib (NOVA trial) and olaparib (SOLO-2 trial) at the time of first DCO (May 2016 and September 2016, respectively). In both trials there was a statistically significant PFS benefit in favour of the active arms (compared to

their placebo), with a similar median PFS in the placebo arms in both the NOVA trial and SOLO-2 trial (5.5 months). No statistically significant difference in PFS was observed in the indirect comparison between niraparib versus olaparib, but non-inferiority was not established given the upper limit of the CI was 1.86 (Table 5).

- 6.17 In both trials the median OS was not reached at the time of first DCO. Indirect comparison of the OS data at the first DCO in both trials revealed no statistically significant difference between niraparib and olaparib, but non-inferiority was not established given the upper limit of the CI was 3.22 (Table 5) .
- 6.18 The pre-PBAC response noted that comparison of baseline characteristics of the trials indicated that the NOVA trial population was of worse prognosis compared to SOLO-2, in terms of poorer performance status and greater exposure to chemotherapy.
- 6.19 The updated OS results of SOLO-2 (final DCO, February 2020, after a median of 65 months of follow-up) showed borderline significant OS benefit with the use of olaparib compared to placebo (HR= 0.74, 95%CI: 0.54, 1.00). After adjusting for the treatment switching from the placebo arm to a subsequent PARPi (38%) using a Rank Preserving Structure Failure Time Model (RPSFT), there was a reduction in the median survival in the SOLO-2 placebo arm from 38.8 months to 35.4 months resulting in an OS hazard ratio of 0.56 (95%CI: 0.35, 0.97). The PBAC noted that, in contrast, the final DCO of NOVA did not demonstrate a statistically significant difference for the unadjusted OS HR (0.93, 95%CI: 0.633, 1.355) and after adjusting for subsequent treatment with PARPi (46%) the estimate of the HR for OS was 0.66 (95%CI: 0.44, 0.99). The PBAC noted that the adjusted OS HR and the methodology applied (inverse probability of censoring weighted methodology) had not been independently evaluated as it was provided with the pre-PBAC response.

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Table 5: Results of PFS and OS in the NOVA and SOLO-2 trials with indirect comparison among patients with gBRCAm

	NOVA trial (ITT, N= 203)	SOLO-2 trial (ITT, N= 295)	Absolute difference	ITC – NIRA vs OLA: HR (95% CI)
	Niraparib 138/203 (68%)	Olaparib 196/295 (66.4%)		
Progression-free survival (according to BICR)				
DCO, median follow-up months	30/5/16; 16.4*	19/9/16; 22	-	-
Patients with event	59 (42.8%)	81 (41.3%)	1.5%	-
Median PFS months (95% CI)	21.0 (12.9, NE)	30.2 (19.8, NE)	9.2 months	-
HR (95%CI) compared to placebo	0.27 (0.173, 0.410)	0.25 (0.18, 0.35)	-	1.080 (0.626, 1.862)
Overall survival				
Patients with event	16 (11.6%)	45 (23.0%)	11.4%	-
Median OS months (95% CI)	NR	NR	NA	-
HR (95%CI) compared to placebo	0.91 (0.360, 2.282)	0.80 (0.50, 1.31)	-	1.1375 (0.401, 3.223)**
HR (95%CI) final DCO	0.93 (0.633, 1.355)	0.74 (0.54, 1.00)		

Source: Table 48, p77 and Table 49, p79 of the submission

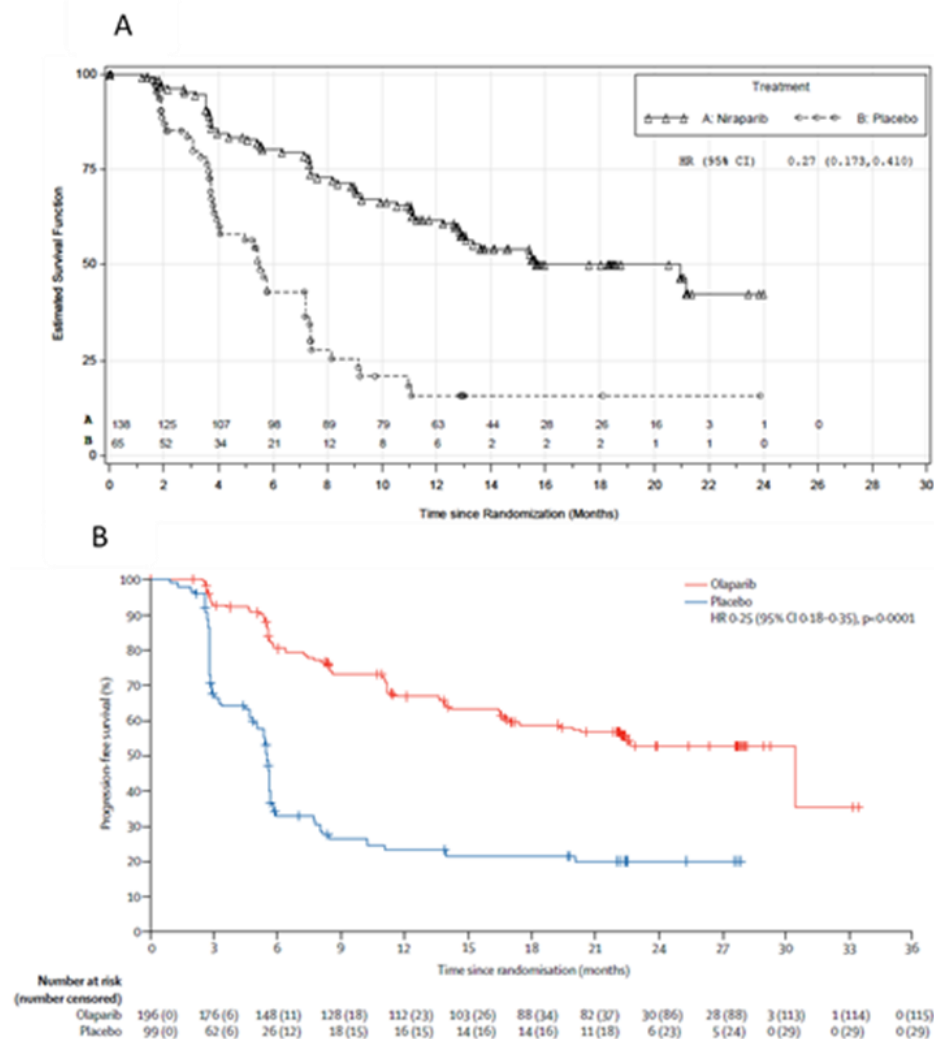
BICR = blinded independent central review; CI = confidence interval; DCO = data cut off; FAS = full analysis set; gBRCAm = germline BRCA1/2 pathogenic and likely pathogenic gene variants; HR = hazard ratio; ITT = intent to treat; ITC = indirect treatment comparison, NA= not applicable; NR= not reported; OS= overall survival; PFS= progression free survival

*Overall median duration of follow up is 15.7 months if calculated as the date of randomisation to date of death, or last contact date for patients still alive (NOVA CSR, p276, Table 14.1.1.2)

**Calculated during the evaluation using the same statistical method (Bucher et al., 1979), on R software.^a

^aNote that the results (denoted by **) are derived from post-hoc analyses conducted during 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

Figure 3: PFS based on BCIR assessment in (A) NOVA trial and (B) SOLO-2 trial in gBRCAm patient population



Source: Figure 14 and Figure 15 of the submission, p78

BICR = blinded independent central review; gBRCAm = germline BRCA1/2 pathogenic and likely pathogenic gene variants, PFS= progression free survival

6.20 Regarding the secondary outcomes: an improvement in TFST, PFS2 and time to second subsequent treatment (TSST) was observed in both the NOVA and SOLO-2 trials. Overall the magnitude of benefit from niraparib and olaparib was similar. No statistically significant difference was observed from the indirect comparison for the secondary outcomes.

6.21 Regarding the quality of life assessment, no significant difference was observed in mean changes from baseline in FOSI score (NOVA trial) or Trial Outcome Index (TOI) score (SOLO-2 trial) for niraparib and olaparib versus placebo, respectively. Of note, in the NOVA trial, patients had a relatively high baseline score for quality of life assessment, and thus the effect of niraparib on patients with low baseline quality of life score (or performance status) remains unknown.

- 6.22 The submission claimed that the indirect comparison between niraparib and olaparib had confirmed non-inferiority in terms of PFS. This claim was based on a suggested non-inferiority margin (HR= 1.125 (95%CI: 0.58, 2.18)) driven from the indirect comparison of the effect of different PARPi on PFS among patients with gBRCAm versus sBRCAm (para 6.12 olaparib Public Summary Document (PSD), March 2020 PBAC meeting). However, the PBAC considered that the basis of the proposed non-inferiority margin was problematic and the value proposed (1.72) appeared to be unreasonably high.
- 6.23 The ESC also noted the 9.2 month absolute difference in median PFS between the olaparib arm of the SOLO-1 trial and the niraparib arm of the NOVA trial, while median PFS in the placebo groups was similar (5.5 months in both trials). Noting that this was a naïve comparison, the ESC considered that this was suggestive of a possible difference in PFS between treatments in favour of olaparib, and cast further doubt on the claim of non-inferiority for niraparib. The pre-PBAC response argued that the HR was the appropriate basis for consideration of non-inferiority, that PFS at a given timepoint may be affected by the schedule of assessments for PFS and that the point estimates of PFS lacked robustness, with few patients in either trial at risk at the time of median PFS.
- 6.24 Exploratory subgroup analyses for the HRD positive, HRD negative and sBRCAm subgroups were presented in the submission. The HR for PFS for subgroups (with nominal 95% CIs, not adjusted for multiplicity) were:
- gBRCAm: 0.27 (0.17, 0.41)
 - sBRCAm: 0.27 (0.08, 0.90)
 - HRD-pos, BRCAwt: 0.38 (0.23, 0.63)
 - HRD-neg: 0.58 (0.36, 0.92)
- 6.25 The clinical claim for the non-BRCAm group was based on patients in the NOVA trial without gBRCAm, which included patients (~13%) who had a somatic BRCA1/2 pathogenic or likely pathogenic variant (sBRCAm). As patients with germline or somatic BRCAm had a better response to treatment than patients in the non-gBRCAm cohort, inclusion of sBRCAm patients in this group is likely to overestimate the clinical benefit for the true non-BRCAm group. In the PSCR the Sponsor maintained that the PFS results for the non-gBRCAm cohort in NOVA are applicable to the non-BRCAm population and argued that with limited representation (13%) in the non-gBRCAm cohort, patients with sBRCAm would be unlikely to influence the results substantively in favour of niraparib. The PSCR stated that results for PFS in the HRD positive subgroup of the non-gBRCAm cohort indicated no difference to the HR when including or excluding sBRCAm patients (HR = 0.38 with or without sBRCAm patients). However the ESC noted that their inclusion may still influence the HR for the overall non-BRCAm population, and though the magnitude of impact may be small, the HR for the true non-BRCA population remains unknown.

- 6.26 The submission noted that the evidence for the dosing regimen proposed in the submission was based on:
- Post hoc analysis from the NOVA trial which showed that patients with body weight <77kg or baseline platelet count <150,000/ μ l had higher risk to develop grade 3 or 4 thrombocytopenia compared to patients with body weight >77kg or baseline platelet count >150,000/ μ l (97/280 (35%) versus 10/85 (12%) respectively) and were more likely to require early dose modification, with only 17% of patients remaining on 300 mg by Month 4; and
 - A phase III, multicentre, randomised trial of niraparib versus placebo in the first-line HGSOc setting (PRIMA trial), which included a protocol amendment adopting individualised dosing based on the previously mentioned post-hoc analysis.
- 6.27 In support of the efficacy of the ISD for niraparib used in the economic and financial models, the PSCR stated that results in the NORA trial were comparable to those observed in the NOVA trial (BICR PFS HR=0.22 (95% CI: 0.12, 0.39) for gBRCAm patients and HR=0.40 (95% CI: 0.26, 0.61) for non-gBRCAm).

