PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **ZEJULA**

niraparib capsules

niraparib tablets

100 mg niraparib (as niraparib tosylate), oral

Antineoplastic agent

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZEJULA (niraparib capsules and tablets) is indicated:

- as monotherapy for the maintenance treatment of female adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
- as monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

ZEJULA is contraindicated in patients who are:

- Hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Breast-feeding (see 7.1.2 Breast-feeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with ZEJULA should be initiated and supervised by a health professional experienced in the use of anti-cancer medicinal products.
- Myelodysplastic Syndrome/Acute Myeloid Leukaemia (MDS/AML) has been reported in patients exposed to ZEJULA. Some cases have been fatal (see 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).
- ZEJULA can cause bone marrow suppression (see 4.2 Recommended Dose and Dosage Adjustment, Table 3).
- Hypertension, including hypertensive crisis, has been reported with the use of ZEJULA (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).
- ZEJULA can cause foetal harm when administered to a pregnant woman (see 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients should have recovered from prior haematologic toxicities prior to starting ZEJULA (≤ Grade 1) (see 7 WARNINGS AND PRECAUTIONS, Haematologic and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Haematologic Testing).

Dose adjustments may be required for patients with hepatic insufficiency (see 4.2 Recommended Dose and Dose Adjustment).

4.2 Recommended Dose and Dosage Adjustment

First-Line Maintenance Treatment of Advanced Ovarian Cancer

- For patients weighing less than 77 kg or with a platelet count of less than 150,000/µL, the recommended dose of ZEJULA is 200 mg (two 100-mg capsules or tablets) taken orally once daily.
- For patients weighing greater than or equal to 77 kg and who have a platelet count greater than or equal to 150,000/µL, the recommended dose of ZEJULA is 300 mg (three 100-mg capsules or tablets) taken orally once daily.

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

ZEJULA treatment should be continued until disease progression or unacceptable toxicity.

Maintenance Treatment of Recurrent Ovarian Cancer

The recommended dose of ZEJULA as monotherapy is 300 mg (three 100 mg capsules or tablets) taken orally once daily.

Patients with low body weight: Approximately 25% of patients in the Phase III Trial (NOVA) 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.

ZEJULA treatment should be continued until disease progression or unacceptable toxicity.

Dose Adjustments for Adverse Reactions
To manage adverse reactions, consider interrupting the treatment, reducing the dose, or discontinuing the dose. The recommended dose modifications in the case of adverse reactions are found in Table 1**,** Table 2 and Table 3.

Table 1 – Recommended dose modifications for adverse reactions

Starting dose level	**200 mg/day**	**300 mg/day**
First dose reduction	100 mg/day* (one 100 mg capsule)	200 mg/day (two 100 mg capsules or tablets)
Second dose reduction	Discontinue medication	100 mg/day* (one 100 mg capsule or tablet)

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

Table 2 – Dose modifications for non-haematologic adverse reactions

Non-haematologic CTCAE* ≥ Grade 3 adverse reaction that persists despite treatment/prophylaxis**	• Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction. • Resume ZEJULA at a reduced dose per Table 1.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered ZEJULA 100 mg/day	Discontinue medication.

*CTCAE=Common Terminology Criteria for Adverse Events
**Prophylaxis includes, but is not limited to, medications to prevent nausea, vomiting, diarrhoea, constipation, headache, back pain, myalgia, arthralgia, insomnia, decreased appetite, or dry mouth.

Table 3 – Dose modifications for haematologic adverse reactions

Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time (see 7 WARNINGS AND PRECAUTIONS, Haematologic).	
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. • If platelet count is <75,000/µL, resume at a reduced dose.
	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.
Haematologic 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 drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Resume ZEJULA at a reduced dose.
Myelodysplastic syndrome or acute myeloid leukemia (MDS/AML)	• If MDS/AML is confirmed, discontinue ZEJULA (see 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

Hepatic Insufficiency

No dose adjustment is needed in patients with mild hepatic impairment (total bilirubin ≤1.5 x upper limit of normal [ULN] and any aspartate transaminase [AST] level, or bilirubin ≤ ULN and AST > ULN). For patients with moderate hepatic impairment (total bilirubin >1.5–3.0 x ULN and any AST), the

recommended starting dose of niraparib is 200 mg once daily (see 10.3 Pharmacokinetics). Monitor patients for hematologic toxicity and reduce the dose further, if needed. The safety of ZEJULA in patients with severe hepatic impairment (total bilirubin >3.0 x ULN and any AST) is unknown.

