Summary Report of Benefit-Risk Assessment

ZEJULA FILM-COATED TABLET 100MG, 200MG, 300MG

NEW DRUG APPLICATION

Active Ingredient(s)	Niraparib
Product Registrant	GlaxoSmithKline Pte Ltd
Product Registration Number	SIN16459P, SIN16460P, SIN16461P
Application Route	Full evaluation
Date of Approval	01 April 2022

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A INTRODUCTION

Zejula is indicated:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy; and
- 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. The overall survival benefit in patients without germline breast cancer gene (BRCA) mutation ovarian cancer has not been demonstrated.

The active substance, niraparib, inhibits poly (ADP-ribose) polymerase enzymes (PARP-1 and PARP-2) and increases the formation of PARP-DNA complexes resulting in DNA damage and apoptosis of tumour cells.

Zejula film coated tablets contain 100 mg, 200 mg or 300 mg of niraparib (as niraparib tosylate monohydrate). The excipients used are crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and silicon dioxide. Components of the film coat include polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, ferrosferric oxide, FD&C Blue #2 (for 200 mg), FD&C Blue #1 (for 300 mg) and yellow iron oxide (for 300 mg).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, niraparib as niraparib tosylate monohydrate, is manufactured at Changzhou SynTheAll Pharmaceutical Co., Ltd, Changzhou, China. The drug products, Zejula Film-coated Tablet 100 mg, 200 mg and 300 mg, are manufactured at Mayne Pharma, Inc., Greenville, United States of America.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented was adequate to support the approved storage condition and re-test period. The drug substance was packed in low-density polyethylene (LDPE) continuous liner sealed with a clamp, followed by packaging into another LDPE bag and sealed with a cable tie, thereafter, packaging into a high-density polyethylene (HDPE) drum which is sealed

with a clamp and locking ring. The drug substance is approved for storage at or below 25°C with a re-test period of 48 months.

Drug product:
The tablet is manufactured using a dry granulation approach, followed by film-coating. The process is considered a standard process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30 ºC. The container closure system is a OPA/aluminium/PVC/aluminium/vinyl/acrylic blister pack containing 7 tablets per blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of niraparib was supported by two pivotal clinical studies, Study PR-30-5011-C (NOVA) for the maintenance treatment of recurrent ovarian cancer, and Study PR-30-5017C (PRIMA) for the maintenance treatment of advanced ovarian cancer.

During the clinical development, the capsule formulation was used in the clinical studies. Bioequivalence between niraparib capsule and the commercial tablet formulation was demonstrated in Study 3000-01-004, which was a Phase 1, open-label, two-stage, randomised, single-dose, crossover, fasted, bioequivalence study in patients with advanced solid tumours. The calculated 90% confidence interval (CI) of the geometric means ratios for ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} between niraparib capsule and niraparib tablet were within the bioequivalence prespecified acceptance range of 0.800 and 1.250.

<u>Recurrent ovarian cancer</u>

The NOVA study was a Phase 3, randomised, double-blind, placebo-controlled study that compared niraparib with placebo as maintenance treatment in female adult patients with recurrent, high-grade serous epithelial ovarian cancer who were in complete or partial response for more than 6 months after their penultimate platinum-based chemotherapy. All patients were to have completed at least two previous courses of platinum-containing therapy, not have any measurable lesion >2 cm at study entry and have CA-125 levels that were normal following their last platinum regimen or had decreased by >90% during their last regimen and stable (no increase by >15%) for at least 7 days. Patients were enrolled into two cohorts based on the presence (gBRCAmut) or absence (non-gBRCAmut) of germline BRCA mutation.

Patients were randomised within 8 weeks after completion of their last dose of platinum-based chemotherapy in a 2:1 ratio to receive either oral niraparib 300 mg (three capsules of 100 mg

capsule) or placebo (three matching capsules) once daily in continuous 28-day cycles. The randomisation in each cohort was stratified by time to progression after the penultimate platinum therapy before enrolment (6 to <12 months and ≥12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR or PR). The dose of niraparib could be interrupted and/or reduced to a minimum dose of 100 mg once daily during the study if the patient experienced adverse reactions. Treatment with study drug was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Patients who were randomised to the placebo arm were not allowed to cross over to receive niraparib treatment at any time during the study.

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from randomisation to first documentation of progression or death due to any cause as determined by the blinded independent central review (BICR). The secondary efficacy endpoints were the time to first subsequent treatment (TFST), time to second subsequent treatment (TSST), chemotherapy-free interval (CFI), progression-free survival 2 (PFS2), overall survival (OS), time to CA-125 progression, and patient-reported outcomes.

The primary hypothesis on PFS was independently tested for each of the gBRCAmut and non-gBRCAmut cohort to control the type I error rate. Within the non-gBRCAmut cohort, the primary hypothesis was first tested in patients with homologous recombinant (HR) deficient tumour. If the study rejected the primary hypothesis in the HR deficient tumour patient population within the non-gBRCAmut cohort, the non-gBRCAmut cohort regardless of HR tumour status would then be tested for the primary hypothesis. Otherwise, PFS was to be analysed as exploratory endpoint in the overall non-gBRCAmut cohort. The secondary efficacy endpoints were to be analysed in the same manner as that for the primary efficacy endpoint.

A total of 553 patients were randomised into the study, comprising 372 patients in the niraparib arm and 181 patients in the placebo arm. Of these, 36.7% were enrolled into the gBRCAmut cohort and 63.3% of patients were enrolled into the non-gBRCAmut cohort. Among those in the non-gBRCAmut cohort, 46.3% of patients had HR deficient tumour, 38.3% of patients had HR proficient tumour, while the HR tumour status was not available for 15.4% of patients. The median treatment duration was 8.2 months (range: 0 - 61 months) in the niraparib arm and 5.4 months (range: 0 - 65 months) in the placebo arm.

The patient demographics and baseline characteristics were well-balanced between the treatment arms and patient cohorts. The median age was 60.0 years (range: 33 – 84 years), and 35.3% of patients were ≥65 years of age. The majority of patients were White (86.8%), had ovary as the primary tumour site (83.7%) and had serous histology tumours (94.4%). Within the gBRCAmut cohort, 63% of patients had gBRCA1 mutation variant and 34.0% had gBRCA2 mutation variant. Most of the patients (68.2%) had received 2 prior lines of platinum therapy, including 57.1% of patients in gBRCAmut cohort and 74.6% of patients in the non-gBRCAmut cohorts.

The results showed that maintenance treatment with niraparib demonstrated statistically significantly improved PFS compared with placebo in the gBRCAmut cohort (hazard ratio 0.27; 95% CI: 0.173 – 0.410; p<0.0001) and the non-gBRCAmut cohort (hazard ratio 0.45; 95% CI: 0.338 – 0.607; p<0.0001). Within the non-gBRCAmut cohort, statistically significantly improvement in PFS was similarly observed with niraparib compared with placebo in patients with HR deficient tumour (hazard ratio 0.38; 95% CI: 0.243 – 0.586; p<0.0001). The results of the secondary endpoints (TFST, CFI, PFS2, TSST) supported the primary endpoint findings.

The final OS analysis was confounded due to high percentage of missing survival status data (49%), subsequent PARP inhibitors use after progression in the placebo arm (46%), and missing information on subsequent PARP inhibitor use during follow-up (31%). Hence, no conclusion can be drawn on the survival benefits in either the gBRCAmut cohort or the non-BRCAmut cohort.

Pre-specified subgroup analyses demonstrated consistent treatment effect for the primary endpoint across subgroups analysed in the gBRCAmut and non-gBRCAmut cohorts, including age group (18 to <65 years, ≥65 years), race (White, Other), region (USA and Canada, rest of world), time to progression before study enrolment (6 to <12 months, ≥12 months), bevacizumab use (yes, no), best overall response on last platinum regimen (CR, PR), total cumulative number of prior chemotherapy (2, >2), total number of prior platinum regimen (2, >2), and BRCA mutation variant in the gBRCAmut cohort (BRCA1, BRCA2).

Summary of Key Efficacy Results (NOVA study)

	Niraparib	**Placebo**	**Hazard ratio [c] (95% CI)**	**p-value [d]**
Primary endpoint, Progression-free survival (PFS)				
gBRCAmut cohort, n	138	65		
Median PFS (months) [a]	21.0	5.5	0.27	<0.0001
95% CI	(12.9 – NE)	(3.8 – 7.2)	(0.173 – 0.410)	
Non-gBRCAmut cohort, n	234	116		
Median PFS (months) [a]	9.3	3.9	0.45	<0.0001
95% CI	(7.2 – 11.2)	(3.7 – 5.5)	(0.338 – 0.607)	
Non-gBRCAmut/HR deficient cohort, n	106	56		
Median PFS (months) [b]	12.9	3.8	0.38	<0.0001
95% CI	(8.1 – 15.9)	(3.5 – 5.7)	(0.243 – 0.586)	
Non-gBRCAmut/HR proficient cohort, n	92	42		
Median PFS (months) [b]	6.9	3.8	0.58	0.0226
95% CI	(5.6 – 9.6)	(3.7 – 5.6)	(0.361 – 0.922)	
Secondary endpoint, Overall Survival (OS)				
gBRCAmut cohort, n	138	65		
Median OS (months) [a]	43.6	41.6	0.93	0.6934
95% CI	(35.8 – 53.0)	(29.3 – 52.9)	(0.633 – 1.355)	
Non-gBRCAmut cohort, n	234	116		
Median OS (months) [a]	31.1	36.5	1.10	0.5010
95% CI	(27.8 – 37.3)	(27.9 – 41.6)	(0.831 – 1.459)	
Secondary endpoint, Progression-free survival after the first subsequent therapy (PFS2)				
gBRCAmut cohort, n	138	65		
Median PFS2 (months) [a]	30.4	22.7	0.67	0.0224
95% CI	(25.0 – 33.4)	(17.8 – 25.6)	(0.479 – 0.948)	
Non-gBRCAmut cohort, n	234	116		
Median PFS2 (months) [a]	18.5	15.6	0.81	0.1149
95% CI	(16.8 – 21.7)	(13.2 – 22.8)	(0.632 – 1.050)	
Secondary endpoint, Time to first subsequent therapy (TFST)				
gBRCAmut cohort, n	138	65		
Median TFST (months) [a]	19.1	8.6	0.54	0.0002
95% CI	(15.0 – 21.9)	(6.7 – 11.2)	(0.384 – 0.747)	
Non-gBRCAmut cohort, n	234	116		

Median TFST (months) [a] 95% CI	11.8 (9.9 – 13.6)	7.4 (5.8 – 8.7)	0.62 (0.481 – 0.797)	0.0002
Secondary endpoint, Chemotherapy-free interval (CFI)				
gBRCAmut cohort, n Median TFST (months) [b] 95% CI	138 22.8 (17.9 – NE)	65 9.4 (7.9 – 10.6)	 0.26 (0.166 – 0.409)	 <0.0001
Non-gBRCAmut cohort, n Median TFST (months) [b] 95% CI	234 12.7 (11.0 – 14.7)	116 8.6 (6.9 – 10.0)	 0.50 (0.370 – 0.666)	 <0.0001

BICR: blinded independent central review; CI: confidence interval; CFI: chemotherapy-free interval; gBRCAmut: germline breast cancer gene mutation; HR: homologous recombination; n: number of patients; NE: not estimated; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival 2; TFST: time to first subsequent therapy

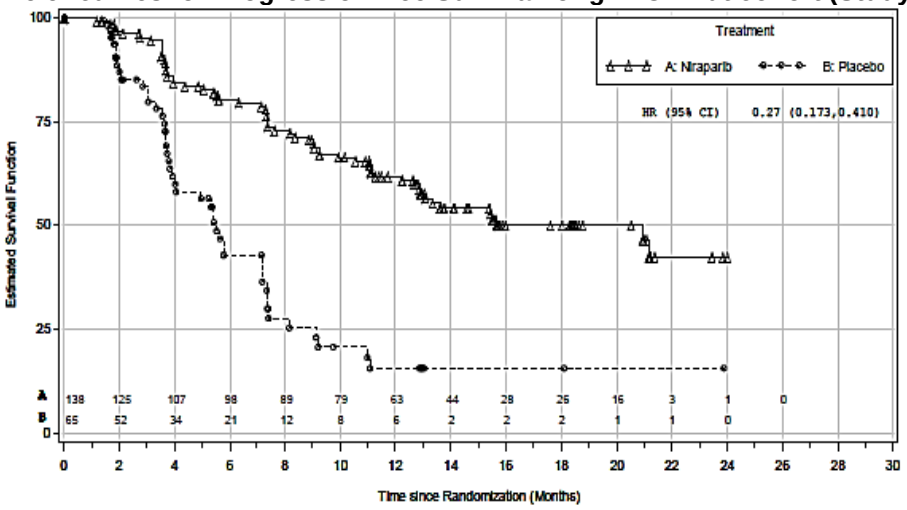
[a] Based on final analyses at data cut-off date of 1 October 2020.