Comparative harms

- 6.28 A summary of the adverse events in each of the NOVA and SOLO-2 trials is presented in the below table.

Table 6: Summary and comparisons of adverse events in NOVA and SOLO-2 trials

	NOVA (SAF) DCO: 30/5/16				SOLO-2 (SAF) DCO: 19/9/16	
	Non-gBRCAm		gBRCAm		gBRCAm	
	Niraparib	Placebo	Niraparib	Placebo	Olaparib	Placebo
	N=231	N=114	N=136	N=65	N=195	N=99
DCO, median follow-up months	30/5/16; 15.7*		30/5/16; 16.4^		19/9/16; 22***	
Any TEAE	231 (100.0)	110 (96.5)	136 (100.0)	61 (93.8)	192# (98.5)	94 (94.9)
Risk difference (95%CI)**	3.50% (-0.09%, 7.09%)		6.20% (0.31%, 12.00%)		3.51% (-1.14%, 8.16%)	
Relative risk (95%CI)**	1.04 (0.99, 1.07)		1.07 (1.00, 1.13)		1.04 (0.99, 1.09)	
Niraparib versus olaparib risk difference (95%CI)**	-----		1.54% (-0.19%, 3.27%)			
Niraparib versus olaparib relative risk (95%CI)**	-----		1.02 (0.99, 1.03)			
Grade 3-4 TEAE	164 (71.0)	27 (23.7)	108 (79.4)	14 (21.5)	72 (36.9)	18 (18.2)
Risk difference (95%CI)*	47.3% (38%, 57%)		57.9% (45.8%, 70.0%)		18.7% (8.56%, 28.9%)	
Relative risk (95%CI) **	3.0 (2.13, 4.21)		3.69 (2.30, 5.91)		2.03 (1.29, 3.21)	
Niraparib versus olaparib risk difference (95%CI)**	-----		42.5% (32.9%, 52.1%)			
Niraparib versus olaparib relative risk (95%CI) **	-----		2.15 (1.76, 2.63)			
SAEs	68 (29.4)	20 (17.5)	42 (30.9)	7 (10.8)	35 (17.9)	8 (8.1)
Risk difference (95%CI)**	11.9% (2.78%, 21.02%)		20.1% (9.29%, 30.93%)		9.87% (2.26%, 17.5%)	
Relative risk (95%CI) **	1.68 (1.08, 2.62)		2.87 (1.36, 6.03)		2.22 (1.07, 4.61)	
Niraparib versus olaparib risk difference (95%CI)**	-----		12.9% (3.5%, 22.4%)			
Niraparib versus olaparib relative risk (95%CI)**	-----		1.72 (1.16, 2.55)			
TEAEs leading to discontinuation	36 (15.6)	3 (2.6)	18 (13.2)	1 (1.5)	21 (10.8)	2 (2.0)
Risk difference (95%CI)**	13.0% (7.43%, 18.58%)		11.7% (5.26%, 18.13%)		8.75% (3.59%, 13.9%)	
Relative risk (95%CI)**	5.92 (1.86, 18.82)		8.60 (1.17, 63.1)		5.33 (1.28, 22.3)	
Niraparib versus olaparib risk difference (95%CI)**	-----		2.47% (-4.70%, 9.63%)			
Niraparib versus olaparib relative risk (95%CI)**	-----		1.23 (0.68, 2.22)			
TEAEs leading to death (on-treatment)	0	0	0	0	0	0

Source: Table 53 of the submission, p84

DCO = data cut-off; gBRCAm = germline BRCA1/2 pathogenic and likely pathogenic gene variants; NIRA = niraparib; PBO = placebo; SAF = safety population; TEAE = treatment emergent adverse event, SAEs= serious adverse events.

#192 TEAEs as per FDA olaparib assessment Table 37 and EMA olaparib assessment Table 42. Pujade-Lauraine 2017 reports 191 TEAEs

*Calculated as the date of randomisation to date of death, or last contact date for patients still alive (NOVA CSR, p277, Table 14.1.1.2)

^ Kaplan Meier estimate of potential follow-up (reverse Kaplan-Meier), treating death as censors, and censored observations as events (NOVA CSR, p276, Table 14.1.1.2)

*** Median follow-up for progression free survival (Pujade-Lauraine 2017, p 1278)

**Calculated during the evaluation using R software.##

Note that the results denoted by (**) presented in Table 6 are derived from post-hoc analyses conducted during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for NOVA and SOLO-2 trials. 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

6.29 Overall, no on-treatment deaths were reported in either trial. Almost all patients in the intervention and placebo arms experienced at least one treatment-emergent

adverse event (TEAE). In both trials, there were more TEAEs leading to treatment discontinuation in the intervention arm compared to placebo.

- 6.30 **In the non-gBRCAm cohort**, compared to placebo, niraparib was associated with an increased risk of grade 3-4 TEAEs (71% versus 23.7%), increased risk of serious adverse events (SAEs) (29.4% versus 17.5%) and increased risk of treatment discontinuation due to TEAEs (15.6% versus 2.6%).
- 6.31 **In the gBRCAm cohort**, compared to olaparib (from SOLO-2 trial), niraparib was associated with an increased risk of grade 3-4 TEAEs (79.4% versus 36.9%), increased risk of SAEs (30.9% versus 17.9%), and comparable rates of treatment discontinuation due to TEAEs (13.2% versus 10.8%). These higher rates were observed despite the shorter median treatment duration for niraparib (12 months) compared to olaparib (19.4 months).
- 6.32 The PSCR disagreed with the interpretation of safety data in the commentary, arguing:
- circumstances are likely to differ in practice with proactive management of niraparib dosing upon treatment commencement;
 - comparing safety in the gBRCAm cohort was a selective interpretation of the evidence and was inappropriate when no differences in the safety profile for niraparib were observed across the non-gBRCAm and gBRCAm populations and NOVA was not powered for safety outcomes in these subgroups;
 - the indirect comparison for safety was inappropriate considering the significant differences in placebo event rates across the trials (Grade 3/4 TEAEs, SAEs), indicating an inconsistent baseline liability for toxicity in the NOVA and SOLO-2 trial populations; and
 - The pre-PBAC response further argued that the conclusion of inferior safety on the basis of grade 3/4 events disregards clinically significant AEs, (such as SAEs and treatment discontinuations) which were comparable in the intervention arms of NOVA gBRCAm (13.2%) and SOLO-2 (10.8%).
- 6.33 The ESC noted that in the NOVA trial randomisation was conducted separately for each cohort, therefore considering the safety of the gBRCAm cohort separately (as for efficacy) was likely to be appropriate, though noting the limitations of the reduced sample size. The pre-PBAC response argued that there was no evidence to indicate that the safety profile for niraparib would differ in the BRCAm population.
- 6.34 The submission claimed that with the use of the ISD, there would be a reduction in risk of grade 3-4 TEAEs. The ESC considered that this claim was not supported by trial evidence presented in the submission. The PSCR provided safety outcomes from the NORA trial which the sponsor claimed indicated an improvement in the safety profile of niraparib with the incorporation of the ISD, particularly with regards to grade ≥ 3 haematological toxicities (thrombocytopenia: 9.6% anaemia: 13.9%), SAEs (16.3%)

and the limited extent of treatment discontinuations (4.2%). The ESC noted that this trial was only published as an abstract and this data had not been evaluated.

- 6.35 The submission presented updated safety data from the SOLO-2 trial after 65 months of follow up. Rates of grade 3-4 TEAEs from NOVA versus SOLO-2 were (79.4% versus 46.2%), with higher dose interruptions (83.1% versus 49.7%) and higher dose reductions due to TEAEs (81.6% versus 27.7%).
- 6.36 The rate of acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) was not increased in the niraparib treatment arm (compared to placebo in the NOVA trial (1.4% versus 1.1 % respectively)); however, long-term follow-up is recommended taking into consideration the increased rate of AML/MDS observed with olaparib in the SOLO-2 trial (8.2%).

Benefits/harms

- 6.37 **For the non-gBRCAm patient population**, a summary of the benefits and harms of niraparib versus SMM (no active treatment) is presented in Table 7.

Table 7: Summary of comparative benefits and harms for niraparib versus placebo in the non-gBRCAm patient population

Benefits						
Progression-free survival (PFS) (DCO May 2016) according to BICR						
Event	Niraparib	Placebo	Absolute Difference		HR (95% CI)	
Progressed or died, n (%)	125/234 (53.4%)	88/116 (75.9%)	22.5%		0.45 (0.338, 0.607)	
Median PFS (95% CI), months	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	5.4 months			
PFS at 12 months [^] (95 % CI)	0.41 (0.33, 0.48)	0.14 (0.08, 0.22)	27%*			
PFS at 24 months [^] (95 % CI)	0.27 (0.19, 0.35)	0.12 (0.06, 0.21)	15%*			
Overall survival (OS) (DCO May 2016)						
Deaths, n/N (%)	44/234 (18.8%)	27/116 (23.3%)	4.5%		0.74 (0.452, 1.200)	
Median OS (95% CI) months	NR	NR	NA			
OS at 12 months [^] (95 % CI)	0.93 (0.89, 0.96)	0.90 (0.82, 0.94)	3%#			
OS at 24 months [^] (95 % CI)	0.71 (0.61, 0.78)	0.62 (0.48, 0.74)	9%#			
Harms						
	Niraparib n/N	Placebo n/N	Relative risk (95% CI)^{\$}	Event rate/100 patients		Risk difference (95% CI)^{\$}
				Niraparib	Placebo	
TEAEs of grade 3-4	164/231	27/114	3.0 (2.13, 4.21)	71	23.7	47% (38%, 57%)
Serious TEAEs	68/231	20/114	1.68 (1.08, 2.62)	29.4	17.5	11.9% (2.78%, 21.02%)
TEAEs leading to discontinuation of study drug	36/231	3/114	5.92 (1.86, 18.82)	15.6	2.6	13.0% (7.43%, 18.58%)

Source: Table 44 of the submission, p71, table 45 of the submission, p74, and table 53 of the submission, p84

BICR = blinded independent central review; CI = confidence interval; DCO = data cut-off; gBRCAm = germline BRCA1/2 pathogenic and likely pathogenic gene variants; HR = hazard ratio; TEAEs = treatment related adverse events

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

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

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

\$ Relative risk and risk difference were calculated during the evaluation using R software.**

**Note that the results denoted by (*, #, \$) presented in Table 7 are derived from post-hoc analyses conducted by the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for NOVA. 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

6.38 Based on the direct evidence presented in the submission in the non-gBRCAm patient population, for every 100 patients treated with niraparib in comparison to SMM (no active treatment), and followed over a median duration of 15.7 months:

- Approximately 15 more patients would remain progression-free at 24 months;
- Approximately 47 more patients would experience a grade 3-4 treatment-related adverse event;
- Approximately 12 more patients would experience a serious treatment-related adverse event;
- Approximately 13 more patients would experience a treatment-related adverse event that leads to treatment discontinuation.

6.39 **For the gBRCAm patient population**, the NOVA and SOLO-2 trials had different durations of follow-up. No data for PFS or OS at 12 and 24 months were available in the SOLO-2 trial. The difference in safety between the two trials was based on a naïve indirect comparison. Overall, the results presented in the submission did not allow for a quantitative comparison of the benefits and harms of niraparib and olaparib. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.40 The submission described niraparib as:

- Superior in terms of effectiveness for PFS compared with SMM for patients with non-BRCAM (based on a direct comparison between niraparib and placebo for patients with non-gBRCA from the NOVA trial);
- Non-inferior in terms of effectiveness for PFS compared with olaparib in patients with gBRCAm (based on a one-step indirect comparison between niraparib (NOVA) and olaparib (SOLO-2) for patients with gBRCA; and
- Having a manageable safety profile in both patient populations.