Renal Insufficiency
No dose adjustment is necessary for patients with mild to moderate renal impairment. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

4.4 Administration

Instruct patients to take their dose of ZEJULA at approximately the same time each day. Each capsule or tablet should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

4.5 Missed Dose

In the case of a missed dose of ZEJULA, instruct patients to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of ZEJULA, an additional dose should not be taken.

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	capsule 100 mg niraparib, as niraparib tosylate	FD&C Blue #1, FD&C Red #3, FD&C Yellow #5 (tartrazine), gelatin, lactose monohydrate, magnesium stearate, pharmaceutical grade printing ink, and titanium dioxide.
oral	tablet 100 mg niraparib, as niraparib tosylate	Crospovidone, ferrosoferric oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, silicon dioxide, talc, titanium dioxide

ZEJULA capsules are packaged as unit dose blister in cartons of 56 × 1 and 84 × 1 capsules.

100 mg capsule having a white body with “100 mg” printed in black ink, and a purple cap with “Niraparib” printed in white ink.

ZEJULA tablets are packaged as unit dose blister in cartons of 28 × 1, 56 × 1, and 84 × 1 tablets.

100 mg tablets are immediate release, gray, oval-shaped, film coated tablets, debossed with "100" on one side and "Zejula" on the other side.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received ZEJULA. In the monotherapy and combination therapy clinical studies, MDS/AML occurred in 1% of patients treated with niraparib (N=2,244), with 41% of cases having a fatal outcome (see 8.1 Adverse Reaction Overview, Myelodysplastic syndrome/Acute myeloid leukaemia).

The duration of ZEJULA treatment in patients prior to developing MDS/AML varied from 0.5 months to 4.9 years. All patients had received previous chemotherapy with platinum and some had also received other DNA damaging agents and radiotherapy. For suspected MDS/AML or prolonged hematological toxicities, refer the patient to a hematologist for further evaluation. Discontinue ZEJULA if MDS/AML is confirmed.

Cardiovascular

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA. Pre-existing hypertension should be adequately controlled before starting ZEJULA treatment.

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 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, Grade 3 to 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 76.5 days (range: 4 to 504 days). Discontinuation due to hypertension occurred in <1% of patients.

Monitor blood pressure and heart rate (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Cardiovascular Monitoring). Medically manage hypertension with antihypertensive medications and adjustment of the dose of ZEJULA, if necessary (see 4.2 Recommended Dose and Dosage Adjustment). ZEJULA should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Driving and Operating Machinery

ZEJULA has moderate influence on the ability to drive or use machines. Patients who take ZEJULA may experience asthenia, fatigue, difficulty concentrating and dizziness. For patients who experience these symptoms, due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Haematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients treated with ZEJULA.

In the PRIMA clinical study, the overall incidence of Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA.

Discontinuation due to thrombocytopenia, anemia, 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, anemia and neutropenia were reported, respectively, in 21%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients.

In the NOVA clinical study, Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients.

Pancytopenia has been observed in patients receiving niraparib in both PRIMA (1 patient, 0.2%) and NOVA (3 patients, 0.8%).

Careful monitoring of haematological parameters is required (see 4.2 Recommended Dose and Dosage Adjustment, Table 3 and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Haematologic Testing).

Immune

ZEJULA capsules contain tartrazine (FD&C Yellow #5), which may cause allergic-type reactions.

Monitoring and Laboratory Tests

Cardiovascular Monitoring: Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Haematologic Testing: Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If haematological toxicities occur, dose interruption, dose reduction, and additional haematological monitoring is required (see 4.2 Recommended Dose and Dosage Adjustment, Table 3). If haematologic toxicity does not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a haematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics.

Pregnancy Testing: A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and at one month after receiving the last dose of ZEJULA (see 7.1.1 Pregnant Women).