[b] Based on data cut-off date of 30 May 2016.

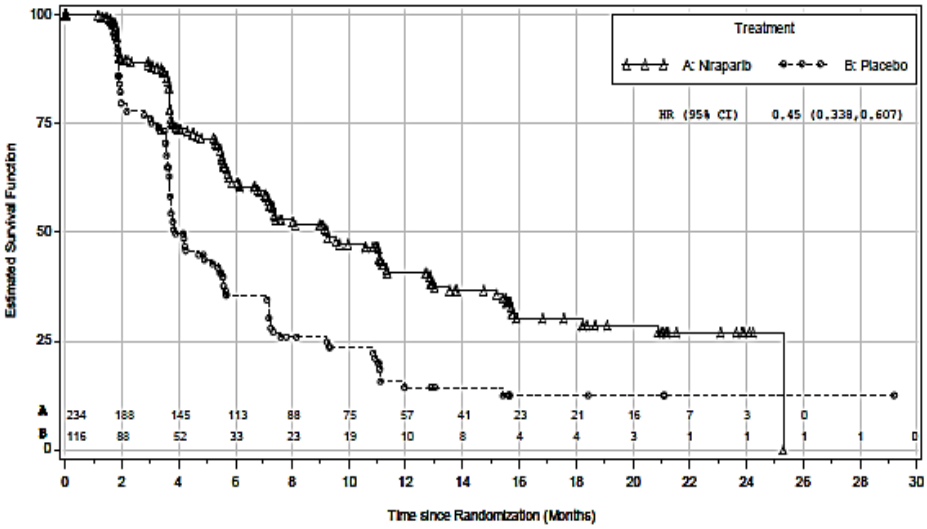
[c] Niraparib versus placebo, based on the stratified Cox proportional hazards model using randomisation stratification factors.

[d] Based on stratified log-rank test using randomisation stratification factors

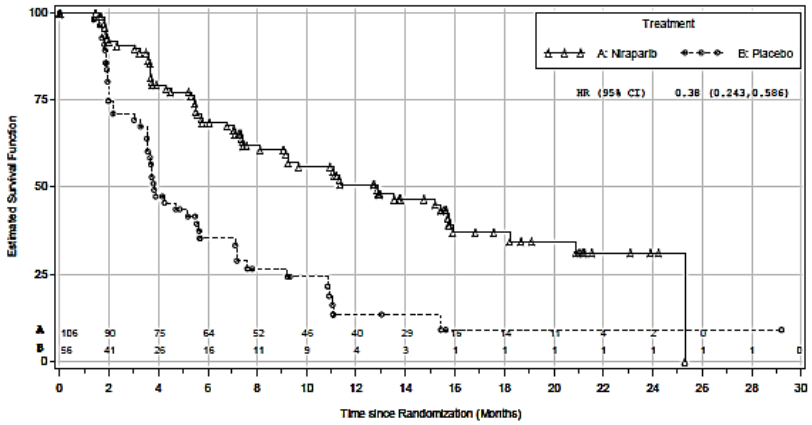
Kaplan-Meier curves for Progression-free Survival for gBRCAmut cohort (Study NOVA)



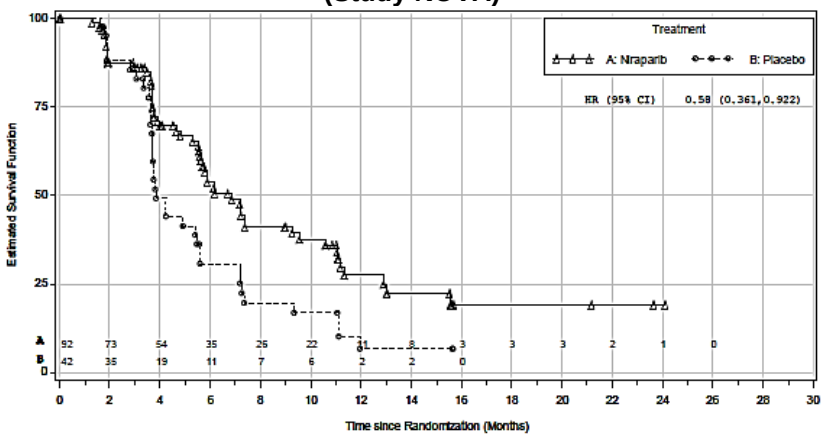
Kaplan-Meier curves for Progression-free Survival for non-gBRCAmut cohort (Study NOVA)



Kaplan-Meier curves for Progression-free Survival for non-gBRCAmut/HR deficient cohort (Study NOVA)



Kaplan-Meier curves for Progression-free Survival for non-gBRCAmut/HR proficient cohort (Study NOVA)



Overall, the results in NOVA study supported the treatment benefit of niraparib in the maintenance treatment of patients with platinum-sensitive, relapsed, and high grade serous epithelial ovarian cancer who are in response to platinum-based chemotherapy. The survival benefit in patients without germline BRCA mutation ovarian cancer has not been demonstrated.

Advanced ovarian cancer

The PRIMA study was a Phase 3, randomised, double-blind, placebo-controlled study that compared niraparib with placebo as maintenance treatment in female adult patients with advanced (FIGO Stage III or IV) epithelial high-grade ovarian cancer who are in complete or partial response following completion of their first-line platinum-containing chemotherapy.

Patients were initially randomised within 12 weeks after completion of their last chemotherapy cycle in a 2:1 ratio to receive either a fixed starting dose of niraparib 300 mg (three capsules of 100 mg capsules) or placebo (three matching capsules) once daily in continuous 28-day cycles (referred to as the fixed starting dose cohort). The randomisation was stratified by best response to first-line platinum chemotherapy, receipt of neoadjuvant chemotherapy, and HR tumour status.

At protocol amendment 2, the starting dose was modified and assigned based on individual patient's baseline body weight and/or platelet count (referred to as the individualised starting dose cohort). Patients who were randomised to niraparib arm and had a baseline body weight of ≥77kg and baseline platelet count of ≥150,000/μL were assigned to receive a starting dose of 300 mg niraparib, while patients who had a baseline body weight of <77kg or baseline platelet count of <150,000/μL were assigned to receive a starting dose of 200 mg niraparib. The dose of niraparib could be escalated to 300 mg for patients who had received a starting dose of 200 mg if there was no treatment interruption of discontinuation due to adverse reactions during the first two cycles of treatment.

For the fixed starting dose and individualised starting dose cohorts, the dose of niraparib could be interrupted and/or reduced up to a minimum dose of 100 mg once daily during the study if the patient experienced adverse reactions. Treatment with study drug was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Patients who were randomised to the placebo arm were not allowed to cross over to receive niraparib treatment at any time during the study.

The primary efficacy endpoint was PFS assessed by BICR. The key secondary efficacy endpoint was OS. Other secondary endpoints included TFST, PFS2, time to CA-125 progression, outcomes for the next anticancer therapy following study treatment, and patient-reported outcomes. The primary hypothesis (PFS) was tested in hierarchical order to control the type I error rate. If the study rejected the primary hypothesis in the patient population with HR deficient tumour, the overall intent-to-treat (ITT) population regardless of HR tumour status would then be tested for the primary hypothesis. Otherwise, PFS was to be analysed as exploratory endpoint in the overall ITT population. The secondary efficacy endpoints were to be analysed in the same manner as for the primary efficacy endpoint. An interim analysis of OS was performed at the time of the primary PFS analysis with appropriate adjustment for multiplicity.

A total of 733 patients were randomised into the study, comprising 487 patients in the niraparib arm and 246 patients in the placebo arm. A total of 30.4% of patients in the overall ITT population had BRCAmut tumour and 50.9% of patients had HR deficient tumour. The median treatment duration was 11.1 months (range: 0 to 29 months) in the niraparib arm and 8.3 months (range: 0 to 28 months) in the placebo arm.

The patient demographics and baseline characteristics were well-balanced between the treatment arms. The median age was 62.0 years (range: 32 - 88 years), and 30.0% of patients were ≥65 years of age. The majority of patients were White (89.3%), had ovary as the primary tumour site (80.4%), and had serous histology tumours (94.8%). Of the 223 patients with BRCAmut tumour, 66.4% of patients had BRCA1 mutation variant and 33.6% had BRCA2 mutation variant.

The results showed that maintenance treatment with niraparib demonstrated statistically significant improvements in PFS compared with placebo in the HR deficient tumour patient population (hazard ratio 0.43; 95% CI: 0.310 – 0.588; p<0.0001) and the overall ITT population (hazard ratio 0.62; 95% CI: 0.502 – 0.755; p<0.0001).

The key secondary endpoint of OS was immature at the data cut-off date of 17 May 2019 with only 79 death events, including 48 (9.9%) patients in the niraparib arm and 31 (12.7%) patients in the placebo arm. The hazard ratio for OS was 0.61 (95% CI: 0.265 – 1.388) in the HR deficient tumour patient population and 0.70 (95% CI: 0.442 – 1.106) in the overall ITT population. Similarly, the data for the other secondary endpoints (TFST and PFS2) were

immature as of the data cut-off date. Nonetheless, the secondary endpoint results showed a trend that favoured the niraparib arm.

The post-hoc exploratory analyses demonstrated comparable PFS benefit between the fixed starting dose cohort (hazard ratio 0.62; 95% CI: 0.465 – 0.833) and the individualised starting dose cohort (hazard ratio 0.68; 95% CI: 0.49 – 0.94) in the overall ITT population. Within the HR deficient tumour patient population, comparable PFS benefit was observed between the fixed starting dose cohort (hazard ratio 0.46; 95% CI: 0.296 – 0.706) and the individualised starting dose cohort (hazard ratio 0.54; 95% CI: 0.33 – 0.91).

Pre-specified subgroup analyses demonstrated consistent treatment effect for the primary endpoint across subgroups analysed in the overall population and HR deficient tumour patient population, including age group (<65years, ≥65 years), race (White, non-White), ECOG performance status (0, 1), stage of disease at initial diagnosis (stage III, stage IV), receipt of neoadjuvant chemotherapy (yes, no), best response to first-line platinum regimen (CR, PR), tumour BRCA status (tBRCA mutation, tBRCA wild-type), baseline CA-125 level (≤upper limit of normal [ULN], >ULN), region (North America, rest of world), and HR tumour status (HR deficient, HR proficient, HR not determined).