6.41 The evidence of effectiveness and safety in the NOVA trial and the results of the indirect comparison are uncertain as:

- The proposed individualised dosage was tested in a different patient population and a different setting and is not consistent with the Australian PI and it is unclear whether efficacy is maintained when the 200 mg individualised starting dose is used in this setting.
- No mature OS data were presented in this submission and even based on the updated OS data provided in the pre-PBAC response it remains unknown if the observed PFS improvement will be translated into an OS benefit. In the SOLO-2 trial, the strongly significant PFS observed was translated to a marginal OS benefit;
- For the BRCAM population the suitability of the nominated non-inferiority margin is questionable; and
- For the non-BRCAM population the PFS and OS benefit would be reduced if patients with sBRCAM are excluded as patients with sBRCAM had a better response to treatment than the overall non-gBRCA group.

6.42 For the BRCAM population the PBAC considered that the claim of non-inferior comparative effectiveness to olaparib was not adequately supported by the data. For the non-BRCA population the PBAC considered that the claim of superior comparative effectiveness to placebo was reasonable based on PFS benefit, however the magnitude of benefit was small and of uncertain clinical relevance, particularly for patients with HRD negative tumours.

6.43 The PBAC considered that the claim of manageable safety in both populations was not adequately supported by the data. The PBAC noted that niraparib had higher rates of

grade 3-4 adverse events (compared to either SMM or olaparib). The PBAC considered that the safety of niraparib, using a starting dose of niraparib of 300 mg daily as in the NOVA trial, appeared inferior to olaparib based on the available data. The PBAC considered that the comparative safety for niraparib was inferior to SMM.

Economic analysis

- 6.44 The submission presented two economic evaluations:
- A modelled economic evaluation cost-utility analysis (CUA) comparing niraparib with SMM for the maintenance treatment of non-BRCAM PSR HGSO; and
 - A cost-minimisation analysis (CMA) comparing niraparib with olaparib for the maintenance treatment of BRCAM PSR HGSO.
- 6.45 The proposed price of niraparib was based on a weighted price for the CUA and CMA populations, where the proposed cost in the non-BRCAM setting was less than [REDACTED] of the cost proposed in the BRCAM setting (\$ [REDACTED] versus \$12,673.34 DPMQ per 84 capsule pack). Therefore, the price of niraparib depends on accurately predicting the extent to which niraparib will replace olaparib and the relative proportions of patients, in the 2L maintenance setting, who are BRCAM and non-BRCAM. With the recent listing of olaparib as maintenance treatment in the first-line setting, it is likely that the proportion of patients treated with niraparib who have BRCAM PSR HGSO would be considerably lower than the estimate used in the submission (based on the prevalence of BRCA1/2 pathogenic variants). The pre-PBAC response acknowledged that the 1L listing of olaparib will result in a reduction in the estimated cost-offsets in the financial estimates and estimated a 64% reduction in the eligible 2L BRCAM population, while also noting the extent of impact resulting from the 1L listing is uncertain and further changes to the treatment landscape are likely.
- 6.46 In both the modelled economic analysis of niraparib compared with SMM in the non-BRCAM population and the cost-minimisation of niraparib compared with olaparib in the BRCAM population was based on the individualised starting dose regimen. Therefore, the submission presented a translation study, whereby the niraparib exposure in NOVA was adjusted to account for the difference between the fixed starting dose and the proposed individualised starting dose, based on the dosing data for the individualised starting dose cohort in PRIMA.

Table 8: Translation of fixed starting dose in NOVA to individualised starting dose

	PRIMA fixed dosing	PRIMA individualised dosing	Dose intensity reduction, %	NOVA fixed dosing	Estimated individualised dosing^a
Daily dose intensity – over total treatment duration, mg/day ^b					
Mean (SD)	181.4	162.1	10.6%	180.7	161.5

Source: Table 125, p164 of the submission.

SD = standard deviation.

^a NOVA fixed dosing multiplied by one minus the dose intensity reduction from PRIMA.

^b Dose intensity was calculated as sum of the daily doses actually consumed divided by total treatment duration. Treatment duration was defined as the period from first to last dose, including days when no doses were received by the patient.*

* Note that the mean dose of treatment stated in Table 8 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.

- 6.47 The PBAC noted that there were a number of concerns regarding the methodology used to translate the niraparib dosing and estimation of the extent of dose interruptions. In addition, patient characteristics in the 1L setting are likely to be different to those in the 2L maintenance setting and dose distributions from PRIMA were based on a small sample size.
- 6.48 The ESC considered that in the absence of TGA approval to the change in dosing and given the uncertainty regarding the impact on safety and efficacy, it was not appropriate to base the economic evaluations, in either population, on the ISD. Further, if TGA approval does follow, an economic evaluation using trial effectiveness and adjusted dosing is likely to over-estimate the cost-effectiveness of niraparib. Sensitivity analyses using the dosing applied in NOVA are shown in Table 14 (CUA) and Table 15 (CMA). The pre-PBAC response argued that it was appropriate that the base case economic analysis reflects the sponsor’s intentions regarding the TGA approved dosing and that with the improved safety profile it is not unreasonable to expect an overall net improvement in patient outcomes.

Cost-effectiveness analysis - non-BRCAM PSR HGSOC population

6.49 The submission presented a stepped economic evaluation based on a direct randomised trial comparing niraparib and SMM in the non-BRCAM PSR HGSOC population (NOVA). The type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation are presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Population	non-BRCAM platinum-sensitive, relapsed HGSOC
Treatments	Niraparib vs SMM
Time horizon	10 years in the model base case versus mean follow-up of 15.8 months in the trial.
Outcomes	LYs and QALYs
Methods used to generate results	Partitioned survival model
Health states	Progression free (PF), progressed disease (PD), and dead.
Cycle length	1 month
Allocation to health states	Kaplan-Meier estimates for PFS and OS for the non-gBRCAM cohort in NOVA and extrapolated PFS and OS curves.
Extrapolation method	Dependent parametric functions fitted to the Kaplan-Meier survival estimates in each treatment arm, with the log-normal function selected in the base case for both OS and PFS based on visual validity and goodness of fit. Convergence was not assumed to occur within the modelled time horizon. 92% of the incremental LYs gained and 84% of the incremental QALYs gained occur in the extrapolated period.
Health related quality of life	Trial based. Progression-free: niraparib = 0.741, SMM = 0.734 Progressed disease: niraparib = 0.713, SMM = 0.679
Utilisation of niraparib	Dosage data from NOVA (fixed starting dose of 300 mg/day) was translated to account for the proposed individualised starting dose regimen using data from the PRIMA trial. ^a The duration of treatment was based directly on Kaplan-Meier estimates of time to treatment discontinuation (TTD) from NOVA and extrapolated TTD data.
Specific costs	Management of AEs associated with niraparib maintenance treatment Post-progression costs included: medicine costs of subsequent anti-cancer treatment, costs of managing AEs associated with subsequent treatment, and terminal care costs.

Source: Table 64 p99, Section 3A.5.1 p123; Section 3A.4.3, Table 79, p130 and Section 3A.6 of the submission.

AE = adverse event; gBRCAM = germline BRCA1/2 pathogenic and likely pathogenic variants; HGSOC = high-grade serous ovarian cancer; LY = life-year; QALY = quality-adjusted life-year; SMM = standard medical management.

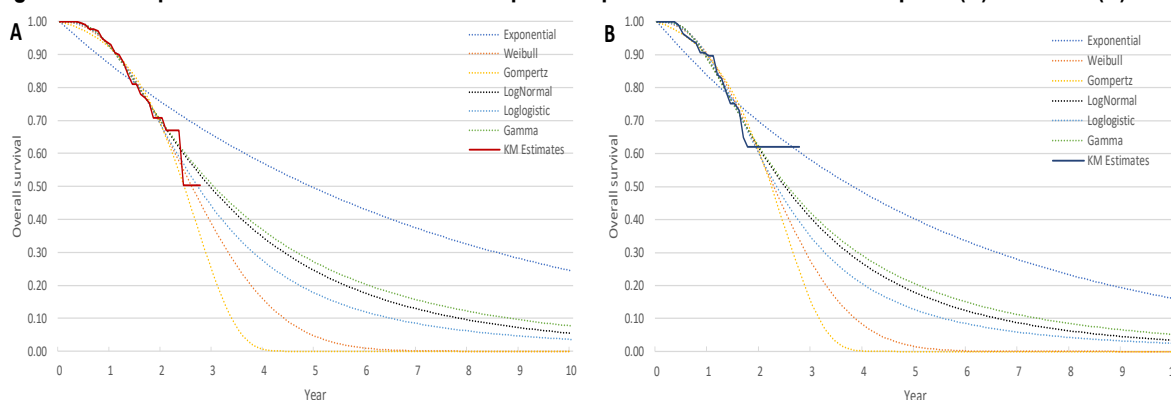
^a PRIMA was a randomised placebo-controlled trial of niraparib as maintenance therapy in the first-line setting in patients with PR HGSOC, in which the individualised starting dose regimen was applied following a protocol amendment during the conduct of the trial.

6.50 Kaplan-Meier PFS and OS data for the non-gBRCAM cohort in NOVA was applied up to the mean duration of follow-up in the trial. As discussed above, at least 13% of patients in the non-gBRCAM cohort in NOVA had somatic BRCA pathogenic variants. The submission did not address the likely impact of this on the applicability of the effectiveness of niraparib, as observed in the non-gBRCAM cohort of NOVA, to the narrower BRCA wild type (non-BRCAM) population.

6.51 Based predominantly on goodness of fit statistics, in the base case, a log-normal parametric model was used to extrapolate both PFS and OS over the remaining time horizon of the model. Due to the immaturity of the OS data from NOVA, there were insufficient trial data to reliably determine the most appropriate parametric model to apply in the extrapolation. The goodness of fit statistics for

the log-normal, the log-logistic and the Gamma parametric models were very similar. Given the uncertainty inherent in extrapolating the immature OS data over a 10 year time horizon, and the fact that the trial has not yet established that niraparib is statistically superior to placebo in terms of OS, it would have been more appropriate to use a more conservative parametric function to model the OS gains associated with niraparib over SMM. The results of the economic model were sensitive to the parametric function used to extrapolate OS. The ESC noted that the extrapolation of OS data was naïve given the immaturity of the OS data and that using the log-logistic functional form (the second best fit based on information criteria) increased the ICER to \$55,000 to < \$75,000. The PSCR proposed that shortening the time horizon from 10 years to 7.5 years was the most practical approach to addressing uncertainty in the extrapolated OS data. The ESC noted that the model was relatively insensitive to changes in the time horizon between 7.5 and 12.5 years, whereas it was sensitive to changes in the extrapolation function.

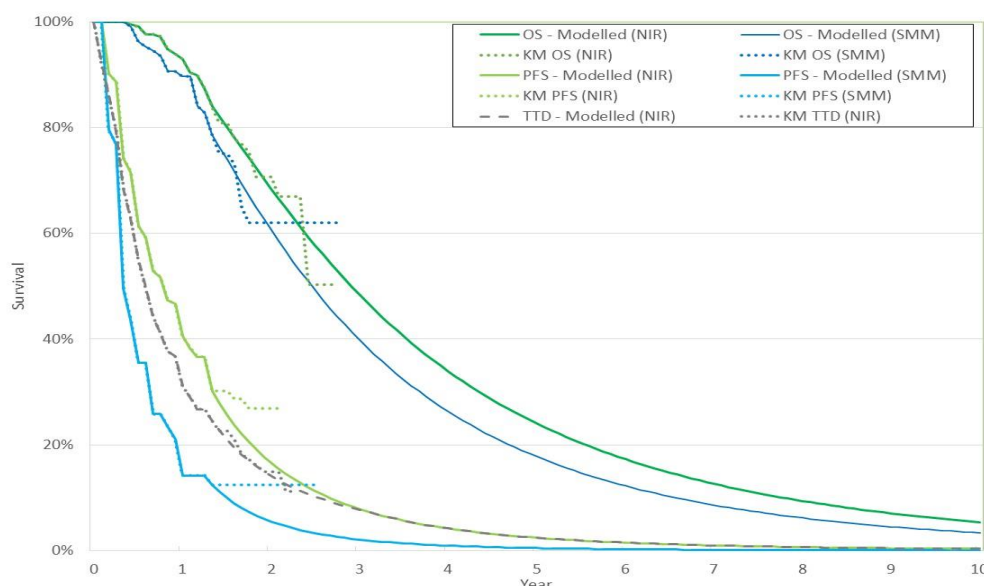
Figure 4: OS Kaplan-Meier estimates and fitted dependent parametric functions for niraparib (A) and SMM (B)



Source: Figure 35, p115 and Figure 36, p116 of the submission.
 KM = Kaplan-Meier; OS = overall survival; SMM = standard medical management.