Neurologic

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 8.5 Post-Market Adverse Reactions). PRES is a rare neurologic disorder that can present with the following signs and symptoms: 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.

Reproductive Health: Female and Male Potential

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 fertility. A reversible reduction of spermatogenesis was observed in male rats and dogs (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical data regarding the use of ZEJULA in pregnant women. Based on its mechanism of action, ZEJULA has the potential to cause teratogenicity and/or embryo-foetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) and therefore should not be used during pregnancy (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, 10 CLINICAL PHARMACOLOGY and 16 NON-CLINICAL TOXICOLOGY). Apprise pregnant women of the potential risk to a foetus.

If a woman becomes pregnant while receiving ZEJULA, she should be apprised of the potential hazard to the foetus and the potential risk for loss of pregnancy.

7.1.2 Breast-feeding

It is unknown if niraparib or its metabolites are excreted in human milk.

Because of the potential for serious adverse reactions in breastfed infants from ZEJULA, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): In PRIMA, 39% of patients were aged ≥65 years and 10% were aged ≥75 years. In NOVA, 35% of patients were aged ≥65 years and 8% were ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The monotherapy pooled dataset includes 851 patients with platinum-sensitive ovarian, fallopian tube, and primary peritoneal cancer in the Phase 3 randomized, double-blind, placebo-controlled international studies NOVA and PRIMA. In PRIMA safety population, the median overall treatment duration was 11.1 months in the ZEJULA group and 8.3 months for placebo. Among those patients in PRIMA who were administered a starting dose of ZEJULA based on baseline weight or platelet count, the median duration of treatment was 11.0 months in the ZEJULA group and 8.3 months for placebo. In

NOVA, the median total treatment duration in all patients was 250 days in the ZEJULA group and 163 days for placebo.

The adverse reactions of all grades occurring in >10% of the patients who received ZEJULA in the monotherapy pooled dataset were nausea, anemia, thrombocytopenia, fatigue, constipation, vomiting, headache, insomnia, platelet count decreased, neutropenia, abdominal pain, decreased appetite, diarrhea, dyspnea, hypertension, asthenia, dizziness, neutrophil count decreased, cough, arthralgia, back pain, white blood cell count decreased, and hot flashes.

In the PRIMA study, serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Among those patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%), and thrombocytopenia (7%).

In the NOVA study, serious adverse reactions occurred in 34% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were thrombocytopenia (11%), anemia (4%), and small intestinal obstruction (2.5%).

In the PRIMA study, 385 (80%) of the 484 patients who received ZEJULA had dose interruptions due to adverse reactions. Fifty-two percent of patients had a dose interruption in Cycle 1 of treatment. The most common adverse reactions leading to study drug interruption in ZEJULA treated patients were thrombocytopenia (37%), anemia (31%), and platelet count decreased (23%). Dose reductions due to adverse reactions were reported in 343 (71%) of the 484 patients who received ZEJULA. Nine percent of patients had a dose reduction in Cycle 1 and 47% of patients in Cycle 2. The permanent discontinuation rate due to adverse reactions in the study was 12%. Discontinuation due thrombocytopenia, anemia, nausea and neutropenia occurred in 4%, 2%, 1% and 1% of patients, respectively. Among those patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%). Permanent discontinuation due to adverse reactions occurred in 14% of these patients and the most common ones (>2%) were thrombocytopenia and anemia (3.0% each), and nausea (2.4%).

Adverse reactions in the NOVA study led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in the study was 15%. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 1%, and 2% of patients, respectively.

Myelodysplastic syndrome/Acute myeloid leukaemia

In the monotherapy and combination therapy clinical studies, MDS/AML occurred in 1% of patients treated with ZEJULA (N=2,244), 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 gBRCAmut 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. Some of the patients had a history of other previous cancer in addition to ovarian 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 gBRCAmut and non-gBRCAmut 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.

Thrombocytopenia

In the PRIMA study, 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 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 the NOVA study, thrombocytopenia of any grade was reported in about 60% of the patients receiving ZEJULA and about 29% of the patients experienced Grade 3/4 thrombocytopenia. 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 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.