Summary of Key Efficacy Results (PRIMA study)

	Niraparib	**Placebo**	**Hazard ratio [b] (95% CI)**	**p-value [c]**
Primary endpoint, Progression-free survival (PFS) [a]				
HR deficient population, n	247	126		
Median PFS (months)	21.9	10.4	0.43	<0.0001
95% CI	(19.3, NE)	(8.1, 12.1)	(0.310 – 0.588)	
Overall ITT population, n	487	246		
Median PFS (months)	13.8	8.2	0.62	<0.0001
95% CI	(11.5, 14.9)	(7.3, 8.5)	(0.502 – 0.755)	
Key secondary endpoint, Overall Survival (OS) [a]				
HR deficient population, n	247	126		
Median OS (months)	30.3	NE	0.61	0.2323
95% CI	(30.3, NE)	(25.0, NE)	(0.265 – 1.388)	
Overall ITT population, n	487	246		
Median OS (months)	30.3	NE	0.70	0.1238
95% CI	(30.3, NE)	(25.0, NE)	(0.442 – 1.106)	
Secondary endpoint, Progression-free survival after the first subsequent therapy (PFS2)				
HR deficient population, n	247	126		
Median PFS2 (months)	NE	NE	0.84	0.5311
95% CI	(25.3, NE)	(NE, NE)	(0.485 – 1.453)	
Overall ITT population, n	487	246		
Median PFS2 (months)	27.2	NE	0.81	0.2242
95% CI	(25.3, NE)	(NE, NE)	(0.577 – 1.139)	
Secondary endpoint, Time to first subsequent therapy (TFST)				
HR deficient population, n	247	126		
Median TFST (months)	NE	13.7	0.46	<0.0001
95% CI	(24.7, NE)	(11.6, 19.3)	(0.330 – 0.640)	
Overall ITT population, n	487	246		
Median TFST (months)	18.6	12.0	0.65	0.0001
95% CI	(15.8, 24.7)	(10.3, 13.9)	(0.521 – 0.802)	

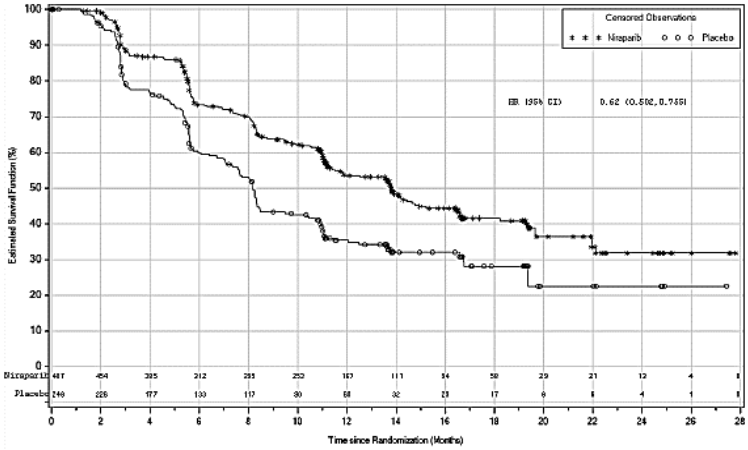
BICR: blinded independent central review; CI: confidence interval; HR: homologous recombination; ITT: intent-to-treat; n: number of patients; NE: not estimated; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival 2; TFST: time to first subsequent therapy

[a] Based on data cut-off date of 17 May 2019.

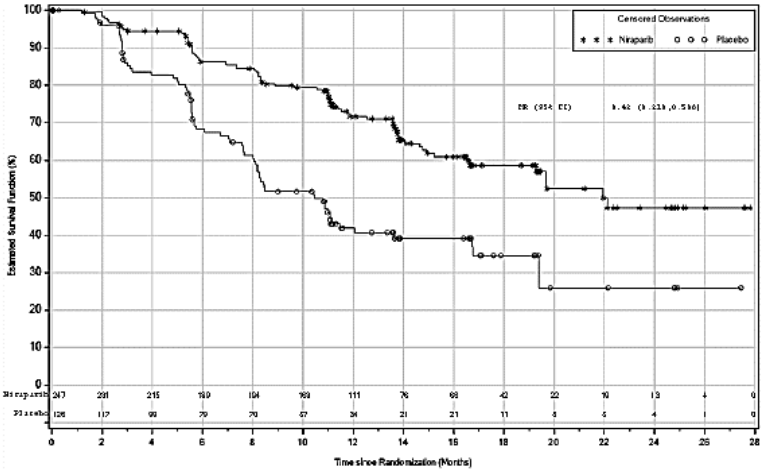
[b] Niraparib versus placebo, based on the stratified Cox proportional hazards model using randomisation stratification factors.

[c] Based on stratified log-rank test using randomisation stratification factors

Kaplan-Meier curves for Progression-free Survival for Overall ITT population (Study PRIMA)



Kaplan-Meier curves for Progression-free Survival for HR deficient cohort (Study PRIMA)



Overall, the results in PRIMA study supported the efficacy of niraparib in the maintenance treatment of patients with advanced epithelial high-grade ovarian cancer who are in response following completion of first-line platinum-based chemotherapy.

D ASSESSMENT OF CLINICAL SAFETY

Recurrent ovarian cancer

The safety data on the use of niraparib in the maintenance treatment of recurrent ovarian cancer were mainly derived from Study NOVA, comprising a total of 546 patients (367 patients in the niraparib arm and 179 patients in the placebo arm). The median treatment duration was 8.2 months (range: 0 – 61 months) in the niraparib arm and 5.4 months (range: 0 – 65 months) in the placebo arm.

Overall of Safety Profile (Study NOVA, Safety Analysis Set)

Number (%) of patients with:	Niraparib (N=367)	Placebo (N=179)
Any TEAE	367 (100)	172 (96.1)
Any study drug-related TEAE	359 (97.8)	126 (70.4)
Any TEAE grade ≥3 in severity	280 (76.3)	42 (23.5)
Any study drug-related TEAE grade ≥3 in severity	242 (65.9)	8 (4.5)
Any serious TEAE	123 (33.5)	27 (15.1)
Any study drug-related serious TEAE	69 (18.8)	2 (1.1)
Any TEAE with outcome death	3 (0.8%)	0
Any TEAE leading to dose reduction of study drug	254 (69.2)	9 (5.0)
Any TEAE leading to dose interruption of study drug	254 (69.2)	26 (14.5)
Any TEAE leading to discontinuation of study drug	64 (17.4)	4 (2.2)

N: number of patients; TEAE: treatment-emergent adverse event

The percentage of patients who experienced study drug-related treatment-emergent adverse events (TEAEs) was higher in niraparib arm (97.8%) compared to the placebo arm (70.4%). TEAEs related to study drug that were reported more frequently in niraparib arm compared to the placebo arm included nausea (69.5% vs 25.7%), anaemia (48.0% vs 4.5%), thrombocytopenia (45.2% vs 2.2%), fatigue (38.4% vs 21.8%), vomiting (24.8% vs 6.1%), constipation (23.4% vs 9.5%), platelet count decreased (21.0% vs 1.7%), decreased appetite (20.2% vs 9.5%), neutropenia (17.7% vs 2.8%), asthenia (15.0% vs 5.0%), neutrophil count decreased (13.9% vs 1.7%), diarrhoea (12.5% vs 10.1%), headache (12.0% vs 3.9%), white blood cell count decreased (11.2% vs 2.2%), insomnia (10.6% vs 2.8%) and dizziness (10.1% vs 2.8%). Patients treated with a starting dose of 300 mg niraparib compared to 200 mg niraparib reported higher rates of TEAEs of nausea (67.8% vs 26.8%), thrombocytopenia (45.2% vs 24.8%), and fatigue (34.1% vs 26.0%).

Grade 3 or 4 TEAEs related to study drug were reported in 65.9% of patients in niraparib arm and 4.5% of patients in the placebo arm. The commonly reported grade 3 or 4 TEAEs related to study drug that were reported more frequently in niraparib arm compared to the placebo arm included thrombocytopenia (28.6% vs 0.6%), anaemia (25.3% vs 0%), neutropenia (11.4% vs 0.6%), neutrophil count decreased (9.3% vs 0.6%) and platelet count decrease (7.9% vs 0%). Patients treated with a starting dose of 300 mg niraparib compared to 200 mg niraparib reported higher rates of grade 3 or 4 TEAEs of thrombocytopenia (28.1% vs 5.1%), anaemia (15.0% vs 15.7%), neutrophil count decreased (8.4% vs 2.4%), platelet count decreased (7.1% vs 0.8%), neutropenia (9.5% vs 5.9%), hypertension (4.6% vs 4.7%) and fatigue (5.2% vs 1.2%).

TEAEs that led to the permanent discontinuation of study drug were reported more frequently in niraparib arm than the placebo arm (17.4% vs 2.2%). The difference was driven by higher percentage of patients in niraparib arm compared to the placebo arm who experienced fatigue (2.5% vs 0%), thrombocytopenia (2.2% vs 0.6%), nausea (1.9% vs 0%), platelet count decreased (1.6% vs 0%), anaemia (1.4% vs 0%), and neutrophil count decreased (1.1% vs 0%). A higher percentage of patients in the niraparib arm (69.2%) had at least one dose reduction of study drug due to TEAE as compared to the placebo arm (5.0%). TEAEs that led to the dose reduction of study drug that were reported more frequently in niraparib arm than the placebo arm included thrombocytopenia (30.2% vs 0.6%), anaemia (18.0% vs 0%), platelet count decreased (10.4% vs 0%) and nausea (5.2% vs 0%).

There were 3 cases of deaths in the niraparib arm, of which, 2 deaths were due to acute myelogenous leukaemia (AML) that were assessed by the Investigator to be related to

niraparib. The other death event was due to sepsis and acute kidney injury and was assessed by the Investigator to be likely related to niraparib.

The notable safety concerns with niraparib in Study NOVA were myelosuppression, myelodysplastic syndrome (MDS)/AML, and hypertension. The incidence of MDS/AML was higher in niraparib arm (3.0%) as compared to the placebo arm (1.7%). The increased risk and causality of MDS/AML events with niraparib were not well-defined given the background medical history of these patients who had been exposed to multiple prior lines of chemotherapies and the longer duration of exposure to niraparib than placebo. There were higher proportion of patients in the niraparib arm compared to the placebo arm who experienced hypertension events (23% vs 5%), grade 3 or 4 hypertension event (9% vs 2%) and grade 3 hypertensive crisis (<1% vs 0%). These safety concerns have been described in the relevant sections of the package insert including recommendations for dose interruptions and/or modifications to manage myelosuppression, warnings and precautions. These AEs will be monitored as part of routine pharmacovigilance.

Advanced ovarian cancer

The safety data on the use of niraparib in the maintenance treatment of advanced ovarian cancer were mainly derived from Study PRIMA, comprising a total of 728 patients (484 patients in niraparib arm and 244 patients in placebo arm). The total exposure of patients to study drug was longer in niraparib arm (median 11.1 months; range 0.0 – 29.0 months) compared to the placebo arm (median 8.3 months; range 0.0 – 28.0 months).