6.52 The parametrically extrapolated OS, PFS and time to treatment discontinuation (TTD) curves applied in the base case of the model are illustrated in Figure 5. The OS curves for niraparib and SMM did not converge within the 10 year time horizon, despite no statistically significant OS benefit demonstrated in the clinical data presented. Given the uncertainty in the extent of any OS benefit associated with niraparib over SMM, it would have been more conservative to adjust the niraparib OS survival curve to ensure convergence with the SMM OS curve within the time horizon of the model.

Figure 5: Parametrically extrapolated survival curves applied in the base case economic model



Source: Figure 32 p114, Figure 37 p117 and Figure 42 p120 of the submission; Excel workbook 'Zejula (niraparib) non-BRCAM CEA', spreadsheet 'Survival Traces'.

KM = Kaplan-Meier; NIR = niraparib; OS = overall survival; PFS = progression-free survival; SMM = standard medical management; TTD = time to treatment discontinuation

- 6.53 Patients in the niraparib arm spent less time in the progressed disease (PD) health state (2.15 years) than those in the SMM arm (2.26 years), despite the assumption that they had a better utility than those in the SMM arm (0.713 vs 0.679).
- 6.54 The submission derived health state utilities from the EQ-5D-5L data from NOVA using a mapping algorithm from Norman et al (2013)², which was an Australian pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Norman et al (2013) clearly notes that the study was exploratory, and producing an Australian algorithm for the EQ-5D-5L was not the primary purpose of the experiment. Therefore, the validity of the algorithm used to translate the trial EQ-5D-5L data to utility values was uncertain.
- 6.55 Treatment-specific utilities were applied in both the progression-free (PF) and the PD health states. The use of treatment specific utilities in both the PF and PD health states was poorly supported by the quality-of-life data from NOVA. Oza et al (2018)³ reported that the adjusted least squares mean health utility index values derived from the NOVA EQ-5D-5L data, using the US value set, were similar between the niraparib and placebo treatment arms, and the between group differences were less than the MCID when averaged across the pre-progression time-points. The utilities in the PD health state were based on a

² Norman R, Cronin P, et al. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. *Appl Health Econ Health Policy*. 2013; 11 (3):287-98.

³ Oza AM, Matulonis UA, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. *The Lancet Oncology*. 2018; 19 (8):1117-25.

single EQ-5D-5L assessment conducted at 8 weeks post-progression. The PSCR argued that the utility weights were directly informed by the pivotal evidence and are the most appropriate source of utilities for the base case. The ESC noted that the standard deviations for the utility values are high and results may be driven by outliers. Further, the ESC noted that the treatment specific increment was higher in the progressed disease group (0.034) than in the progression free group (0.007), which appears implausible. The ESC noted that using the non-treatment specific utilities increased the ICER to \$75,000 to < \$95,000 and using utilities from the NICE evaluation of olaparib increased the ICER to \$55,000 to < \$75,000.

- 6.56 Costs associated with monitoring for and managing niraparib-related AEs were included in the model. The submission stated that the difference in the incidence of treatment emergent serious AEs between the two arms of NOVA was almost entirely due to the difference in the incidence of serious thrombocytopenia (niraparib 10.9% vs placebo 0%) and anaemia (niraparib 3.8% vs placebo 0%). To account for this, a hospitalisation cost was applied to the proportion of patients in the niraparib arm experiencing thrombocytopenia and anaemia serious AEs, and the cost of a blood transfusion was applied to the proportion of patients in the niraparib arm experiencing grade 3/4 anaemia events. As the costs of managing AEs were limited to two specific serious AEs and were based on the number of patients experiencing at least one event, rather than the total number of events, they are likely to be underestimated. However, the model was not sensitive to this input.
- 6.57 Based on utilisation of subsequent lines of anti-cancer treatment received in the non-gBRCAm cohort of NOVA, it was assumed that patients in the niraparib arm receive an average of 1.42 courses of subsequent anti-cancer treatment, compared with 1.65 courses in the SMM arm. All patients who received at least one subsequent anti-cancer treatment were assumed to experience treatment-related AEs (56.3% and 71.1% of patients in the niraparib and SMM arms, respectively). These assumptions were not adequately supported by the trial data. At the data cut-off, 21% (49/234) of patients in the niraparib arm and 12% (14/116) in the placebo arm were still receiving randomised study treatment. In addition, the duration of follow-up was not long enough to capture all subsequent lines of therapy received. This will have underestimated the likely full extent of use of subsequent lines of therapy, especially in the niraparib arm, where progression was delayed relative to the SMM arm. The assumption that utilisation of subsequent treatments would be considerably higher in the SMM arm than in the niraparib arm may have biased the costings of subsequent anti-cancer therapies, and the management of the AEs associated with them, in favour of niraparib. The PSCR argued that the modelling of an additional 0.22 lines of subsequent chemotherapy for patients on SMM compared to niraparib was appropriate because patients with HGSOc often receive multiple lines of chemotherapy over their lifetime, with decreasing efficacy (time to progression), as

such patients who receive subsequent chemotherapy earlier become increasingly more likely to experience disease progression and another line of treatment.

6.58 The submission stated that a terminal care cost was applied at death in the economic model to account for the difference in overall survival expected between niraparib and SMM, while acknowledging that over a lifetime time horizon, all patients would be attributed this cost. While including palliative care costs at end of life may be reasonable, the cost applied included hospitalisations, emergency department visits, clinician visits, pathology, and procedures and associated costs in the last 6 months of life⁴. Many of these costs will be accrued as part of standard care of cancer patients and are, therefore, likely to have been double-counted. The inclusion of the terminal care cost favoured niraparib. The PSCR argued that safety costs are derived from AEs primarily occurring in the first few months of treatment, therefore the extent by which health care costs may be double counted was limited to monitoring costs, which account for only a small proportion of the terminal care costs.

6.59 The key drivers of the model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ ██████ ¹ /QALY gained.
Dose regimen for niraparib	Dosing data from NOVA was translated to account for the proposed individualised starting dose regimen.	High, favours niraparib. Use of the fixed starting dose data from NOVA increased the ICER to \$ ██████ ² /QALY gained.
Extrapolation	A log-normal parametric model was used to extrapolate OS beyond the mean follow-up of 15.8 months in the trial.	High, favours niraparib. Use of a log-logistic parametric model increased the ICER to \$ ██████ ¹ /QALY gained.
Utilities	Treatment-specific utilities, based on the ITT population from NOVA, were applied in both the progression free and the progressed disease health states.	High, favours niraparib. The use of non-treatment specific utilities from the literature increased the ICER to \$ ██████ ¹ /QALY gained. The use of non-treatment specific utilities based on the ITT population from NOVA increased the ICER to \$ ██████ ² /QALY.

Source: Compiled during the evaluation based on Section 3A.9 of the submission and the sensitivity analyses performed during the evaluation.

ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; QALY = quality-adjusted life-year; OS = overall survival.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

⁴ Reeve R, Srasuebku P, *et al.* Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. *BMC Palliat Care*. 2018; 17 (1):1.

6.60 The results of the stepped economic evaluation are presented in Table 11.

Table 11: Results of the stepped economic evaluation – non-BRCAM population

Step and component	Niraparib	SMM	Increment
Step 1: trial-based costs and outcomes, 24 month time horizon			
Costs	\$ [redacted]	\$0	\$ [redacted]
LYG	1.75	1.67	0.08
Incremental cost/extra LY gained			\$ [redacted] ^{a,1}
Step 2: time horizon extended to 10 years			
Costs	\$ [redacted]	\$0	\$ [redacted]
LYG	3.30	2.89	0.41
Incremental cost/extra LY gained			\$ [redacted] ²
Step 3: utility weights applied			
Costs	\$ [redacted]	\$0	\$ [redacted]
QALYs	2.39	2.00	0.39
Incremental cost/extra QALY gained			\$ [redacted] ²
Step 4: incorporation of healthcare resource use			
Costs ^b	\$ [redacted]	\$44,968	\$ [redacted]
QALYs	2.39	2.00	0.39
Incremental cost/extra QALY gained ^b			\$ [redacted] ²
Step 5: translation of NOVA fixed starting dose regimen to individualised starting dose regimen			
Costs ^b	\$ [redacted]	\$44,968	\$ [redacted]
QALYs	2.39	2.00	0.39
Incremental cost/extra QALY gained (base case)^b			\$ [redacted]³

Source: Table 113, of the submission; Excel workbook 'Zejula (niraparib) non-BRCAM CEA'

QALY = quality-adjusted life-year; LY = life-year; SMM = standard medical management

^a Table 113 of the submission reported an ICER of \$ [redacted] /LY gained but this was the cost per QALY gained.

^b The calculation of costs for CBCs in cells BB12:BB195 of the 'Trace-Niraparib' spreadsheet were corrected to refer to column 7 of the table array 'Costs!\$C\$112:\$J118', rather than column 5 (Oncologist visit (PD)) of array 'Costs!\$C\$112:\$H1187, and the calculation of costs for GP consultations in cells BC12:BC195 of the 'Trace-Niraparib' spreadsheet were corrected to refer to column 8 of the table array 'Costs!\$C\$112:\$J118', rather than column 6 (Serum CA-125 level(PD)) of array 'Costs!\$C\$112:\$H1187.

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

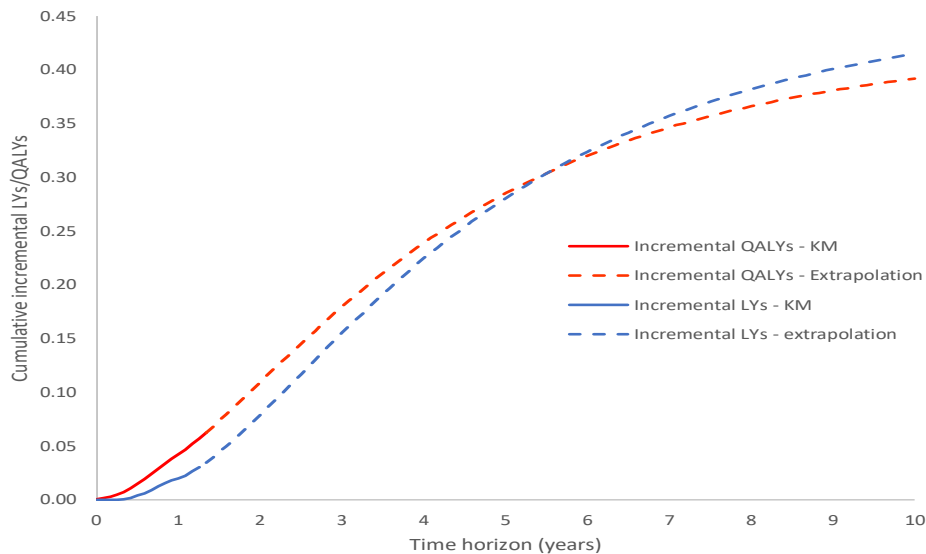
² \$75,000 to < \$95,000

³ \$55,000 to < \$75,000

⁴ \$155,000 to < \$255,000

6.61 In the base case of the economic model, 92% of the incremental life-years (LYs) gained (4.9 months) and 84% of the incremental quality-adjusted life-years (QALYs) gained (4.7 months), were accrued over the extrapolated period of the model (Figure 6).