Pneumonitis

There were a total of 7 cases (0.8 %) of pneumonitis in the patients treated with ZEJULA compared to only 1 case (0.24 %) in the patients given the placebo from the pooled dataset of NOVA and PRIMA. These were of Grade 1/2 in severity. Of these 7 patients, 1 had discontinued and 3 had interrupted or/and reduced niraparib dose due to pneumonitis. In 3 of these 7 cases therapeutic measures for pneumonitis were taken.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA study.

All Patients Receiving ZEJULA in PRIMA

Table 5 summarizes the common adverse reactions observed in all patients treated with ZEJULA in the PRIMA study.

Table 5 – Adverse Drug Reactions Reported in ≥10% of Patients Receiving ZEJULA in Overall Population in PRIMA

	Overall Population			
	Grades 1-4[a]		Grades 3-4[a]	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
Blood and Lymphatic System Disorders				
Anemia	64	18	31	2
Thrombocytopenia	66	5	39	0.4
Neutropenia[b]	42	8	21	1
Leukopenia[c]	28	9	5	0.4
Gastrointestinal Disorders				
Nausea	57	28	1	1
Vomiting	22	12	1	1
Constipation[d]	40	20	1	0.4
Abdominal pain	35	44	2	1
Diarrhea	19	23	1	0.4
General Disorders and Administration Site Conditions				
Fatigue[e]	51	41	3	1
Investigations				
AST/ALT elevation	11	7	2	0.4
Metabolism and Nutrition Disorders				
Decreased appetite	19	8	1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	39	38	1	0
Nervous System Disorders				
Headache	26	15	0.4	0
Dizziness	15	11	0	0.4
Psychiatric Disorders				
Insomnia	25	14	1	0.4
Renal and Urinary Disorders				
Acute kidney injury[g]	12	5	0.2	0

	Overall Population			
	Grades 1-4[a]		Grades 3-4[a]	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[h]	22	13	0.4	1
Cough	18	15	0	0.4
Vascular Disorders				
Hypertension	18	7	6	1

[a]CTCAE=Common Terminology Criteria for Adverse Events version 4.02
[b]Neutropenia includes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.
[c]Includes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.
[d]Includes constipation, intestinal obstruction, and large intestinal obstruction.
[e]Includes fatigue, asthenia, muscular weakness, malaise, and somnolence.
[f]Includes arthralgia, back pain, pain in extremity, myalgia and other related terms.
[g]Acute kidney injury includes preferred terms of blood creatine increased, blood creatinine increased, blood urea increased, renal failure, and acute kidney injury.
[h]Includes dyspnea, painful respiration, pleuritic pain, and wheezing.

Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA

Table 6 summarizes the common adverse reactions observed in patients who received ZEJULA with the starting dose based on weight and platelet count in the PRIMA study.

Table 6 – Adverse Drug Reactions Reported in ≥10% of Patients Receiving ZEJULA Based on Baseline Weight and Platelet Count (Individualized Starting Dose) in PRIMA

	Individualized Dosing			
	Grades 1-4[a]		Grades 3-4[a]	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Blood and Lymphatic System Disorders				
Anemia	50	28	23	1
Thrombocytopenia	54	5	21	1
Neutropenia[b]	36	8	15	1
Leukopenia[c]	28	11	5	0
Gastrointestinal Disorders				
Nausea	53	21	1	0
Vomiting	17	9	0	1
Constipation[d]	33	16	1	1
Abdominal pain	28	37	2	2
Diarrhea	14	23	1	0
General Disorders and Administration Site Conditions				
Fatigue[e]	48	36	3	0
Investigations				
AST/ALT elevation	8	7	1.8	1.2
Metabolism and Nutrition Disorders				
Decreased appetite	19	5	1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	37	41	1	0
Nervous System Disorders				
Headache	22	17	1	0
Dizziness	11	11	0	0

	Individualized Dosing			
	Grades 1-4[a]		Grades 3-4[a]	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Psychiatric Disorders				
Insomnia	21	14	0	0
Renal and Urinary Disorders				
Acute kidney injury[g]	12	5	1	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[h]	19	12	0	1
Cough	15	21	0	0
Vascular Disorders				
Hypertension	17	9	5	2

[a]CTCAE=Common Terminology Criteria for Adverse Events version 4.02
[b]Neutropenia includes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.
[c]Includes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.
[d]Includes constipation, intestinal obstruction, and large intestinal obstruction.
[e]Includes fatigue, asthenia, muscular weakness, malaise, and somnolence.
[f]Includes arthralgia, back pain, pain in extremity, myalgia and other related terms.
[g]Acute kidney injury includes preferred terms of blood creatine increased, blood creatinine increased, blood urea increased, renal failure, and acute kidney injury.
[h]Includes dyspnea, painful respiration, pleuritic pain, and wheezing.