Overall of Safety Profile (Study PRIMA, Safety Analysis Set)

Number (%) of patients with:	**Niraparib (N=484)**	**Placebo (N=244)**
Any TEAE	478 (98.8)	224 (91.8)
Any study drug-related TEAE	466 (96.3)	168 (68.9)
Any TEAE grade ≥3 in severity	341 (70.5)	46 (18.9)
Any study drug-related TEAE grade ≥3 in severity	316 (65.3)	16 (6.6)
Any serious TEAE	156 (32.2)	32 (13.1)
Any study drug-related TEAE	118 (24.4)	6 (2.5)
Any TEAE with outcome death	2 (0.4)	1 (0.4%)
Any TEAE leading to dose reduction of study drug	343 (70.9)	20 (8.2)
Any TEAE leading to dose interruption of study drug	385 (79.5)	44 (18.0)
Any TEAE leading to discontinuation of study drug	58 (12.0)	6 (2.5)

N: number of patients; TEAE: treatment-emergent adverse event

The percentage of patients who experienced study drug-related TEAEs was higher in niraparib arm (96.3%) than placebo arm (68.9%). TEAEs related to study drug that were reported more frequently in niraparib arm compared to the placebo arm included anaemia (60.5% vs 12.7%), nausea (50.6% vs 20.1%), thrombocytopenia (45.2% vs 3.3%), fatigue (29.8% vs 23.0%), platelet count decreased (26.9% vs 1.2%), neutropenia (26.0% vs 5.7%), and constipation (25.8% vs 5.7%). Patients in the individualised starting dose cohort experienced lower incidences of TEAEs compared to the fixed starting dose cohort, including TEAEs of anaemia (49.7% vs 70.8%), thrombocytopenia (33.7% vs 52.4%), constipation (31.4% vs 43.2%), vomiting (16.6% vs 25.4%), platelet count decreased (22.5% vs 30.2%), diarrhoea (13.6% vs 21.6%), neutrophil count decreased (12.4% vs 19.4%), headache (21.9% vs 28.3%), and abdominal pain (17.8% vs 24.1%).

Grade 3 or 4 TEAEs related to study drug were reported in higher percentage of patients in the niraparib arm (65.3%) as compared to the placebo arm (6.6%). The commonly reported grade 3 or 4 TEAEs related to study drug included anaemia (30.2% vs 0.4%), thrombocytopenia (28.7% vs 0%), neutropenia (12.4% vs 0.8%), platelet count decreased (13.0% vs 0%) and neutrophil count decreased (7.6% vs 0%). The individualised starting dose cohort experienced lower incidences of grade 3 or 4 TEAEs as compared to the fixed starting dose cohort (60.4% vs 75.9%).

TEAEs that led to the permanent discontinuation of study drug were reported more frequently in niraparib arm than the placebo arm (12.0% vs 3.0%). The difference was driven by higher percentage of patients who experienced thrombocytopenia (3.7% vs 0%), anaemia (1.9% vs 0%), neutropenia (1.2% vs 0%), nausea (1.2% vs 0%), platelet count decreased (0.6% vs 0%), neutrophil count decreased (0.6% vs 0%), fatigue (0.8% vs 0%) and dizziness (0.6% vs 0%). A higher percentage of patients experienced at least one dose reduction of study drug due to TEAEs in niraparib arm (70.9%) compared to the placebo arm (8.2%). TEAEs leading to dose reduction of study drug that were reported more frequently in niraparib arm compared to the placebo arm included thrombocytopenia (50.8% vs 2.0%), anaemia (27.1% vs 0.8%), neutropenia (8.1% vs 1.2%), platelet count decreased (18.6% vs 0%), neutrophil count decreased (5.0% vs 1.6%) and nausea (2.9% vs 0%).

There were 2 cases of deaths in the niraparib arm and 1 case of death in the placebo arm. The death events were assessed by the Investigator as not related to study drug.

Similar to Study NOVA, the major safety concerns with niraparib in Study PRIMA were myelosuppression, MDS/AML, and hypertension. MDS/AML was reported in 1 patient (0.2%) in niraparib arm and none in the placebo arm. A higher percentage of patients in niraparib arm experienced hypertension event (18% vs 7%) and grade 3 or 4 hypertension event (6% vs 1%) as compared to the placebo arm. There was no hypertensive crisis event reported in Study PRIMA. These safety concerns have been described in the dosing regimen, warnings and precaution, and/or adverse drug reaction section of the package insert and will be monitored as part of routine pharmacovigilance.

Overall, the safety profile of niraparib was considered acceptable for the intended population given the poor prognosis of the disease. The individualised starting dose regimen of niraparib presented a more tolerable safety profile compared to the fixed starting dose regimen. Appropriate warnings and precautions have been put in place in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Advanced and recurrent ovarian cancer are serious, life-threatening and incurable diseases. The majority of patients experienced disease recurrence despite good response to first-line standard of care and may eventually become resistant or refractory to repeated rounds of platinum-containing chemotherapy.

The NOVA study demonstrated that niraparib as maintenance treatment for platinum-sensitive recurrent ovarian cancer showed statistically significantly improvement in median PFS of 21 months compared to 5.5 months in the placebo arm in patients with gBRCAmut tumours (hazard ratio 0.27; 95% CI: 0.173 – 0.410). Consistent results were observed in the non-gBRCAmut and HR deficient recurrent ovarian tumour cohort with a median PFS of 9.3 months

in the niraparib arm vs 3.9 months in the placebo arm (hazard ratio 0.38; 95% CI: 0.243 – 0.586). The OS benefit in patients without gBRCAmut tumours has not been demonstrated.

The PRIMA study demonstrated that niraparib as maintenance treatment for advanced ovarian cancer in patients who were in response to first-line platinum-based chemotherapy showed statistically significantly improvement in median PFS of 21.9 months compared to 10.4 months in the placebo arm in patients with HR deficient tumour (hazard ratio 0.43; 95% CI: 0.310 – 0.588).

The safety profile of niraparib was considered acceptable relative to its treatment benefit considering the poor prognosis of the disease. Niraparib-related myelosuppression and hypertension could be managed through dose interruption, dose reduction and/or treatment discontinuation. These safety concerns have been adequately addressed in the package insert with relevant warnings and precautions as well as dose adjustment recommendations. The potential risk of MDS/AML with niraparib will be monitored as part of routine pharmacovigilance.

Overall, the benefit-risk profile of niraparib in the maintenance treatment of adult patients with advanced or relapsed high-grade ovarian cancer who are in response to platinum-based chemotherapy was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of niraparib outweighed the risks in the maintenance treatment of:

- Patients with platinum-sensitive relapsed high grade ovarian cancer who are in response to platinum-based chemotherapy; and
- Patients with advanced high-grade ovarian cancer who are in response following completion of first-line platinum-based chemotherapy.

Approval of the product registration was granted on 01 April 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

ZEJULA

Niraparib

QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablet

ZEJULA 100 mg tablet is gray, oval-shaped, film-coated tablet debossed with “100” on one side and “Zejula” on the other.

ZEJULA 200 mg tablet is blue, oval-shaped, film-coated tablet debossed with “200” on one side and “Zejula” on the other.

ZEJULA 300 mg tablet is green, oval-shaped, film-coated tablet debossed with “300” on one side and “Zejula” on the other.

Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg, 200 mg or 300 mg niraparib.

CLINICAL INFORMATION

Indications

ZEJULA is indicated:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

- 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. The overall survival benefit in patients without germline BRCA mutation ovarian cancer has not been demonstrated (see *Clinical Studies* section).

Dosage and Administration

Pharmaceutical Form

Tablet.

Posology

First-line ovarian cancer maintenance treatment

The recommended starting dose of *ZEJULA* is 200 mg taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/μL, the recommended starting dose of *ZEJULA* is 300 mg taken once daily.

For the maintenance treatment of advanced ovarian cancer, patients should start treatment with *ZEJULA* no later than 12 weeks after their most recent platinum-containing regimen.

Recurrent ovarian cancer maintenance treatment

The dose is 300 mg once daily.

Patients with low body weight in recurrent ovarian cancer maintenance treatment
Approximately 25 % of patients in the NOVA study weighed less than 58 kg, and approximately 25 % of patients weighed more than 77 kg. The incidence of Grade 3 or 4 ADRs was greater among low body weight patients (78 %) than high body weight patients (53 %). Only 13 % of low body weight patients remained at a dose of 300 mg beyond Cycle 3. A starting dose of 200 mg for patients weighing less than 58 kg may be considered.

For the maintenance treatment of recurrent ovarian cancer, patients should start treatment with *ZEJULA* no later than 8 weeks after their most recent platinum-containing regimen.

Patients should be encouraged to take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.

Treatment should be continued until disease progression or unacceptable toxicity.

Missing dose
If patients miss a dose, they should take their next dose at its regularly scheduled time.

Dose adjustments for adverse reactions
Recommendations for dose modifications for adverse reactions are provided in Tables 1, 2 and 3.

In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to interrupt the treatment and then resume at the lower dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that *ZEJULA* be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that ZEJULA be discontinued.

Table 1: Recommended dose modifications for adverse reactions

Starting dose	200 mg/day	300 mg/day
First dose reduction	100 mg/day	200 mg/day
Second dose reduction	Discontinue medication.	100 mg/day[a]

[a]If further dose reduction below 100 mg/day is required, discontinue *ZEJULA*.

Table 2: Dose modifications for non-haematological adverse reactions

Non-haematological CTCAE[a] ≥ Grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	First occurrence: • Withhold *ZEJULA* for a maximum of 28 days or until resolution of adverse reaction. • Resume *ZEJULA* at a reduced dose level per Table 1.
	Second occurrence: • Withhold *ZEJULA* for a maximum of 28 days or until resolution of adverse reaction. • Resume *ZEJULA* at a reduced dose or discontinue per Table 1.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered *ZEJULA* 100 mg/day	Discontinue treatment.

[a]CTCAE=Common Terminology Criteria for Adverse Events

Table 3: Dose modifications for haematological adverse reactions

Haematological adverse reactions have been observed during the treatment with *ZEJULA* especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts (CBCs) weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor CBCs monthly and periodically after this time (see *Warnings and Precautions*). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematological adverse reaction requiring transfusion or haematopoietic growth factor support	• For patients with platelet count ≤ 10,000/μL, platelet transfusion should be considered. If there are other risk factors for bleeding such as co-administration of anticoagulation or antiplatelet medicinal products, consider interrupting these substances and/or transfusion at a higher platelet count. • Resume *ZEJULA* at a reduced dose.
Platelet count < 100,000/μL	First occurrence: • Withhold *ZEJULA* for a maximum of 28 days and monitor blood counts weekly until platelet

	counts return to ≥ 100,000/µL. • Resume *ZEJULA* at same or reduced dose per Table 1 based on clinical evaluation. • If platelet count is < 75,000/µL at any time, resume at a reduced dose per Table 1.
	Second occurrence: • Withhold *ZEJULA* for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume *ZEJULA* at a reduced dose per Table 1. • Discontinue *ZEJULA* if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.
Neutrophil < 1,000/µL or Haemoglobin < 8 g/dL	• Withhold *ZEJULA* for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1,500/µL or haemoglobin returns to ≥ 9 g/dL. • Resume *ZEJULA* at a reduced dose per Table 1. • Discontinue *ZEJULA* if neutrophils and/or haemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue *ZEJULA*.

Method of Administration

Swallow tablets whole with water. Do not chew or crush tablets.

ZEJULA can be taken without regard to meals.

Children and Adolescents

The safety and efficacy of niraparib in children and adolescents below 18 years of age have not yet been established.

Elderly

No dose adjustment is necessary for elderly patients (≥ 65 years). There are limited clinical data in patients aged 75 years or over.

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end stage renal disease undergoing haemodialysis; use with caution in these patients (see *Pharmacokinetics*).

Hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment (either aspartate aminotransferase (AST) >upper limit of normal (ULN) and total bilirubin (TB) ≤ULN or any AST and TB > 1.0x – 1.5x ULN). For patients with moderate hepatic impairment (any AST and TB > 1.5x – 3x ULN), the recommended starting dose of *ZEJULA* is 200 mg once daily. There are no data in patients with severe hepatic impairment (any AST and TB > 3x ULN); use with caution in these patients (see *Pharmacokinetics*).