Figure 6: Cumulative incremental LYs and QALYs gained over the time horizon of the model



Source: Figure constructed during the evaluation, based on data from the Excel workbook 'Zejula (niraparib) non-BRCAm CEA'
KM = Kaplan-Meier data; LY = life-year; QALY = quality-adjusted life-year.

- 6.62 The incremental QALYs were higher than the incremental LYs up to about 6 years, then lower than the incremental LYs thereafter. This was due to the treatment-specific utilities applied in both the PF and PD health states.
- 6.63 By far the largest contributor to the incremental cost was the cost of niraparib maintenance therapy in the PF health state. The largest cost offsets were those associated with the management of subsequent treatment AEs and terminal care. As discussed above, the assumption that the utilisation of subsequent therapies would be considerably greater in the SMM arm compared with the niraparib arm was poorly supported, while the terminal care cost was likely to be overestimated.
- 6.64 The results of key univariate sensitivity analyses presented in the submission, as well as further univariate and multivariate analyses performed during the evaluation, are summarised below.

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Table 12: Results of key sensitivity analyses

Analyses		Incremental cost	Incremental QALY	ICER	% difference
Base case		\$ [redacted]	0.39	\$ [redacted] ¹	
Univariate sensitivity analyses					
Time horizon (base case 10 years)					
• 7.5 years		\$ [redacted]	0.36	\$ [redacted] ¹	+7.2%
• 12.5 years		\$ [redacted]	0.41	\$ [redacted] ¹	-3.2%
Extrapolation OS (base case log-normal extrapolation)					
• Log-logistic extrapolation		\$ [redacted]	0.35	\$ [redacted] ¹	+14.4%
NOVA dosing (base case NOVA dosing adjusted for proposed individualised starting dose regimen)					
• NOVA fixed starting dose regimen (non-gBRCAm)		\$ [redacted]	0.39	\$ [redacted] ²	+20.0%
Utility values (base case NOVA ITT cohort, adjusted, treatment specific) ^a					
• Non-gBRCAm cohort, adjusted, treatment specific ^b		\$ [redacted]	0.43	\$ [redacted] ¹	-8.6%
• ITT cohort, unadjusted, treatment specific ^c		\$ [redacted]	0.48	\$ [redacted] ³	-17.3%
• ITT cohort, adjusted, non-treatment specific ^d		\$ [redacted]	0.31	\$ [redacted] ²	+26.1%
• Utilities from NICE olaparib TA620 ^{e,f}		\$ [redacted]	0.34	\$ [redacted] ¹	+14.8%
Subsequent treatment costs (base case included pharmaceutical, administration and management of AEs costs)					
• Excluding cost of managing AEs		\$ [redacted]	0.39	\$ [redacted] ¹	+5.8%
• Assuming the same utilisation in both arms		\$ [redacted]	0.39	\$ [redacted] ¹	+7.6%
Terminal care cost (base case \$ [redacted])					
• Excluded (\$0)		\$ [redacted]	0.39	\$ [redacted] ¹	+5.1%
Multivariate sensitivity analyses					
#1	7.5 year time horizon and log-logistic extrapolation OS	\$ [redacted]	0.33	\$ [redacted] ²	+19.2%
#2	Log-logistic extrapolation OS and NICE olaparib utilities	\$ [redacted]	0.30	\$ [redacted] ²	+30.2%
#3	Equal utilisation of subsequent treatments and no end of life care costs	\$ [redacted]	0.39	\$ [redacted] ¹	+12.7%
#4	#2 and no end of life costs	\$ [redacted]	0.30	\$ [redacted] ²	+35.1%
#5	#4 and equal utilisation of subsequent treatments	\$ [redacted]	0.30	\$ [redacted] ²	+44.9%
#6	Fixed starting dose and log-logistic extrapolation OS	\$ [redacted]	0.35	\$ [redacted] ²	+37.0%
#7	#6 and NICE olaparib utilities	\$ [redacted]	0.30	\$ [redacted] ⁴	+56.0%
#8	#7 and no end of life costs	\$ [redacted]	0.30	\$ [redacted] ⁴	+60.9%
#9	#8 and equal utilisation of subsequent treatments	\$ [redacted]	0.30	\$ [redacted] ⁴	+70.6%

Source: Table 118 of the submission; Excel workbook 'Zejula (niraparib) non-BRCaM CEA'

AE = adverse event; ICER = incremental cost-effectiveness ratio; ITT = intention to treat population; NICE = National Institute for Health and Care Excellence; OS = overall survival; QALY = quality-adjusted life-year.

^a Niraparib PF 0.741, niraparib PD 0.713, SMM PF 0.734, SMM PD 0.679

^b Niraparib PF 0.745, niraparib PD 0.716, SMM PF 0.736, SMM PD 0.667

^c Niraparib PF 0.786, niraparib PD 0.739, SMM PF 0.739, SMM PD 0.689

^d The figures for this analysis in Table 118 of the submission could not be replicated. This analysis used the overall utilities reported in cells E95:E96 in the 'settings spreadsheet of the Excel workbook for the cost-utilisation analysis: PF 0.739, PD 0.702 in both treatment arms.

^e Non-treatment specific utilities: PF 0.801, PD 0.719

^f Source: Table 50 NICE Single technology appraisal TA620, Document B Company evidence submission, Appraisal consultation committee papers, <https://www.nice.org.uk/guidance/ta620/evidence>.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$45,000 to < \$55,000

⁴ \$95,000 to < \$115,000

6.65 The results of the sensitivity analyses indicated that the model was sensitive to the use of the translated dosing data for niraparib. This is a major source of uncertainty in

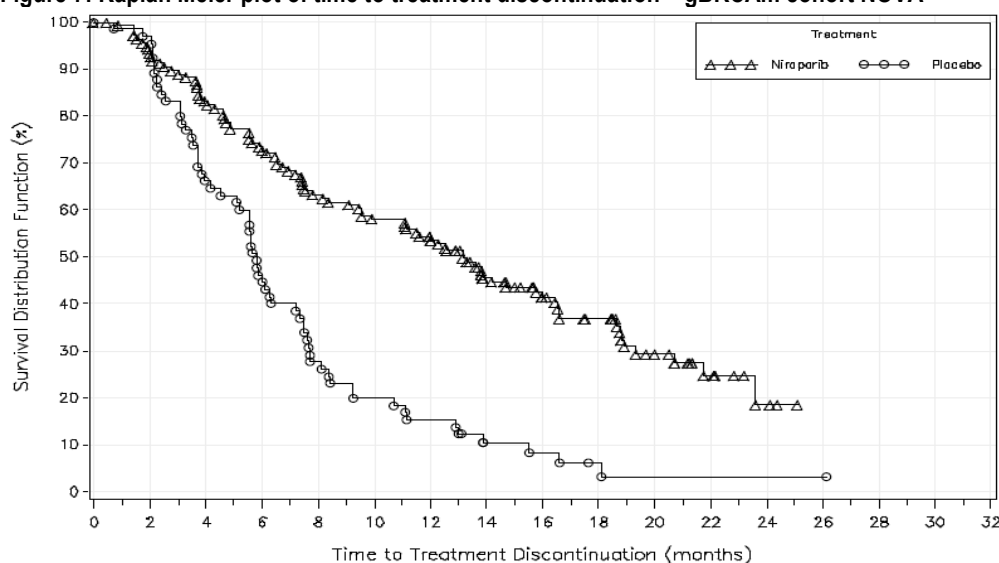
the model. As noted above, the model was also sensitive to the parametric function for extrapolation of OS and the use of treatment specific utilities.

CMA - BRCAM PSR HGSOc population

- 6.66 The submission presented a CMA of niraparib compared with olaparib for PSR HGSOc in the BRCAM population. The equi-effective doses were estimated as niraparib 161 mg⁵ and olaparib 542 mg. Conducting the cost-minimisation analysis on a cost per mg basis, when the cost per patient for niraparib differs by the dose received, while the cost per patient for olaparib is the same regardless of dose, is not appropriate. The cost-minimisation should have been based on the mean cost per patient per course, however the ESC noted that this was also problematic given the limited trial data available. If a cost per mg approach is to be used, it would have been more conservative to assume that all patients treated with olaparib received the 150 mg tablets, consistent with the recommended fixed dose regimen (300 mg twice daily).
- 6.67 The submission's approach to estimating the equi-effective doses assumed that the mean duration of treatment for niraparib and olaparib is the same. This is reasonable only if it is accepted that they are non-inferior in terms of both PFS and safety. However, both drugs are intended to be continued until progression, and the median PFS for BRCAM patients receiving niraparib in NOVA (21 months) was considerably shorter than that for patients receiving olaparib in SOLO-2 (30 months), while the median PFS in the placebo arms of both trials was similar (5.5 months). Similarly, a comparison of the proportion of gBRCAM patients remaining on treatment at 12 and 24 months in SOLO-2 (62% and 45% respectively), with the TTD Kaplan-Meier (KM) data for the gBRCAM cohort in NOVA (Figure 7) suggests that the mean duration of treatment with olaparib in SOLO may have been longer than that for niraparib in NOVA, although this does not take into account the proposed individualised starting dose for niraparib. It may have been more appropriate to use the NOVA data, with modelling of the TTD curve, as for the non-gBRCAM cohort in the CUA.

⁵ 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

Figure 7: Kaplan Meier plot of time to treatment discontinuation – gBRCAm cohort NOVA



Source: Figure 14.1.1 (gBRCAm cohort), p1004 NOVA CSR.

6.68 The equi-effective doses in the CMA were based on the mean dose intensity reported for niraparib and olaparib in the gBRCAm cohort of patients in NOVA and SOLO-2, respectively (Table 13). The dose intensities reported in SOLO-2 were calculated as the total dose divided by the actual duration of treatment excluding dose interruptions, resulting in an overestimation to the actual dose intensity in the trial. In recognition of this, the FDA conducted an analyses including periods of dose interruption, which was subsequently used in the CMA. Comparison of mean dose intensities, inclusive of dose reductions and interruptions, across the two trials is likely to be subject to confounding resulting from differences in the trial populations and the conduct of the trials.

Table 13: Dose intensity in the gBRCAm cohort of NOVA and SOLO-2

NOVA gBRCAm cohort	Niraparib	Placebo
Daily dose intensity – over total treatment duration, mg/day ^a		
Mean (SD)	180.68 (66.35)	288.9 (29.67)
Median (IQR)	187.0 (118.0, 212.5)	298.0 (288.0, 300.0)
SOLO-2 gBRCAm cohort	Olaparib	Placebo
Daily dose intensity – over total treatment duration, mg/day ^b		
Mean (SD)	568.2 (53.1)	592.1 (16.9)
Median (IQR)	597.6 (541.3 – 600)	598.4 (593.0 – 600)
Dose intensity including dose interruptions - over total treatment duration (FDA analysis), mg/day ^c		
Mean	542	582
Median (IQR)	590 (41-600)	596 (300-600)

Source: Table 124, p164 and Table 126, p165 of the submission; Table 14.3.5.13, p11072 NOVA CSR.

FDA = Food and Drug administration; gBRCAm = germline BRCA1/2 pathogenic and likely pathogenic variants; IQR = interquartile range; SD = standard deviation.

^a Dose intensity was calculated as sum of the daily doses actually consumed divided by total treatment duration. Treatment duration was defined as the period from first to last dose, including days when no doses were received by the patient.

^b Defined as the total dose divided by the actual duration of treatment (total duration of treatment excluding any dose interruptions).