Maintenance Treatment of Recurrent Ovarian Cancer

Table 7 summarizes the common adverse reactions observed in patients treated with ZEJULA in NOVA.

Table 7 – Adverse Reactions reported in ≥10% of Patients Receiving ZEJULA in NOVA

	Grades 1-4*		Grades 3-4*	
	ZEJULA N=367 (%)	**Placebo N=179 (%)**	**ZEJULA N=367 (%)**	**Placebo N=179 (%)**
Blood and Lymphatic System Disorders				
Thrombocytopenia	61	5	29	0.6
Anemia	50	7	25	0
Neutropenia†	30	6	20	2
Leukopenia	17	8	5	0
Cardiac Disorders				
Palpitations	10	2	0	0
Gastrointestinal Disorders				
Nausea	74	35	3	1
Constipation	40	20	0.8	2
Vomiting	34	16	2	0.6
Abdominal pain/distention	33	39	2	2
Mucositis/stomatitis	20	6	0.5	0
Diarrhea	20	21	0.3	1
Dyspepsia	18	12	0	0
Dry mouth	10	4	0.3	0
General Disorders and Administration Site Conditions				
Fatigue/Asthenia	57	41	8	0.6
Metabolism and Nutrition Disorders				
Decreased appetite	25	15	0.3	0.6
Infections and Infestations				
Urinary tract infection	13	8	0.8	1

	Grades 1-4*		Grades 3-4*	
	ZEJULA N=367 (%)	**Placebo N=179 (%)**	**ZEJULA N=367 (%)**	**Placebo N=179 (%)**
Investigations				
AST/ ALT elevation	10	5	4	2
Musculoskeletal and Connective Tissue Disorders				
Myalgia	19	20	0.8	0.6
Back pain	18	12	0.8	0
Arthralgia	13	15	0.3	0.6
Nervous System Disorders				
Headache	26	11	0.3	0
Dizziness	18	8	0	0
Dysgeusia	10	4	0	0
Psychiatric Disorders				
Insomnia	27	8	0.3	0
Anxiety	11	7	0.3	0.6
Respiratory, Thoracic, and Mediastinal Disorders				
Nasopharyngitis	23	14	0	0
Dyspnea	20	8	1	1
Cough	16	5	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	21	9	0.5	0
Vascular Disorders				
Hypertension	20	5	9	2

*CTCAE=Common Terminology Criteria for Adverse Events version 4.02

†Neutropenia includes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions and laboratory abnormalities have been identified in <10% of the 851 patients receiving ZEJULA in the NOVA study and the PRIMA study and not included in Table 5 or Table 7:

Blood and Lymphatic System Disorders: Pancytopenia

Cardiac disorders: Tachycardia

Infections and infestations: Conjunctivitis

General disorders and administration site conditions: Peripheral edema

Investigations: Blood alkaline phosphatase increased, blood creatinine increased, gamma-glutamyl transferase increased, weight decreased

Immune system disorders: Hypersensitivity (including anaphylaxis)

Metabolism and nutrition disorders: Hypokalemia

Neoplasms benign, malignant, and unspecified (including cysts and polyps): Acute myeloid leukemia, myelodysplastic syndrome

Psychiatric disorders: Depression, cognitive impairment (e.g., memory impairment, concentration impairment), confusional state/disorientation, hallucination

Respiratory, thoracic and mediastinal disorders: Bronchitis, epistaxis, non-infectious pneumonitis

Skin and Subcutaneous Tissue Disorders: Photosensitivity

Vascular Disorders: Hypertensive crisis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

First-Line Maintenance Treatment of Advanced Ovarian Cancer

All Patients Receiving ZEJULA in PRIMA

Table 8 summarizes the abnormal laboratory findings observed in all patients treated with ZEJULA in the PRIMA study.