Contraindications

Hypersensitivity to the niraparib or to any of the excipients listed in Excipients.

Breast-feeding (see *Pregnancy and Lactation*).

Warnings and Precautions

Haematological adverse reactions

Haematological adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with *ZEJULA* (see *Adverse Reactions*).

If a patient develops severe persistent haematological toxicity including pancytopenia that does not resolve within 28 days following interruption, *ZEJULA* should be discontinued.

Test complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time to monitor for clinically significant changes in any haematological parameter during treatment (*see Posology*).

Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution (see *Adverse Reactions*).

Myelodysplastic syndrome/acute myeloid leukaemia

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received *ZEJULA* (see *Adverse Reactions*).

In clinical trials, the duration of *ZEJULA* treatment in patients prior to developing

MDS/AML varied from 0.5 months to >4.9 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow suppression.

For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS/AML is confirmed, treatment with *ZEJULA* should be discontinued.

Hypertension, including hypertensive crisis

Hypertension, including hypertensive crisis, has been reported with the use of *ZEJULA* (see *Adverse Reactions*). Pre-existing hypertension should be adequately controlled before starting *ZEJULA* treatment. Blood pressure and heart rate should be monitored at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with *ZEJULA*.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the *ZEJULA* dose (see *Posology*), if necessary. In the clinical programme, blood pressure measurements were obtained on Day 1 of each 28-day cycle while the patient remained on *ZEJULA*. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without *ZEJULA* dose adjustment (see *Posology*). *ZEJULA* should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Home blood pressure monitoring may be considered for appropriate patients with instruction to contact their health care provider in case of rise in blood pressure.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports (0.09 % of clinical trial patients) of *ZEJULA*-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES) (see *Adverse Reactions*). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of *ZEJULA*. The safety of reinitiating *ZEJULA* therapy in patients previously experiencing PRES is not known.

Pregnancy/contraception

ZEJULA should not be used during pregnancy or in women of childbearing potential not willing to use highly effective contraception during therapy and for 6 months after receiving the last dose of *ZEJULA* (see *Pregnancy*). A pregnancy test should be performed on all women of childbearing potential prior to treatment.

Interactions

Pharmacodynamic interactions

The combination of *ZEJULA* with vaccines or immunosuppressant agents has not been studied.

The data on *ZEJULA* in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

Pharmacokinetic interactions

Effect of other medicinal products on niraparib

Niraparib as a substrate of CYPs (CYP1A2 and CYP3A4)
Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) *in vivo*. Oxidative metabolism of niraparib is minimal *in vivo*. No dose adjustment for *ZEJULA* is required when administered concomitantly with medicinal products known to inhibit (e.g. itraconazole, ritonavir, and clarithromycin) or induce CYP enzymes (e.g. rifampin, carbamazepine, and phenytoin).

Niraparib as a substrate of efflux transporters (P-gp, BCRP, BSEP, MRP2, and MATE1/2)
Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely. Therefore, no dose adjustment for *ZEJULA* is required when administered concomitantly with medicinal products known to inhibit P-gp (e.g. amiodarone, verapamil) or BCRP (e.g. osimertinib, velpatasvir, and eltrombopag).

Niraparib is not a substrate of bile salt export pump (BSEP), or multidrug resistance-associated protein 2 (MRP2). The major primary metabolite M1 is not a substrate of P-gp, BCRP, BSEP, or MRP2. Niraparib is not a substrate of multidrug and toxin extrusion (MATE)-1 or 2, while M1 is a substrate of both.

Niraparib as a substrate of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)
Neither niraparib nor M1 is a substrate of organic anion transport polypeptide 1B1 (OATP1B1), 1B3(OATP1B3), or organic cation transporter 1 (OCT1). No dose adjustment for *ZEJULA* is required when administered concomitantly with medicinal products known to inhibit OATP1B1 or 1B3 (e.g. gemfibrozil, ritonavir), or OCT1 (e.g. dolutegravir) uptake transporters.

Niraparib as a substrate of renal uptake transporters (OAT1, OAT3, and OCT2)
Neither niraparib nor M1 is a substrate of organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2). No dose adjustment for *ZEJULA* is required when administered concomitantly with medicinal products known to inhibit OAT1 (e.g.

probenecid) or OAT3 (e.g. probenecid, diclofenac), or OCT2 uptake transporters (e.g. cimetidine, quinidine).

Effect of niraparib on other medicinal products

Inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)
Neither niraparib nor M1 is an inhibitor of any active substance-metabolising CYP enzymes, namely CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Even though inhibition of CYP3A4 in the liver is not expected, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when *ZEJULA* is combined with active substances the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g. ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

Inhibition of UDP-glucuronosyltransferases (UGTs)
Niraparib did not exhibit inhibitory effect against the UGT isoforms (UGT1A1, UGT1A4, UGT1A9, and UGT2B7) up to 200 µM *in vitro*. Therefore, the potential for a clinically relevant inhibition of UGTs by niraparib is minimal.

Induction of CYPs (CYP1A2 and CYP3A4)
Neither niraparib nor M1 is a CYP3A4 inducer *in vitro*. *In vitro*, niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect could not be completely ruled out. M1 is not a CYP1A2 inducer. Therefore, caution is recommended when *ZEJULA* is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (e.g. clozapine, theophylline, and ropinirole).

Inhibition of efflux transporters (P-gp, BCRP, BSEP, and MATE1/2)
Niraparib is not an inhibitor of BSEP. *In vitro*, niraparib inhibits P-gp very weakly and BCRP with an IC_{50} = 161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters, although unlikely, cannot be excluded. Caution is then recommended when *ZEJULA* is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

Niraparib is an inhibitor of MATE1 and -2 with IC_{50} of 0.18 µM and ≤ 0.14 µM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (e.g. metformin) cannot be excluded.

Inhibition of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)
Neither niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1) or 1B3 (OATP1B3).

In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC_{50} = 34.4 µM. Caution is recommended when *ZEJULA* is combined with active substances that undergo an uptake transport by OCT1 such as metformin.

Inhibition of renal uptake transporters (OAT1, OAT3, and OCT2)
Neither niraparib nor M1 inhibits organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2).

Pregnancy and Lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use highly effective contraception during therapy and for 6 months after receiving the last dose of *ZEJULA*.

Fertility

There are no clinical data on the effects of niraparib on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs (see *Animal toxicology and/or pharmacology*).

Pregnancy

There are no or limited amount of data from the use of niraparib in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted. However, based on its mechanism of action, niraparib could cause embryonic or foetal harm, including embryo-lethal and teratogenic effects, when administered to a pregnant woman. *ZEJULA* should not be used during pregnancy.

Lactation

It is unknown whether niraparib or its metabolites are excreted in human milk. Breast-feeding is contraindicated during administration of *ZEJULA* and for 1 month after receiving the last dose (see *Contraindications*).

Effects on Ability to Drive and Use Machines

ZEJULA may influence the ability to drive or use machines. Patients who take *ZEJULA* may experience asthenia, fatigue, difficulty concentrating and dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

Adverse Reactions

Clinical trial data

Tabulated list of adverse reactions

The following adverse reactions have been identified based on pooled data generated from the PRIMA and NOVA clinical trials in patients receiving *ZEJULA* monotherapy and during post-marketing experience (see *Table 4*).

Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Tabulated list of adverse reactions[a]

System Organ Class	**Frequency of all CTCAE[b] grades**	**Frequency of CTCAE[b] grade 3 or 4**
Infections and infestations	**Very common** Urinary tract infection **Common** Bronchitis, conjunctivitis	**Uncommon** Urinary tract infection, bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Common** Myelodysplastic syndrome/ acute myeloid leukaemia	**Common** Myelodysplastic syndrome/ acute myeloid leukaemia
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia, leukopenia **Common** Neutropenic infection **Uncommon** Febrile neutropenia, pancytopenia, neutropenic sepsis	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Neutropenic infection, febrile neutropenia, neutropenic sepsis, pancytopenia
Immune system disorders	**Common** Hypersensitivity (including anaphylaxis)	**Uncommon** Hypersensitivity (including anaphylaxis)
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression, cognitive impairment (memory impairment, concentration impairment) **Uncommon** Confusional state/disorientation, hallucination	**Uncommon** Insomnia, anxiety, depression, confusional state/disorientation, hallucination

System Organ Class	Frequency of all CTCAE[b] grades	Frequency of CTCAE[b] grade 3 or 4
Nervous system disorders	**Very common** Headache, dizziness **Common** Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)	**Uncommon** Headache **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension **Rare** Hypertensive crisis
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnoea, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Non-infectious pneumonitis	**Uncommon** Dyspnoea, epistaxis, non-infectious pneumonitis
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, mucositis, stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucositis, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	**Common** Photosensitivity, rash	**Uncommon** Photosensitivity, rash
Musculoskeletal and connective tissue disorders	**Very common** Back pain, arthralgia **Common** Myalgia	**Uncommon** Back pain, arthralgia, myalgia
General disorders and administration site conditions	**Very common** Fatigue, asthenia **Common** Oedema peripheral	**Common** Fatigue, asthenia
Investigations	**Common** Gamma-glutamyl transferase increased, AST increased, blood creatinine increased, ALT increased, blood alkaline phosphatase increased, weight decreased	**Common** Gamma-glutamyl transferase increased, ALT increased **Uncommon** AST increased, blood alkaline phosphatase increased

[a.] Frequency based on niraparib clinical trial data not limited to pivotal NOVA or PRIMA monotherapy studies.

[b.] CTCAE=Common Terminology Criteria for Adverse Events version 4.02

The adverse reactions noted in the group of patients who were administered a 200 mg starting dose of *ZEJULA* based on baseline weight or platelet count were of similar or lesser frequency compared to the group administered 300 mg (Table 4). See Warnings and Precautions for specific information regarding frequency of thrombocytopenia, anaemia and neutropenia.

The most common serious adverse reactions >1% (treatment-emergent frequencies) were thrombocytopenia and anaemia.

Description of selected adverse reactions
Haematological adverse reactions (thrombocytopenia, anaemia, neutropenia) including clinical diagnoses and/or laboratory findings generally occurred early during *ZEJULA* treatment with the incidence decreasing over time.

In the clinical programme, haematological adverse reactions were managed with laboratory monitoring and dose modifications (see *Posology*).

In the PRIMA study, patients eligible for *ZEJULA* therapy had the following baseline haematological parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/µL; platelets ≥ 100,000 cells/µL and haemoglobin ≥ 10 g/dL prior to therapy. The overall incidence of Grade ≥3 thrombocytopenia, anaemia and neutropenia in clinical and/or laboratory findings were reported, respectively, in 39 %, 31 %, and 21 % of patients receiving *ZEJULA*. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 4 %, 2 %, and 2 % of patients.

In patients who were administered a starting dose of niraparib based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anaemia and neutropenia were reported, respectively, in 22 %, 23 %, and 15 % of patients receiving *ZEJULA*. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 3 %, 3 %, and 2 % of patients.

In the NOVA study, patients eligible for *ZEJULA* therapy had the following baseline haematological parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/µL; platelets ≥ 100,000 cells/µL and haemoglobin ≥ 9 g/dL prior to therapy. Haematological adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with *ZEJULA*.

Grade ≥3 thrombocytopenia, anaemia and neutropenia were reported, respectively, in 29%, 25 %, and 20 % of patients receiving *ZEJULA*. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 3 %, 1 %, and 2 % of patients.

Thrombocytopenia

In the PRIMA study overall, 39 % of *ZEJULA*-treated patients experienced Grade 3-4 thrombocytopenia compared to 0.4 % of placebo-treated patients with a median time

from first dose to first onset in the *ZEJULA* arm of 22 days (range: 15 to 335 days) and with a median duration of 6 days (range: 1 to 374 days). Discontinuation due to thrombocytopenia occurred in 4 % of patients.