^c FDA analysis of dose intensity in SOLO-2: Table 23, p68, Olaparib Multidisciplinary Review 208558Orig1s000, 2017).*

* 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

- 6.69 The use of the mean dose intensity, which is over the entire duration of follow-up, does not accurately reflect the ‘steady-state’ doses, especially for niraparib, where the majority of patients in NOVA underwent dose reductions, predominantly over the first 3-4 months of treatment. However, the inclusion of dose interruptions will decrease the dose intensity, and is likely to favour niraparib in the CMA, as the proportion of patients experiencing a dose interruption was considerably higher in gBRCAm patients in the niraparib arm of NOVA (84.6%) compared with those receiving olaparib in SOLO-2 (54.4%).
- 6.70 On the basis of these estimated mean daily doses, the submission claimed that, at ‘steady state’, niraparib 161.1⁶ mg and olaparib 542 mg are equi-effective. Due to the indirect nature of the comparison of mean dose intensities across the trials, and the considerable uncertainty regarding the validity of the translated mean dose for niraparib, the equi-effective doses of niraparib and olaparib were highly uncertain.
- 6.71 Incremental costs associated with monitoring for haematological AEs (complete blood counts) and general practitioner appointments for monitoring of blood pressure for patients receiving niraparib were included. This was appropriate. The submission stated that no differences in the incidence of SAEs or Grade 3/4 anaemia events were expected between niraparib and olaparib and, therefore, no safety costs were applied in the CMA. This is only reasonable if it is accepted that niraparib is non-inferior to olaparib in terms of safety.
- 6.72 The cost-minimisation analysis, based on the published approved EMP (AEMP) for olaparib, is presented in Table 14.

⁶ Note that the mean dose of treatment was provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose

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Table 14: Cost-minimisation analysis, as presented in the submission (published AEMP for olaparib)

	Parameter		Source/calculation
	Cost of olaparib		
A	Cost per maximum quantity (112 tablets)	\$6,810.00 ^a	Published AEMP
B	Amount per maximum quantity 100 mg/150 mg tablets	11,200/16,800 mg	
C	Distribution of PBS use (%100 mg/%150 mg)	26.1%/73.9%	PBS statistics ^b
D	Weighted amount per script	15,338.4 mg	$11,200 \times 0.261 + 16,800 \times 0.739$
E	Weighted average price per mg	\$0.44	A/D
F	Mean olaparib dose intensity, mg/day	542.0 mg	Table 13
G	Mean cost per day	\$240.68	E*F
H	Mean cost per 28 days	\$6,739.11	G*28
	Cost of niraparib		
	Olaparib drug cost per 28 days	\$6,739.11	H
I	Incremental monitoring costs per 28 days for niraparib	\$13.70	
J	Cost-minimised niraparib drug cost per 28 days	\$6,725.41	H-I
K	Mean niraparib dose intensity, mg/day	161.5 mg	Table 13
L	Mean dose per 28 days*	4,521 mg	K*28
M	Cost per mg	\$1.49	
N	Amount per script 84 capsule pack/56 capsule pack ^c	8,400 mg/5,600 mg	
	Cost-minimised EMP niraparib 84 capsules	\$12,496.38	M*8,400
	Cost-minimised EMP niraparib 56 capsules	\$8,330.92	M*5,600

Source: Table 131 and Table 132, p169 of the submission.

AEMP = approved ex-manufacturer price; EMP = ex-manufacturer price.

^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 Between January and June 2020, 182 100 mg packs (PBS items 11503K and 11522K) and 514 150 mg packs (PBS items 11528R and 11539H) were utilised. 2020 data is used as 50 mg capsules are currently being phased off the PBS and were still available to initiating patients in 2019.

^c Maximum quantity of one pack per script

*Note that the mean dose of treatment stated in Table 14 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

6.73 Using the weighted average cost per mg for olaparib was not appropriate, as the cost per patient is constant, regardless of which dose is used.

6.74 The following sensitivity analyses were performed during the evaluation:

- Using the mean dose intensity (inclusive of dose interruptions) from NOVA (i.e. untranslated data for fixed starting dose regimen), as in (180.7 mg/day);
- Using the 'steady state' dose distribution for niraparib from NOVA (average weighted mean dose over Months 5-12), non-inclusive of dose interruptions (176.7 mg/day), and the mean dose intensity for olaparib non-inclusive of dose interruptions (568.2 mg/day); and
- Using the cost per mg for the 150 mg tablet of olaparib (\$0.41/mg).

Table 15: Results of the sensitivity analyses performed during the evaluation (published AEMP for olaparib).

	Mean dose*, mg/day		Cost-minimised EMP niraparib	
	Niraparib	Olaparib	84-capsules	56-capsules
Base case				
Translated niraparib dose, dose intensity inclusive of dose interruptions,	161.5	542.0	\$12,496	\$8,331
Sensitivity analyses				
NOVA niraparib dose, dose intensity inclusive of dose interruptions	180.7	542.0	\$██████	\$██████
NOVA niraparib 'steady state' dose distribution (Month 5-12), non-inclusive of dose interruptions	176.7	568.2	\$██████	\$██████
Using the cost per mg for the 150 mg tablet of olaparib (\$0.41/mg). Base case \$0.44/mg ^a	161.5	542.0	\$██████	\$██████

Source: Table compiled during the evaluation using the Excel workbook 'Zejula (niraparib) BRCAM CMA'

AEMP = approved ex-manufacturer price.

^a Base case: weighted cost per mg, assuming a relative use of 100 mg and 150 mg tablets of 26.1% to 73.9%.

*Note that the mean dose of treatment stated in Table 15 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

Drug cost/patient/course

6.75 Due to the approach used in the financial estimates, it was difficult to reliably determine the average cost/patient/course for niraparib in each of the two populations. The estimates presented in the following tables were calculated during the evaluation based on the time on treatment each year and the estimated scripts per patient per year. Similarly, the estimated cost/patient/course for olaparib in the BRCAM population could only be estimated using the weighted average price per mg, as derived in Table 14.

6.76 The estimated cost/patient/course of niraparib for patients with non-BRCAM PSR HGSOc across the sections of the submission is summarised in Table 16. The costs have been derived based on the proposed weighted effective price, as per the requested SPA, rather than the cost-effective price for the non-BRCAM population used in the economic model.

Table 16: Drug cost per patient for niraparib – non-BRCAM PSR HGSOc (requested effective DPMQ)*

	Trial dose and duration	Model	Financial estimates
Mean dose**	Fixed starting dose, 180.7 mg/day	Estimated individualised dose, 161.5 mg/day	Varied by year of treatment
Mean duration	1.1 years ^a	1.1 years ^a	1.1 years ^a
Cost/patient/course	\$██████ ^b	\$██████ ^c	\$██████ ^d

Source: Table 163, p198 of the submission; Spreadsheet 'Trace-Niraparib, Excel workbook 'Zejula (niraparib) non-BRCAM CEA'; Excel workbook 'Zejula (niraparib) BIM'

CUA = cost-utility analysis; DPMQ = dispensed price for maximum quantity; PSR HGSOc = platinum-sensitive relapsed high grade serous ovarian cancer.

^a Extrapolated NOVA time to treatment discontinuation data from CUA

^b NOVA dosing data - fixed starting dose regimen (Step 4 of the CUA)

^c Translated dosing data adjusted for proposed individualised starting dose regimen (Step 5 of the CUA).

* DPMQ niraparib: 84-capsule pack \$██████, 56-capsule pack \$██████

**Note that the mean dose of treatment stated in Table 16 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

- 6.77 In contrast to the NOVA trial, in which niraparib was initiated at a fixed dose of 300 mg/day, the cost/patient/course of niraparib in the model and the financial estimates was based on the translated individualised starting dose data.
- 6.78 The estimated cost/patient/course of niraparib for patients with BRCAm PSR HGSOc across the sections of the submission is summarised in Table 17. The cost of niraparib is based on the requested weighted effective price, rather than the price derived in the CMA.

Table 17: Drug cost per patient for niraparib and olaparib – BRCAm PSR HGSOc (effective DPMQ for niraparib)*

	Niraparib Trial dose and duration	Niraparib CMA	Niraparib Financial estimates	Olaparib Trial dose and duration	Olaparib CMA	Olaparib Financial estimates
Mean dose**	180.7 mg/day ^a	161.5 mg/day ^b	Varied by year of treatment	542 mg/day	542 mg/day	542 mg/day
Mean duration	11.6 months ^c	NA ^d	29.1 months ^e	29.1 months ^e	NA ^d	29.1 months
Cost/patient /course	\$ ██████ ^f	-	\$ ██████	\$221,020 ^h	-	\$218,720 ⁱ

Source: Table 29 and Table 163 of the submission; Excel workbook 'Zejula (niraparib) BRCAm CMA'; Excel workbook 'Zejula (niraparib) BIM'.

CMA = cost-minimisation analysis; DPMQ = dispensed price for maximum quantity; NA = not applicable; PSR HGSOc = platinum-sensitive relapsed high grade serous ovarian cancer.

^a NOVA dosing data - fixed starting dose regimen (Table 29 of the submission)

^b Translated dosing data adjusted for proposed individualised starting dose regimen

^c Truncated mean dose. 35.5% of patients still on treatment (Table 15 NOVA CSR).

^d No specific duration of therapy was defined in the CMA.

^e SOLO-2 dosing data from Povedo 2020 (median follow-up 65 months). Assumed equal duration of treatment for niraparib and olaparib.

^f Estimation only for comparative purposes, assuming dose distribution of 16.3% 300mg, 48.1% 200mg, 35.6% 100mg, as for Month 6 in NOVA (Table 14.3.5.17 of the CSR). Weighted DPMQ = (16.3% x \$ ██████) + (48.1% x 1 + 35.6% x 0.5) x \$ ██████ = \$ ██████. Cost per patient over 11.6 months = \$ ██████/28 x (365.25/12) x 11.6.

^h Calculated as \$6,986.96/28 x (365.25/12) x 29.1.

ⁱ Cost per mg \$0.46 (derived from DPMQ as for EMP in Table 14). Calculated as 542 mg x \$0.46 x (365.25/12) x 29.1.

* DPMQ niraparib: 84-capsule pack \$ ██████, 56-capsule pack \$ ██████. DPMQ olaparib: \$6,986.96.

**Note that the mean dose of treatment stated in Table 17 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

- 6.79 For niraparib, the cost/patient/course based on the NOVA trial data will be an underestimate, as 35.5% of BRCAm patients were still receiving niraparib at the data cut-off. The niraparib cost/patient/course in the financial estimates is likely to be overestimated, as it was derived based on the duration of treatment with olaparib in the SOLO-2 trial (see below). As the cost of olaparib in the financial estimates is considerably higher than the cost of niraparib based on the requested weighted effective price, the cost offsets from substitution of niraparib for olaparib have considerable impact on the financial estimates to the PBS/RPBS.

Estimated PBS usage & financial implications

- 6.80 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the number of patients likely to be treated with niraparib, based on Australian Institute of Health and Welfare incidence data for ovarian, fallopian tube and primary peritoneal cancer, and applying epidemiological data from the literature. As olaparib tablets were only listed on the PBS in December 2018, there are limited

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PBS utilisation data on which to base a market share approach for the BRCAM population.

6.81 The submission estimated the following populations: incident cases of HGSOE, the prevalent patient pool, and patients switching to niraparib from olaparib. The prevalent patient pool consisted of patients with non-BRCAM PSR HGSOE who met the eligibility criteria for niraparib prior to its availability on the PBS, and who remained eligible at the time of listing. Patients in the sponsor’s patient access program would form part of the prevalent pool.