Table 8 – Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA Overall Population in PRIMA

	Overall Population			
	Grades 1-4		Grades 3-4	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
Decreased hemoglobin	87	66	29	1
Decreased platelets	74	13	37	0
Decreased leukocytes	71	36	9	0
Increased glucose	66	57	3	3
Decreased neutrophils	66	25	23	1

	Overall Population			
	Grades 1-4		Grades 3-4	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
Decreased lymphocytes	51	29	7	3
Increased alkaline phosphatase	46	21	1	0.4
Increased creatinine	40	23	0	0
Decreased magnesium	36	34	1	0
Increased aspartate aminotransferase	35	17	1	0.4
Increased alanine aminotransferase	29	17	2	1

Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA

Table 9 summarizes the abnormal laboratory findings observed in patients who received ZEJULA with the starting dose based on weight and platelet count in the PRIMA study.

Table 9 – Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA Overall and Based on Baseline Weight and Platelet Count (Individualized Starting Dose) in PRIMA

	Individualized Dosing			
	Grades 1-4		Grades 3-4	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Decreased hemoglobin	81	70	21	0
Decreased platelets	63	15	18	0
Decreased leukocytes	70	36	6	0
Increased glucose	63	56	2	1
Decreased neutrophils	60	27	15	0
Decreased lymphocytes	52	30	5	4
Increased alkaline phosphatase	43	17	1	0
Increased creatinine	41	22	0	0
Decreased magnesium	44	30	0	0
Increased aspartate aminotransferase	31	19	1	0
Increased alanine aminotransferase	28	15	2	2

Maintenance Treatment of Recurrent Ovarian Cancer

Table 10 summarizes the abnormal laboratory findings observed in patients treated with ZEJULA in NOVA.

Table 10 – Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in NOVA

	Grades 1-4		Grades 3-4	
	ZEJULA N=367 (%)	Placebo N= 179 (%)	ZEJULA N= 367(%)	Placebo N= 179 (%)
Decrease in haemoglobin	85	56	25	0.5
Decrease in platelet count	72	21	35	0.5
Decrease in WBC count	66	37	7	0.7
Decrease in absolute neutrophil count	53	25	21	2
Increase in AST	36	23	1	0
Increase in ALT	28	15	1	2

N=number of patients; WBC=white blood cells; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of ZEJULA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system disorders: posterior reversible encephalopathy syndrome (PRES)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been performed with ZEJULA.

In Vitro Studies

Inhibition of CYPs: Neither niraparib nor the major primary metabolite M1 is an inhibitor of CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when niraparib is combined with active substances with CYP3A4-dependent metabolism.

Induction of CYPs: Neither niraparib nor M1 is a CYP3A4 inducer in vitro. Niraparib weakly induces CYP1A2 in vitro. Therefore, caution is recommended when niraparib is combined with active substances with CYP1A2-dependent metabolism.

Substrate of CYPs: Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) *in vivo*.

Inhibition of 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.

Inhibition of transporter systems: Niraparib is a weak inhibitor of Breast Cancer Resistance Protein (BCRP) and P-glycoprotein (P-gp) with an IC_{50} = 5.8 µM and 161 µM, respectively, but does not inhibit bile salt export pump (BSEP). The M1 metabolite is not an inhibitor of P-gp, BCRP, BSEP, MRP2, or MATE1 or 2. Neither niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic anion transporter 1 (OAT1), 3 (OAT3), or organic cation transporter 2 (OCT2).

Niraparib is an inhibitor of MATE-1 and -2 with IC_{50} of 0.18 µM and ≤ 0.14 µM, respectively. In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC_{50} = 34.4 µM.

Caution is recommended when niraparib is combined with active substances that undergo uptake transport by OCT1.

Substrate of transporter systems: Niraparib is a substrate of P-gp and BCRP. Niraparib is not a substrate of BSEP, MRP2, or MATE1 or 2. The metabolite M1 is not a substrate of P-gp, BCRP, BSEP, or MATE-1 and -2. Neither niraparib nor M1 is a substrate of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic cation transporter 1 (OCT1), organic anion transporter 1 (OAT1), 3 (OAT3), or organic cation transporter 2 (OCT2).