In NOVA, approximately 60 % of patients receiving *ZEJULA* experienced thrombocytopenia of any grade, and 34 % of patients experienced Grade 3/4 thrombocytopenia. In patients with baseline platelet count less than 180,000 cells/µL, thrombocytopenia of any grade and Grade 3/4 occurred in 76 % and 45 % of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2 %. The median duration of thrombocytopenia events of any grade was 23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with *ZEJULA* who develop thrombocytopenia might have an increased risk of haemorrhage. Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3 % of the patients.

In the NOVA study, 48 of 367 (13 %) patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in severity except for one event of Grade 3 petechiae and haematoma observed concurrently with a serious adverse event of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180,000 cells/µL. Approximately 76 % of patients with lower baseline platelets (< 180,000 cells/µL) who received *ZEJULA* experienced thrombocytopenia of any grade, and 45 % of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1 % of patients receiving *ZEJULA*.

Anaemia

In the PRIMA study overall, 31 % of *ZEJULA*-treated patients experienced Grade 3-4 anaemia compared to 2 % of placebo-treated patients with a median time from first dose to first onset in the *ZEJULA* arm of 80 days (range: 15 to 533 days) and with a median duration of 7 days (range: 1 to 119 days). Discontinuation due to anaemia occurred in 2% of patients.

In NOVA, approximately 50 % of patients experienced anaemia of any grade, and 25 % experienced Grade 3/4 anaemia. The median time to onset of anaemia of any grade was 42 days, and 85 days for Grade 3/4 events. The median duration of anaemia of any grade was 63 days, and 8 days for Grade 3/4 events. Anaemia of any grade might persist during *ZEJULA* treatment. In the clinical programme, anaemia was managed with laboratory monitoring, dose modification (see *Posology*), and where appropriate with red blood cell transfusions. Discontinuation due to anaemia occurred in 1 % of patients.

Neutropenia

In the PRIMA study overall, 21 % of *ZEJULA*-treated patients experienced Grade 3-4 neutropenia compared to 1 % of placebo-treated patients with a median time from first

dose to first onset in the *ZEJULA* arm of 29 days (range: 15 to 421 days) and with a median duration of 8 days (range: 1 to 42 days). Discontinuation due to neutropenia occurred in 2 % of patients.

In NOVA, approximately 30 % of patients receiving *ZEJULA* experienced neutropenia of any grade, and 20 % of patients experienced Grade 3/4 neutropenia. The median time to onset of neutropenia of any grade was 27 days, and 29 days for Grade 3/4 events. The median duration of neutropenia of any grade was 26 days, and 13 days for Grade 3/4 events. In addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6 % of patients treated with *ZEJULA* as concomitant therapy for neutropenia. Discontinuation due to neutropenia events occurred in 2 % of patients.

Myelodysplastic syndrome/Acute myeloid leukaemia

In clinical studies, MDS/AML occurred in 1 % patients treated with *ZEJULA*, with 41 % of cases having a fatal outcome. The incidence was higher in patients with relapsed ovarian cancer who had received 2 or more lines of prior platinum chemotherapy and with *gBRCA*mut following 5.6 years survival follow-up. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in g*BRCA*mut carriers. Some of the patients had a history of previous cancer or of bone marrow suppression.

In the PRIMA study, the incidence of MDS/AML was 0.8 % in patients receiving *ZEJULA* and 0.4 % in patients received placebo.

In the NOVA study in patients with relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy, the overall incidence of MDS/AML was 3.5 % in patients receiving *ZEJULA* and 1.7 % in patients receiving placebo at a follow-up of 5.6 years. In g*BRCA*mut and non-g*BRCA*mut cohorts, the incidence of MDS/AML was 6.6 % and 1.7 % in patients receiving *ZEJULA* and 3.1 % and 0.9 % in patients receiving placebo, respectively.

Hypertension

In PRIMA, Grade 3-4 hypertension occurred in 6 % of *ZEJULA*-treated patients compared to 1 % of placebo-treated patients with a median time from first dose to first onset in the *ZEJULA* arm of 50 days (range: 1 to 589 days) and with a median duration of 12 days (range: 1 to 61 days). Discontinuation due to hypertension occurred in 0 % of patients.

In NOVA, hypertension of any grade occurred in 19.3 % of patients treated with *ZEJULA*. Grade 3/4 hypertension occurred in 8.2 % of patients. Discontinuation due to hypertension occurred in <1 % of patients.

Overdose

There is no specific treatment in the event of *ZEJULA* overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should provide general supportive measures and should treat symptomatically.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code

L01XK02

Mechanism of action

Niraparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. *In vitro* studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in the BReast CAncer (*BRCA)* 1 and 2 tumour suppressor genes. In orthotopic high-grade serous ovarian cancer patient-derived xenograft tumours (PDX) grown in mice, niraparib has been shown to reduce tumour growth in *BRCA* 1 and 2 mutant, *BRCA* wild-type but homologous recombination (HR) deficient, and in tumours that are *BRCA* wild-type and without detectable HR deficiency.

Pharmacodynamic effects

Cardiac Electrophysiology

The potential for QTc prolongation with niraparib was evaluated in a randomized, placebo-controlled trial in patients with cancer (367 patients on niraparib and 179 patients on placebo). No large changes in the mean QTc interval (>20 ms) were detected in the trial following the treatment of niraparib 300 mg once daily.

Pharmacokinetics

Absorption

Following a single-dose administration of niraparib 300 mg under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (C_{max}) for niraparib was reached in about 3 hours [804 ng/mL (% CV:50.2 %)]. Following multiple oral doses ofniraparib from 30 mg to 400 mg once daily, accumulation of niraparib was approximately 2 to 3-fold.

The systemic exposures (C_{max} and AUC) to niraparib increased in a dose-proportional manner when the dose of niraparib increased from 30 mg to 400 mg. The absolute bioavailability of niraparib is approximately 73 %, indicating minimal first pass effect.

A concomitant high-fat meal did not significantly affect the pharmacokinetics of niraparib after administration of niraparib 300 mg hard capsule.

The tablet and capsule formulations have been demonstrated to be bioequivalent. Following administration of either one 300 mg tablet or three 100 mg capsules of niraparib in 108 patients with solid tumours under fasting conditions, the 90 % confidence intervals of the geometric mean ratios for tablet compared to capsules for C_{max}, AUC_{last} and AUC_{∞} fell within the limits of bioequivalence (0.80 and 1.25).

Distribution

Niraparib was moderately protein bound in human plasma (83 %), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the V_d/F was 1,074 L in cancer patients, indicating extensive tissue distribution of niraparib.

Metabolism

Niraparib is metabolised primarily by carboxylesterases (CEs) to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites.

Elimination

Following a single oral 300-mg dose of niraparib, the mean terminal half-life ($t_{½}$) of niraparib ranged from 48 to 51 hours (approximately 2 days). In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 16.2 L/h in cancer patients.

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following oral administration of a single 300-mg dose of [^{14}C]-niraparib, on average 86.2 % (range 71 % to 91 %) of the dose was recovered in urine and faeces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and in the faeces for 38.8 % (range 28.3 % to 47.0 %) of the dose. In pooled samples collected over 6 days, 40.0 % of the dose was recovered in the urine primarily as metabolites and 31.6 % of the dose was recovered in the faeces primarily as unchanged niraparib.

Special patient populations

Children

No studies have been conducted to investigate the pharmacokinetics of niraparib in paediatric patients.

Renal impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild (CLCr < 90 to ≥ 60 ml/min) and moderate (CLCr < 60 to ≥ 30 mL/min) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (7- 17 % higher exposure in mild and 17-38 % higher exposure in moderate renal impairment). The difference in exposure is not considered to warrant dose adjustment. No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies (see *Posology*).

Hepatic impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild hepatic impairment did not influence the clearance of niraparib.

In a clinical study of cancer patients using NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUC_{inf} in patients with moderate hepatic impairment (n=8) was 1.56 (90 % CI: 1.06 to 2.30) times the niraparib AUC_{inf} in patients with normal hepatic function (n=9) following administration of a single 300 mg dose. *ZEJULA* dose adjustment is recommended for patients with moderate hepatic impairment (see Posology). Moderate hepatic impairment did not have an effect on niraparib C_{max} or on niraparib protein binding.

The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (see *Posology*).

Age, weight and race

Increasing weight was found to increase niraparib volume of distribution in the population pharmacokinetic analysis. No impact of weight was identified on niraparib clearance or overall exposure.

Increasing age was found to decrease niraparib clearance in the population pharmacokinetic analysis. The average exposure in a 91-year old patient was predicted to be 23 % higher than in a 30-year old patient. The impact of age is not considered to warrant dose adjustment.

There is insufficient data across races to conclude on the impact of race on niraparib pharmacokinetics.

Clinical Studies

First-line ovarian cancer maintenance treatment

PRIMA was a Phase 3 double-blind, placebo-controlled trial in which patients (n=733) in complete or partial response to first-line platinum-based chemotherapy were randomised 2:1 to *ZEJULA* capsules or matched placebo. PRIMA was initiated with a starting dose of 300 mg QD in 475 patients (whereof 317 was randomised to the niraparib arm vs. 158 in the placebo arm) in continuous 28-day cycles. The starting dose in PRIMA was changed

with Amendment 2 of the Protocol. From that point forward, patients with a baseline body weight ⩾77 kg and baseline platelet count ⩾150,000/ μ L were administered *ZEJULA* 300 mg (3×100 mg capsules) (n=34) or placebo (3 capsules) daily (n=21) while patients with a baseline body weight <77 kg or baseline platelet count <150,000/ μ L were administered *ZEJULA* 200 mg (2×100 mg capsules) (n=122) or placebo (2 capsules) daily (n=61).

Patients were randomised post completion of first-line platinum-based chemotherapy plus/minus surgery. Subjects were randomized within 12 weeks of the first day of the last cycle of chemotherapy. Subjects had ⩾6 and ⩽9 cycles of platinum-based therapy. Following interval debulking surgery subjects had ⩾2 post-operative cycles of platinum-based therapy. Patients who had received bevacizumab with chemotherapy but could not receive bevacizumab as maintenance therapy were not excluded from the study. Patients could not have received prior PARP inhibitor therapy, including *ZEJULA*. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no residual disease. Patients with Stage III disease who had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery were excluded. Randomisation was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant chemotherapy (NACT) (Yes vs No); and homologous recombination deficiency (HRD) status [positive (HR deficient) vs negative (HR proficient) or not determined]. Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis. The CA-125 levels should be in the normal range (or a CA-125 decrease by > 90 %) during the patient's front-line therapy and be stable for at least 7 days.

Patients began treatment on Cycle 1/Day 1 (C1/D1) with *ZEJULA* 200 or 300 mg or matched placebo administered QD in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days).

The primary endpoint was progression-free survival (PFS), as determined by blinded independent central review (BICR) per RECIST, version 1.1. Overall survival (OS) was a key secondary objective. PFS testing was performed hierarchically: first in the HR deficient population, then in the overall population. The median age of 62 ranged from 32 to 85 years among patients randomised with *ZEJULA* and 33 to 88 years among patients randomised with placebo. 89 percent of all patients were white. 69 percent of patients randomised with *ZEJULA* and 71% of patients randomised with placebo had an ECOG of 0 at study baseline. In the overall population, 65 % of patients had stage III disease and 35 % had stage IV disease. In the overall population, the primary tumour site in most patients (⩾ 80 %) was the ovary; most patients (> 90 %) had tumours with serous histology. 67 percent of the patients received NACT. 69 percent of the patients had a complete response to the first-line platinum-based chemotherapy. A total of 6 niraparib patients had received bevacizumab as prior treatment for their ovarian cancer.