6.82 The key inputs relied on in the financial estimates are summarised in Table 18.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident of ovarian, fallopian tube and primary peritoneal cancer	AIHW ICD-10 codes C48, C56 and C57 (2000-2016) and NZ Ministry of Health (MoH) 4 character ICD code data.	The use of AIHW data was appropriate. The NZ MoH data was used to determine the proportion of each ICD-10 code that was applicable to the population of interest.
% with high grade carcinoma and % of these that are serous	93.6%, of which 74.1% are serous Australian Ovarian Cancer Study (AOCS), Alsop 2012 and Lindemann 2018 ^a	It was not clear why the submission based the proportion with serous histology only on those with a PFI >6 months after first-line chemotherapy. The proportion with serous histology in all patients was 77%. The PSCR noted there are updated WHO classification guidelines and suggested this estimate be changed to 85.8% to account for tumours with serous or endometrioid histology.
% of HGSOE patients who have PS relapsed disease	43.1% Total of those eligible at second (37.5%), third (4.3%) and fourth line (1.3%). Based on data from the AOCS (Alsop 2012, Lindemann 2018) and Nishio 2009. ⁷	The applicability of the data to current clinical practice was potentially limited by the age of the studies (patients recruited between 1999 and 2006). The treatment algorithm did not incorporate the recent listing of olaparib for maintenance treatment for BRCAM patients in the first-line setting, and will have overestimated the proportion of BRCAM patients eligible for niraparib. This input does not take into account that the proportion of patients remaining platinum sensitive at second and subsequent lines is likely to differ by BRCA mutation status.
% BRCAM	Prevalence of gBRCAM: 22.6% (Alsop 2012) Prevalence of sBRCAM: 6.3% (CGARN 2011) ⁸	The PBAC previously accepted a prevalence of 20.3% for gBRCAM and 5% for sBRCAM (para 7.21, olaparib PSD, November 2019 PBAC Meeting and para 6.46 olaparib PSD, July 2020 PBAC Meeting).

⁷ Alsop K, Fereday S, *et al.* BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol.* 2012; 30 (21):2654-63.

Lindemann K, Gao B, *et al.* Response rates to second-line platinum-based therapy in ovarian cancer patients challenge the clinical definition of platinum resistance. *Gynecol Oncol.* 2018; 150 (2):239-46.

Nishio S, Katsumata N, *et al.* Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy. *J Cancer Res Clin Oncol.* 2009; 135 (4):551-7

⁸ Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011; 474 (7353):609-15.

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Parameter	Value applied and source	Comment
Patients continuing treatment in subsequent years	Non-BRCAM: based on modelled TTD from NOVA BRCAM: based on dosing data from SOLO-2	The use of the SOLO-2 dosing data in the BRCAM population, rather than data from NOVA, was not appropriate, and is likely to have overestimated the duration of treatment in BRCAM patients (see below).
Scripts dispensed	The distribution of doses and compliance rates applied for niraparib in the CUA of niraparib versus SMM in non-BRCAM patients, with adjustment for the proposed individualised starting dose regimen, was applied to both non-BRCAM and BRCAM patients.	The limitations inherent in the submission's approach to adjusting the exposure data for niraparib to account for the proposed individualised starting dose regimen were discussed above.
Cost of olaparib 84-capsule pack 56-capsule pack	Effective DPMQ \$ [REDACTED] \$ [REDACTED]	This was based on the weighted price for non-BRCAM (71.1%) and BRCAM (28.9%) patients. This did not account for the reduced use in BRCAM patients due to the listing of olaparib for first line maintenance treatment.
Offsets for olaparib	Assumed all use of niraparib in patients BRCAM HGSOc would substitute for olaparib.	Likely to be overestimated as the submission did not account for the listing of olaparib for first line maintenance treatment.
CBC	MBS item 65070 (0.8 scheduled fee \$13.56)	While the appropriateness of including GP consultations was uncertain, these costs had minimal impact on the overall cost to the Australian Government health budget.
GP consultation	MBS item 23 (0.8 scheduled fee \$31.00)	

Source: Table 135, p172 and Section 4.1 of the submission; Excel workbook 'Zejula (niraparib) BIM'.

AIHW = Australian Institute of Health and Welfare; CBC = complete blood count; CGARN = Cancer Genome Atlas Research Network; CUA = cost-utility analysis; DPMQ = dispensed price for maximum quantity; gBRCAM = germline BRCA1/2 pathogenic and likely pathogenic variants; GP = general practitioner; HGSOc = high grade serous ovarian cancer; ICD-10 = International Classification of Disease 10th revision; NZ = New Zealand; PFI = platinum-free interval; PSD = Public Summary Document; sBRCAM = somatic BRCA pathogenic and likely pathogenic variants; SMM = standard medical management; TTD = time to treatment discontinuation.

^a The calculations for the % serous histology in the PFI subgroups in Table 143, p181 of the submission do not take into account that only 654 patients received second-line chemotherapy (Figure 1, Lindemann et al (2018)).

- 6.83 The estimated total incidence of ovarian, fallopian tube and peritoneal cancer was linearly extrapolated over the 6 years of the financial estimates. The number of patients with ovarian, fallopian tube and peritoneal cancer who have high-grade carcinoma of serous histology was derived using data from the Australian Ovarian Cancer Study (AOCS).
- 6.84 The submission estimated the proportion of HGSOc patients eligible for niraparib as maintenance therapy in the second-, third- and fourth-line settings, by applying conditional probabilities of receiving platinum-based treatment and of response to treatment at each line of therapy. The uncertainty inherent in each estimate of the proportion of patients receiving platinum-based treatment and the proportion of patients progressing at each line of treatment, was compounded by the multiple calculations required to derive the overall proportion of HGSOc patients who would be eligible for niraparib.
- 6.85 The submission assumed that all patients with incident BRCAM PSR HGSOc would be eligible for niraparib. This did not account for the recent listing of olaparib on the PBS for first line maintenance treatment in patients with BRCAM platinum-sensitive high grade stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer

(HGEOC). The approach resulted in an overestimate of the number of BRCAm HGSOc patients who would be eligible for niraparib, the extent of substitution for use of olaparib in the second and later line setting, and the number of patients likely to switch to niraparib due to intolerance to olaparib. The pre-PBAC response presented revised estimates assuming uptake of olaparib 1L (Yr 1: 60%, Yr 2: 70%, Yr 3-6: 80%), reducing the eligible 2L BRCAm population by 64%, from 500 to 5000 to < 500 patients over the first six years of listing. This increased the net costs to the PBS/RPBS by 26% due to reduced substitution of 2L olaparib.

- 6.86 The submission assumed that there would be a prevalent pool of non-BRCAm patients (approximately < 500 patients), as no maintenance treatment is currently available for these patients. These calculations were highly uncertain as they rely on a number of poorly supported assumptions.
- 6.87 The number of initiating non-BRCAm HGSOc patients continuing treatment in subsequent years (continuing patients) was estimated using TTD data from NOVA. This was appropriate, as a considerable proportion of patients continued treatment beyond 12 months. For BRCAm patients, the submission used treatment duration data from SOLO-2, due to the extended follow-up in this trial compared with NOVA. On the basis of the non-inferiority claim, the submission assumed that the same duration treatment would apply to niraparib. As discussed above, the use of the SOLO-2 data may have overestimated the mean duration of treatment with niraparib in this patient cohort.
- 6.88 For non-BRCAm patients, the distribution of doses and compliance rates were the same as those used in the economic model, with adjustment for the proposed individualised starting dose regimen. It was assumed that the same distribution of doses and compliance rates would apply to BRCAm patients. The limitations inherent in the submission's approach to adjusting the exposure data for niraparib to account for the proposed individualised starting dose regimen were discussed above.
- 6.89 The methodology used to estimate the number of patients likely to be treated and the number of scripts was unnecessarily complex, and added to the uncertainty in the estimates.
- 6.90 All use of niraparib in incident patients with BRCAm HGSOc was assumed to substitute for use of olaparib. The estimates were dependent on the nominated equi-effective doses, which, as discussed above, were highly uncertain.
- 6.91 The submission presented a validation of the estimated number of substituted olaparib scripts based on PBS statistics, however the approach used in the submission was not appropriate, as it was based predominantly on utilisation data for the 50 mg capsule, which the PBAC previously considered was not bioequivalent to the olaparib tablets (para 7.3, olaparib PSD, March 2018 PBAC meeting). The estimates were also highly uncertain, given that the extrapolations were based on only 3 yearly script totals.

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6.92 The estimated net financial implications for the PBS/RPBS are presented in Table 19.

Table 19: Estimated use and financial implications (proposed effective DPMQ of niraparib)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated ^a						
BRCAm	1	1	1	1	1	1
non-BRCAm	1	1	1	1	1	2
Total	1	2	2	2	2	2
Number of scripts dispensed						
84 capsule packs	2	2	2	2	2	2
56 capsule packs	2	2	2	2	2	2
Estimated financial implications niraparib						
BRCAm population	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Non-BRCAm population	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Total cost to PBS/RPBS less copayments	\$ 4	\$ 4	\$ 4	\$ 5	\$ 5	\$ 5
Estimated financial implications for olaparib						
Cost to PBS/RPBS less copayments	-\$ 3	-\$ 3	-\$ 3	-\$ 4	-\$ 4	-\$ 4
Net financial implications						
Net cost to PBS/RPBS	\$ 4	\$ 4	\$ 3	\$ 3	\$ 3	\$ 3
Net cost to MBS	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Net cost to PBS/RPBS/MBS	\$ 4	\$ 4	\$ 3	\$ 3	\$ 3	\$ 3

Source: Table 164, Table 168 and Table 184 of the submission; Spreadsheet '7. Net changes – MBS' Excel workbook 'Zejula (niraparib) BIM'.

DPMQ = dispensed price for maximum volume.

^a Includes patients initiating treatment and patients continuing treatment from previous years.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

6.93 The results of the sensitivity analyses presented in Table 20 indicate that the estimated financial implications for the PBS/RPBS of listing niraparib were highly dependent on the extent of the cost offsets resulting from substitution of niraparib for use of olaparib as second and later line maintenance treatment. The cost of niraparib to the PBS/RPBS was also sensitive to the data used to estimate the mean exposure to niraparib. When the unadjusted fixed starting dose data from NOVA were applied, rather than the translated data for individualised dosing, the total cost of niraparib over the first 6 years of listing increased from approximately \$60 million to < \$70 million to approximately \$70 million to < \$80 million.

Table 20: Sensitivity analyses: net financial impact to the PBS/RPBS (proposed effective price of niraparib).

SA		Total cost Year 1-6	% change
	Base case	\$ [redacted] ¹	
#1	Niraparib dose data from NOVA (unadjusted) Base case: Dosing data adjusted for proposed individualised dosing.	\$ [redacted] ²	+23%
#2	Assuming 20.3% gBRCAm, 5% sBRCAm Base case: 22.6% gBRCAm, 6.3% sBRCAm	\$ [redacted] ¹	+12%
Use of first line olaparib maintenance treatment in BRCAm patients (base case: none)			
#3	Assuming 50% of BRCAm patients with platinum-sensitive HGSOc receive olaparib first-line ^{a, b, c}	\$ [redacted] ³	+42%
#4	Assuming 70% of BRCAm patients with platinum-sensitive HGSOc receive olaparib first-line ^{a, b, c}	\$ [redacted] ⁴	+59%
#5	SA #3, and weighting the price of niraparib assuming the consequent treated population is 18.2% BRCAm and 81.8% non-BRCAm	\$ [redacted] ¹	+12%
#6	SA #4, and weighting the price of niraparib assuming the consequent treated population is 12.9% BRCAm and 87.1% non-BRCAm	\$ [redacted] ¹	+14%

Source: Table 195, p221 of the submission; Excel workbook 'Zejula (niraparib) BIM'.

HGSOc = high grade serous ovarian cancer; SA = sensitivity analysis.