PRIMA demonstrated a statistically significant improvement in PFS for patients randomised to *ZEJULA* as compared with placebo in the HR deficient and overall population (Table 5, and Figures 1 and 2).

Secondary efficacy endpoints included PFS after the first subsequent therapy (PFS2) and OS (Table 5).

Table 5: Efficacy results – PRIMA (determined by BICR)

	HR deficient population		**Overall population**	
	niraparib (N=247)	**placebo (N=126)**	**niraparib (N=487)**	**placebo (N=246)**
PFS median (months; 95% CI)	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
Hazard ratio (HR) (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	
p-value	<0.0001		<0.0001	
PFS2 Hazard ratio (HR) (95% CI)	0.84 (0.485, 1.453)		0.81 (0.577, 1.139)	
OS* Hazard ratio (HR) (95% CI)	0.61 (0.265, 1.388)		0.70 (0.44, 1.11)	

*At the time of primary PFS analysis, an estimated survival at two years after randomization of 84 % for patients receiving *ZEJULA*, as compared to 77 % for patients receiving placebo in the overall population.
Data of PFS2 and OS are currently not mature.

Figure 1: Progression-free survival in patients with HR deficient tumours (ITT population, N=373)

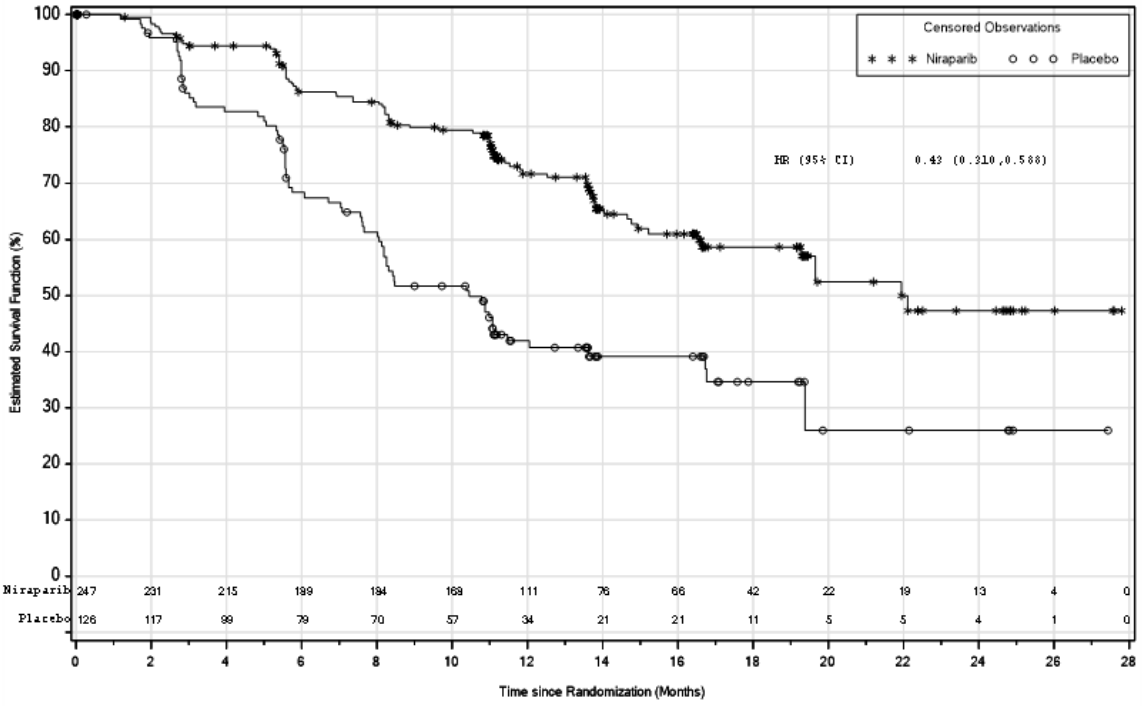
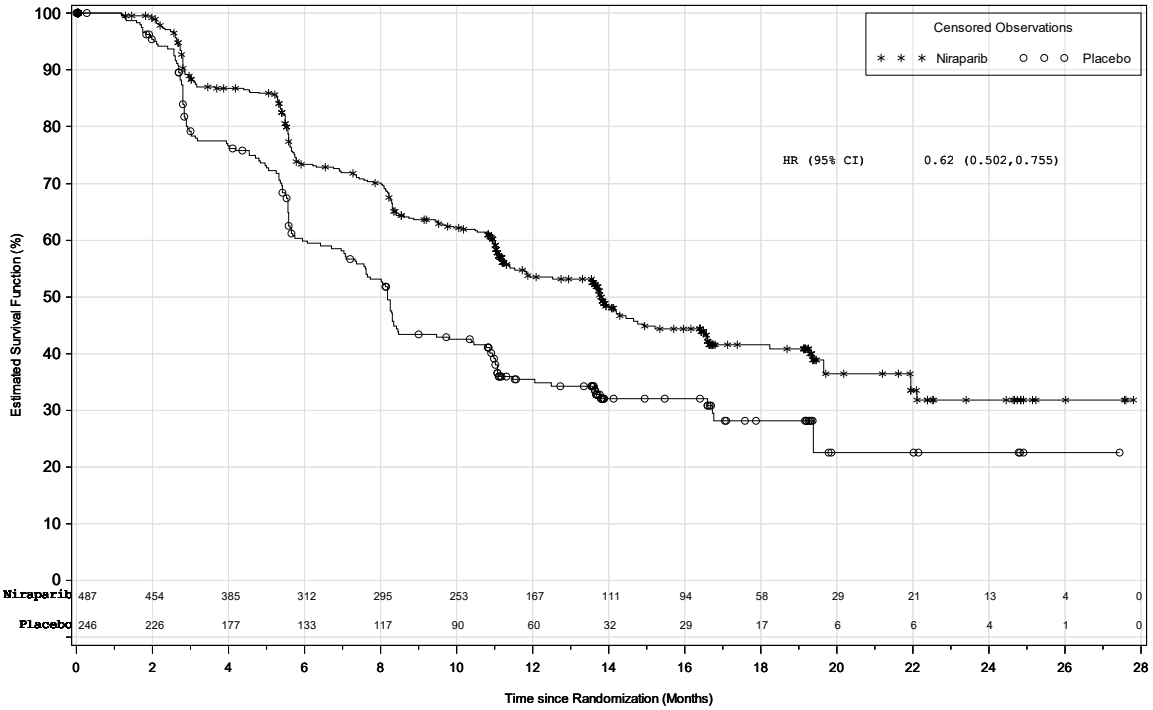


Figure 2: Progression-free survival in the overall population (ITT population, N=733)



Subgroup analyses

Within the HR deficient population, a hazard ratio of 0.40 (95 % CI [0.27, 0.62]) was observed in the subgroup of patients with *BRCA*mut ovarian cancer (N=223). In the subgroup of HR deficient patients without a *BRCA* mutation (N=150), a hazard ratio of 0.50 (95 % CI [0.31, 0.83]) was observed. In the HR proficient population (N=249), a hazard ratio of 0.68 (95 % CI [0.49, 0.94]) was observed.

In exploratory subgroup analyses of patients who were administered 200 or 300 mg dose of *ZEJULA* based on baseline weight or platelet count, comparable efficacy (investigator-assessed PFS) was observed with a hazard ratio of 0.54 (95 % CI [0.33, 0.91]) in the HR deficient population, and with a hazard ratio of 0.68 (95 % CI [0.49, 0.94]) in the overall population. In the HR proficient subgroup, the dose of 200 mg appeared to give a lower treatment effect compared to the 300 mg dose.

Recurrent ovarian cancer maintenance treatment

The safety and efficacy of *ZEJULA* capsule as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (NOVA) in patients with relapsed predominantly high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were platinum sensitive, defined by complete response (CR) or partial response (PR) for more than six months to their penultimate (next to last) platinum-based therapy. To be eligible for *ZEJULA* treatment, the patient should be in response (CR or PR) following completion of last platinum-based chemotherapy. The CA-125 levels should be normal (or a >90 % decrease in CA-125 from baseline) following their last platinum treatment and be stable for at least 7 days. Patients could not have received prior PARP inhibitor therapy, including *ZEJULA*. Eligible patients were assigned to one of two cohorts based on the results of a germline *BRCA* mutation test. Within each cohort, patients were randomised using a 2:1 allocation of *ZEJULA* 300 mg (3 x 100 mg capsules) or placebo (3 capsules) daily in continuous 28-day cycles. Patients were assigned to the g*BRCA*mut cohort based on blood samples for g*BRCA* analysis that were taken prior to randomisation. Testing for t*BRCA* mutation and HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence.

Randomisation within each cohort was stratified by time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months and ≥12 months); use of bevacizumab in conjunction with the penultimate or last platinum regimen; and best response during the most recent platinum regimen (complete response and partial response).

Patients began treatment on Cycle 1/Day 1 (C1/D1) with *ZEJULA* 300 mg or matched placebo administered once daily in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days).

In the NOVA study, 48 % of patients had a dose interruption in Cycle 1. Approximately 47 % of patients restarted at a reduced dose in Cycle 2.

The most commonly used dose in *ZEJULA*-treated patients in the NOVA study was 200 mg.

Progression-free survival was determined per RECIST (Response Evaluation Criteria in Solid Tumors, version 1.1) or clinical signs and symptoms and increased CA-125. PFS was measured from the time of randomisation (which occurred up to 8 weeks after completion of the chemotherapy regimen) to disease progression or death.

The primary efficacy analysis for PFS was determined by blinded central independent assessment and was prospectively defined and assessed for the g*BRCA*mut cohort and the non-g*BRCA*mut cohort separately.

Secondary efficacy endpoints included time to first subsequent therapy (TFST), PFS after the first subsequent therapy (PFS2) and OS (overall survival).

Demographics, baseline disease characteristics, and prior treatment history were generally well balanced between the *ZEJULA* and placebo arms in the g*BRCA*mut (n=203) and the non-g*BRCA*mut cohorts (n=350). Median ages ranged from 57 to 63 years across treatments and cohorts. The primary tumour site in most patients (>80 %) within each cohort was the ovary; most patients (>84 %) had tumours with serous histology. A high proportion of patients in both treatment arms in both cohorts had received 3 or more prior lines of chemotherapy, including 49 % and 34 % of *ZEJULA* patients in the g*BRCA*mut and non-g*BRCA*mut cohorts, respectively. Most patients were age 18 to 64 years (78 %), Caucasian (86 %) and had an ECOG performance status of 0 (68 %).

In the g*BRCA*mut cohort, the median number of treatment cycles was higher in the *ZEJULA* arm than the placebo arm (14 and 7 cycles, respectively). More patients in the *ZEJULA* group continued treatment for more than 12 months than patients in the placebo group (54.4 % and 16.9 % respectively).

In the overall non-g*BRCA*mut cohort, the median number of treatment cycles was higher in the *ZEJULA* arm than in the placebo arm (8 and 5 cycles, respectively). More patients in the *ZEJULA* group continued treatment for more than 12 months than patients in the placebo group (34.2 % and 21.1 %, respectively).

The study met its primary objective of statistically significantly improved PFS for *ZEJULA* maintenance monotherapy compared with placebo in the g*BRCA*mut cohort (HR 0.27; 95 % CI* 0.173, 0.410; $p < 0.0001$) as well as in the overall non-g*BRCA*mut cohort (HR 0.45; 95 % CI* 0.338, 0.607; $p < 0.0001$). Table 6 and Figures 3 and 4 show the results for the PFS primary endpoint for the primary efficacy populations (g*BRCA*mut cohort and the overall non-g*BRCA*mut cohort). A sensitivity analysis of investigator PFS showed the following results for the g*BRCA*mut cohort: HR 0.27 (95 % CI*, 0.182, 0.401; $p < 0.0001$); median PFS 14.8 months (95 % CI*, 12.0, 16.6) for niraparib and median PFS 5.5 months (95 % CI*, 4.9, 7.2) for placebo, and for the non-g*BRCA*mut cohort: HR 0.53 (95 % CI*, 0.405, 0.683; $p < 0.0001$); median PFS 8.7 months (95 % CI*, 7.3, 10.0) for niraparib and median PFS 4.3 months (95 % CI*, 3.7, 5.5) for placebo.

Table 6 shows the results for the secondary endpoints for time to first subsequent treatment (TFST), PFS after the first subsequent therapy (PFS2), and overall survival (OS) for the gBRCAmut cohort and the overall non-gBRCAmut cohort. The final OS analysis was confounded due to missing data and did not show improved OS in either the gBRCAmut cohort or the non-gBRCAmut cohort.

Table 6: Efficacy results – NOVA

	g*BRCA*mut cohort		**Non-g*BRCA*mut cohort**	
	niraparib (N = 138)	**placebo (N = 65)**	**niraparib (N = 234)**	**placebo (N = 116)**
Primary Endpoint (determined by BICR)				
PFS median (months, 95% CI)	**21.0** (12.9, NR)	**5.5** (3.8, 7.2)	**9.3** (7.2, 11.2)	**3.9** (3.7, 5.5)
p-value	< 0.0001		< 0.0001	
Hazard ratio (HR) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)	
Secondary Endpoints**				
Time to first subsequent treatment median (months, 95% CI)	**19.1** (15.0, 21.9)	**8.6** (6.7, 11.2)	**11.8** (9.9, 13.6)	**7.4** (5.8, 8.7)
Hazard ratio (HR) (95% CI)	0.54 (0.38, 0.75)		0.62 (0.48, 0.80)	
Progression-free survival 2 median (months, 95% CI)	**30.4** (25.0, 33.4)	**22.7** (17.8, 25.6)	**18.5** (16.8, 21.7)	**15.6** (13.2, 22.8)
Hazard ratio (HR) (95% CI)	0.67 (0.48, 0.95)		0.81 (0.63, 1.05)	
Overall survival median (months, 95% CI)	**43.6** (35.8, 53.0)	**41.6** (29.3, 52.9)	**31.1** (27.8, 37.3)	**36.5** (27.9, 41.6)
Hazard ratio (HR) (95% CI)	0.93 (0.63, 1.36)		1.10 (0.83, 1.46)	

*CI =confidence interval.,
** Due to the exploratory nature of the analyses and lack of alpha assignment, no definitive conclusions can be drawn from these data.

Prior to unblinding of the study, tumours of patients were tested for the presence of HRD using an experimental HRD test, which evaluates three indirect measures of tumour genome instability: loss of heterozygosity, telomeric allelic imbalance (TAI), and large-scale state transitions. In the HR deficient group, the hazard ratio was 0.38 (95 % CI, 0.243, 0.586; p < 0.0001). In the HR proficient group, the hazard ratio was 0.58 (95 % CI, 0.361, 0.922; p = 0.0226). The experimental test was not able to discriminate which patients would or would not benefit from *ZEJULA* maintenance therapy.

Figure 3: Kaplan-Meier plot for progression-free survival in the g*BRCA*mut cohort based on IRC assessment (ITT population, N = 203)

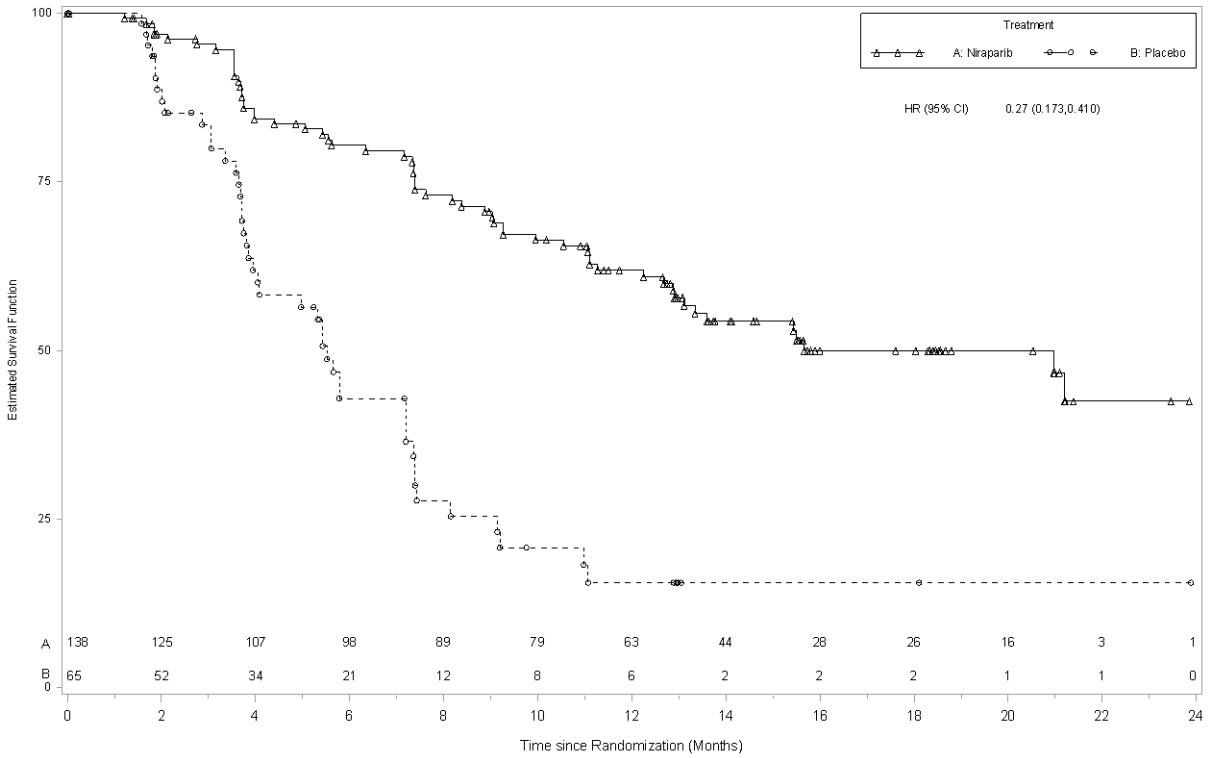
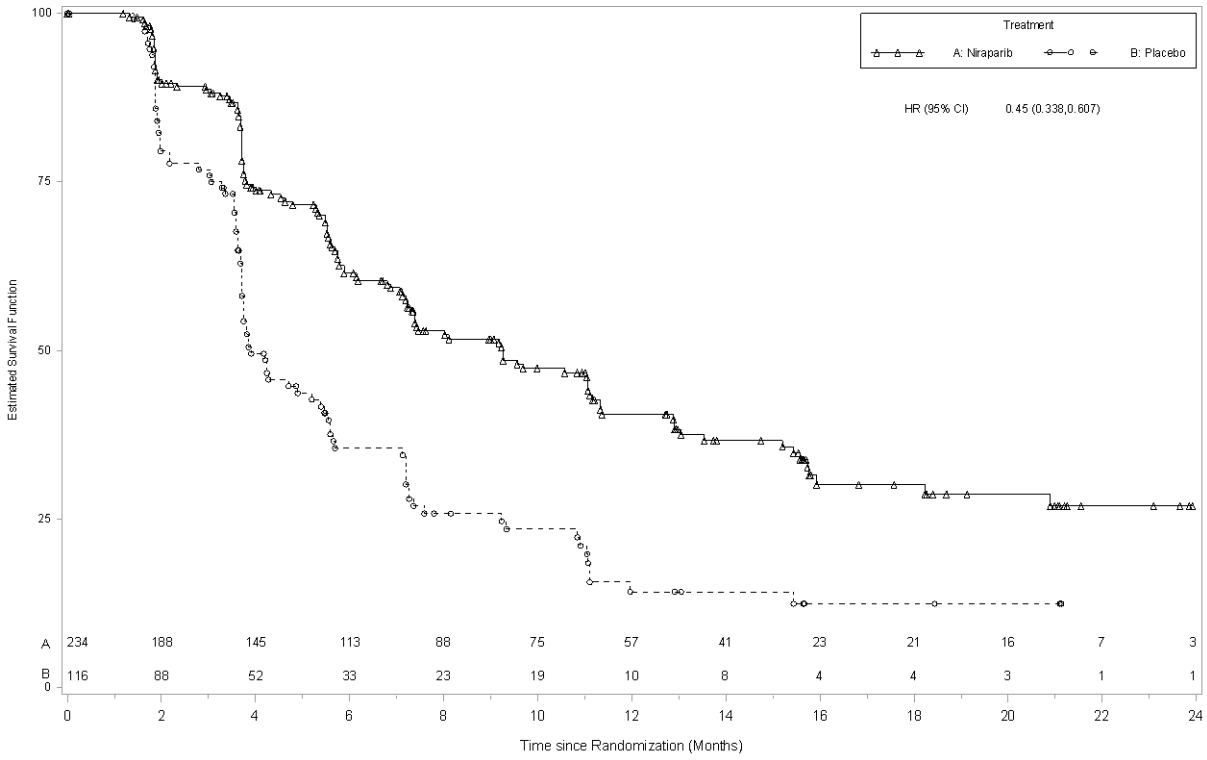


Figure 4: Kaplan-Meier plot for progression-free survival in the non-g*BRCA*mut cohort overall based on IRC assessment (ITT population, N = 350)



Patient-reported outcome (PRO) data from validated survey tools (FOSI and EQ-5D) indicate that *ZEJULA*-treated patients reported no difference from placebo in measures associated with quality of life (QoL).

Non-Clinical Information

Carcinogenesis/mutagenesis

Carcinogenicity studies have not been conducted with niraparib.

Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test but was clastogenic in an *in vitro* mammalian chromosomal aberration assay and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans.

Reproductive toxicology

Reproductive and developmental toxicity studies have not been conducted with niraparib.

Animal toxicology and/or pharmacology

In vitro, niraparib inhibited the dopamine transporter DAT at concentration levels below human exposure levels. In mice, single doses of niraparib increased intracellular levels of dopamine and metabolites in cortex. Reduced locomotor activity was seen in one of two single dose studies in mice. The clinical relevance of these findings is not known. No effect on behavioural and/or neurological parameters have been observed in repeat-dose toxicity studies in rats and dogs at estimated CNS exposure levels similar to or below expected therapeutic exposure levels.

In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months' duration in rats and dogs. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters. Additionally, decreased spermatogenesis was seen in both species. These findings occurred at exposure levels below those seen clinically and were largely reversible within 4 weeks of cessation of dosing.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet Core
Crospovidone,
Lactose monohydrate,
Magnesium stearate,
Microcrystalline cellulose,
Povidone,
Silicon dioxide.

Tablet Coat
Opadry II Gray (100 mg) – polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and ferrosoferric oxide
Opadry II Blue (200 mg) - polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and FD&C Blue #2/Indigo carmine aluminium lake
Opadry II Green (300 mg) - polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, yellow iron oxide and FD&C Blue #1/Brilliant blue FCF alumnium lake
Purified water.

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Nature and Contents of Container

ZEJULA film-coated tablets are available in
OPA/aluminium/PVC/aluminium/vinyl/acrylic blister in cartons of 28, 56 and 84 tablets.

Not all presentations are available in every country.

Incompatibilities

Not applicable.

Use and Handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Registrant

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