^a Assuming 90.8% ((38%+1%+0%)/43.1%) of patients who qualify for niraparib were sensitive to first line platinum. If x% of platinum-sensitive BRCAm patients receive olaparib 1L, the proportion of eligible BRCAm is $90.8\% \times (1 - x\%) + (1 - 90.8\%) = y\%$. This was applied to the proportion of the population who are BRCAm (28.9% x y%) in cell D570 of the spreadsheet '2a. Patients – incident', while maintaining the non-BRCAm population at 71.1%.

^b If 50% of BRCAm patients receive first line olaparib (i.e. x = 50% in the equation above), then y = 10.5% (see note a). If x = 70%, y = 10.5%.

^c Analyses #3 and #4 applied the weighted price of niraparib derived using the weighting proposed in the submission (28.9% BRCAm and 71.1% non-BRCAm)

The redacted values correspond to the following ranges:

¹ \$60 million to < \$70 million

² \$70 million to < \$80 million

³ \$80 million to < \$90 million

⁴ \$90 million to < \$100 million

6.94 DUSC considered the patient estimates presented in the submission to be overestimated and the cost to be underestimated. The main issues were:

- The financial estimates did not consider the impact of the recent listing of olaparib for first line maintenance treatment in patients with BRCAm platinum-sensitive high grade stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer. As a result, the assumed prevalence of BRCAm in the eligible population (28.9%) was likely to be considerably overestimated because an increasing majority of patients with BRCA pathogenic variants are likely to have been treated with olaparib as first line maintenance.
- 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.
- The cost offsets resulting from substitution of niraparib for use of olaparib as second and later line maintenance treatment were likely to be considerably overestimated.

Financial Management – Risk Sharing Arrangements

6.95 The submission stated that, given the requested restriction for niraparib, it is inappropriate for a broader PARP inhibitor agreement to be entered into with olaparib

due to the inability to delineate use of niraparib in BRCAm and non-BRCAm populations via PBS items.

7 PBAC Outcome

- 7.1 The PBAC did not recommend niraparib, for platinum-sensitive, relapsed, high grade serous ovarian, fallopian tube, or primary peritoneal cancer. The PBAC considered that for patients with BRCA1/2 pathogenic gene variants the most appropriate treatment is in the first line maintenance setting so the proposed second line listing would have diminishing clinical relevance over time. More importantly, the PBAC considered that the claim of non-inferior efficacy and safety compared with olaparib was not supported by the data presented, for the 300 mg TGA-approved dose. The PBAC considered that for patients without a BRCA1/2 pathogenic variant, the PFS benefit over standard medical management was difficult to interpret, given the missing long-term data on overall survival in the pivotal NOVA trial. The cost utility model claimed a benefit on overall survival which was not established by the final DCO (1 Oct 2020) for NOVA on either the unadjusted or the adjusted analysis (adjusted for subsequent PARPi use in the control group).
- 7.2 For patients with BRCAm, the PBAC considered the nominated comparator, olaparib, was appropriate. For patients without BRCA pathogenic variants (non-BRCAm), PBAC considered the nominated comparator, standard medical management (follow-up or no active treatment), was appropriate.
- 7.3 The PBAC noted that the evidence presented in the submission was based on a direct comparison of niraparib versus placebo from the NOVA trial in patients with non-gBRCAm and a one-step anchored indirect comparison between niraparib (NOVA trial) versus olaparib (SOLO-2 trial) in patients with gBRCAm with placebo as a common comparator. The PBAC noted that both comparisons were based on the first data cut-off (2016) for NOVA and the pre-PBAC response provided updated overall survival efficacy results for NOVA with a data cut-off of October 2020. The PBAC noted that overall discontinuation from the NOVA trial was >80% in both arms of the trial, with early withdrawals for reasons other than death (23-43%) limiting the survival status data and information regarding subsequent treatments.
- 7.4 The PBAC noted that patients in NOVA were stratified by germline BRCA status and the non-gBRCAm cohort therefore included patients with somatic BRCAm (13%). As patients with germline or somatic BRCAm had a better response to treatment than patients in the non-gBRCAm cohort, the PBAC considered that inclusion of sBRCAm patients in this group is likely to overestimate the clinical benefit for the true non-BRCAm group.
- 7.5 The submission proposed an individualised starting dosage (200 mg or 300 mg based on patient weight and platelet count), which differed from the starting dose in NOVA (300 mg) and is not consistent with the current Australian PI. The PBAC considered the

efficacy and safety of this individualised dose regimen has not been sufficiently established in the relevant population for this submission.

- 7.6 **With regard to the BRCAm population**, in both the NOVA trial and SOLO-2 trial there was a statistically significant PFS benefit in favour of the active arms (compared to placebo), with a similar median PFS in the placebo arms in both the NOVA trial and SOLO-2 trial (5.5 months). No statistically significant difference in PFS was observed in the indirect comparison between niraparib versus olaparib, however the non-inferiority margin proposed was not appropriate.
- 7.7 The PBAC noted that updated OS results of SOLO-2 showed borderline statistically significant OS benefit with the use of olaparib compared to placebo (HR= 0.74, 95%CI: 0.54, 1.00). Following adjustment for treatment switching using a RPSFT model the treatment effect was larger (OS HR = 0.56, 95%CI: 0.35, 0.97). The PBAC noted that the final DCO of NOVA did not demonstrate a statistically significant difference for the unadjusted OS HR (0.93, 95%CI: 0.633, 1.355) and the HR for OS after adjusting for subsequent treatment with PARPi (46%) was HR= 0.66, 95%CI: 0.44, 0.99). The PBAC noted that the adjusted OS HR and the methodology applied had not been independently evaluated as it was provided with the pre-PBAC response. The PBAC considered that it was unclear whether niraparib is non-inferior to olaparib in patients with BRCA1/2 pathogenic variants, especially given the lack of demonstrated OS benefit for niraparib compared with placebo.
- 7.8 The PBAC noted that niraparib had higher rates of grade 3-4 adverse events compared to olaparib. The PBAC also noted the shorter median treatment duration for niraparib (12 months) compared to olaparib (19.4 months) which may also reflect additional toxicity for niraparib. The PBAC considered that the safety of niraparib, using a starting dose of niraparib of 300 mg daily as in the NOVA trial, appeared inferior to olaparib based on the available data.
- 7.9 **With regard to the non-BRCAm population** the PBAC noted that compared to placebo, niraparib resulted in 5.4 months increase in median PFS with HR = 0.45 (95%CI: 0.34, 0.61). The PBAC considered that for patients with BRCAwt niraparib appeared superior in PFS to no active treatment, however the PFS benefit was difficult to interpret, especially in HRD negative patients within the BRCAwt group, given the missing long-term data for overall survival in the NOVA trial
- 7.10 The PBAC noted that at the final data cut (October 2020) a higher proportion of patients had died in the niraparib arm than the placebo arm and the unadjusted OS HR numerically favoured placebo, though there was no statistically significant difference. The PBAC noted that the NOVA trial was not powered to detect differences in OS. Further, the interpretation of OS outcomes in the final data cut were hindered by missing survival status data and information regarding subsequent treatments as a result of the high rates of discontinuations from the study.
- 7.11 The PBAC noted that, compared to standard medical management, niraparib had higher rates of grade 3-4 TEAEs (71% versus 23.7%), increased risk of SAEs (29.4%

versus 17.5%) and increased risk of treatment discontinuation due to TEAEs (15.6% versus 2.6%). The PBAC also noted the increased incidence of AML and MDS as a class effect of PARP inhibitors, and considered that long-term safety data from the NOVA trial was required to evaluate this life-threatening adverse event for niraparib. The PBAC considered that the comparative safety for niraparib was inferior to SMM.

- 7.12 The PBAC noted that, compared with the BRCAm patients, the PFS benefit appears to be reduced in the BRCAwt HRD positive population and further reduced in the BRCAwt HRD negative population. The PBAC considered it is unknown if the observed PFS improvement will be translated into an OS benefit and that to accept the sponsor's CUA model for niraparib it would be necessary to establish that there is an overall survival benefit for niraparib in the non-BRCAm population.
- 7.13 For both the economic analyses presented, the PBAC noted that there were problems with the methodology applied in translating dosing in NOVA based on dosing data for the individualised starting dose cohort in PRIMA. The PBAC considered that reducing the dose in the CUA economic model (without also adjusting the efficacy) was inappropriate and likely to result in a substantially lower ICER due to either underestimating of the cost of niraparib or overestimating the incremental benefit for niraparib. Similarly, reducing the dose for niraparib in the CMA, while assuming non-inferior efficacy is maintained was inappropriate and would lead to an inflated price for niraparib.
- 7.14 The proposed price of niraparib was based on a weighted price for the CUA and CMA populations, where the proposed cost in the non-BRCAm setting was less than [REDACTED] of the cost proposed in the BRCAm setting (\$[REDACTED] versus \$12,673.34 DPMQ per 84 capsule pack). Therefore, the price of niraparib depends on the relative proportions of patients in the 2L maintenance setting who are BRCAm and non-BRCAm. The PBAC considered that 2L utilisation of niraparib in BRCAm patients is likely to be low as the preferred place for PARP inhibitors is in 1L maintenance treatment.
- 7.15 **For the BRCAm population** the submission presented a cost-minimisation analysis comparing niraparib with olaparib. The equi-effective doses were estimated as niraparib 161 mg⁹ and olaparib 542 mg. Due to the indirect nature of the comparison of mean dose intensities across the trials, and the considerable uncertainty regarding the validity of the translated mean dose for niraparib, the PBAC considered that the equi-effective doses of niraparib and olaparib were highly uncertain. More importantly, the PBAC considered that as non-inferiority to olaparib was not accepted the CMA was not appropriate.
- 7.16 **For the non-BRCAm population** the submission presented a modelled economic evaluation comparing niraparib with SMM based on outcomes from the NOVA trial. The PBAC noted that the outcomes used in the model for the non-BRCA population

⁹ 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

included patients with sBRCAm and therefore the cost-effectiveness may be overestimated. The PBAC also noted that due to the immaturity of the 2016 OS data from NOVA, there were insufficient trial data to reliably determine the most appropriate parametric model to apply in the extrapolation and considered that the time horizon of 10 years was too long for patients in the 2L maintenance setting. In addition, the use of treatment-specific utilities, which were more divergent in the progressed disease health state, was inadequately justified. The PBAC also noted that the economic model was sensitive to the use of the translated dosing data. More importantly, the PBAC considered that with the limitations in the interpretation and applicability of the clinical data and uncertainty regarding the clinical claim, the cost-effectiveness for niraparib in the non-BRCAM population could not be assessed.

7.17 The PBAC noted that DUSC considered the patient estimates presented in the submission to be overestimated and the cost to be underestimated. PBAC agreed with DUSC that the main issues are:

- The financial estimates did not consider the impact of the recent listing of olaparib for first line maintenance treatment in patients with BRCAm. As a result, the assumed prevalence of BRCAm in the eligible population (28.9%) was likely to be considerably overestimated because an increasing majority of patients with BRCA pathogenic variants are likely to have been treated with olaparib as first line maintenance. The PBAC noted that this was revised in the pre-PBAC response.
- The number of patients switching from olaparib to niraparib is likely to be very small and the PBAC agreed with DUSC that these patients could reasonably be removed from the estimates.
- The cost offsets resulting from substitution of niraparib for use of olaparib as second and later line maintenance treatment were likely to be considerably overestimated.

7.18 The PBAC considered that a resubmission would need to address the uncertainty in the clinical claims by demonstrating an overall survival benefit for niraparib compared with standard medical management. In addition, substantial revisions to the economic models (as per paragraphs 7.15 and 7.16) and financial estimates would be required (as per paragraph 7.17).

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

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

GSK is disappointed by the PBAC's decision to not recommend niraparib (Zejula), for platinum-sensitive relapsed, high grade serous ovarian, fallopian tube, or primary peritoneal cancer in which there are limited maintenance treatment options. However, we remain committed to working with the PBAC to ensure Australian women with ovarian cancer have timely access to Zejula.