9.3 Drug-Behavioural Interactions

Photosensitivity has been observed in patients exposed to ZEJULA in the NOVA study (0.12 with niraparib vs 0.01 with placebo; adjusted for patient years of exposure) and in the PRIMA study (0.07 with niraparib vs 0.01 with placebo; adjusted for patient years of exposure), and also in the post-market setting. Patients should be counselled to avoid sun exposure when possible while on treatment.

9.4 Drug-Drug Interactions

Niraparib is metabolized via carboxylesterases and conjugation (UGT). Caution should be exercised if niraparib is to be co-administered with known inhibitors or inducers of these pathways.

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Administration of ZEJULA (3 x 100 mg) with a high-fat high-calorie meal resulted in a 22% decrease in C_{max} relative to administration of ZEJULA (3 x 100 mg) under fasted conditions. Food did not significantly affect the overall exposure of niraparib (AUC_T and AUC_I).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 *BRCA1/2*. Niraparib reduced tumour growth in mouse xenograft models of human cancer cell lines with defective *BRCA*1/2 function and in patient-derived xenograft tumour models with homologous recombination deficiency that had either mutated or wild type *BRCA*1/2, and in tumours that are *BRCA* wild-type and without detectable homologous recombination deficiency. Niraparib concentrated in tumour tissue and, despite being a P-gp substrate, crossed the blood-brain barrier in pre-clinical models.

10.2 Pharmacodynamics

Cardiovascular Effects

Niraparib has the potential to cause effects on pulse rate and blood pressure in patients receiving the recommended dose, which may be related to pharmacological inhibition of the dopamine transporter (DAT), norepinephrine transporter (NET) and serotonin transporter (SERT) (see 16 NON-CLINICAL TOXICOLOGY).

In the PRIMA study, mean pulse rate and blood pressure increased over baseline in the niraparib arm relative to the placebo arm at most on-study assessments. Mean greatest increases from baseline in pulse rate on treatment were 22.4 and 14.0 beats/min in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in systolic blood pressure on treatment were 24.4 and 19.6 mmHg in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in diastolic blood pressure on treatment were 15.9 and 13.9 mmHg in the niraparib and placebo arms, respectively.

In the NOVA study, mean pulse rate and blood pressure increased over baseline in the niraparib arm relative to the placebo arm at all on-study assessments. Mean greatest increases from baseline in pulse rate on treatment were 24.1 and 15.8 beats/min in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in systolic blood pressure on treatment were 24.5 and 18.3 mmHg in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in diastolic blood pressure on treatment were 16.5 and 11.6 mmHg in the niraparib and placebo arms, respectively.

Cardiac Electrophysiology

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

10.3 Pharmacokinetics

Table 11 – Summary of Niraparib Pharmacokinetic Parameters following a single dose administration of 300 mg niraparib

	C_{max}	T_{max}	$t_{1/2}$ (h)	$AUC_{0-\infty}$
Single dose mean	804 ng/mL	3.1 h[1]	50.5 h	29016 ng.h/mL

[1] T_{max} given as median

Niraparib exhibits linear pharmacokinetics. The systemic exposures (C_{max} and AUC) of niraparib increased in a dose-proportional manner with daily doses ranging from 30 mg (0.1 times the approved recommended dosage) to 400 mg (1.3 times the approved recommended dosage). The accumulation ratio of niraparib exposure following 21 days of repeated daily doses was approximately 2-fold for doses ranging from 30 mg to 400 mg.

Absorption

The absolute bioavailability of niraparib is approximately 73%.

Concomitant intake of a high-fat meal (800-1,000 calories with approximately 50% of total caloric content of the meal from fat) did not significantly affect the exposure of niraparib.

Distribution

Niraparib is 83% bound to human plasma proteins, mainly with serum albumin. In a population pharmacokinetic analysis, the total volume of distribution (Vss/F) of niraparib was 1074 L in cancer patients.

Metabolism

Niraparib is metabolized 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

Niraparib is eliminated via multiple pathways, including liver metabolism, hepatobiliary excretion, and renal elimination, with a relatively long elimination half-life. In a population pharmacokinetic analysis, the apparent clearance (CL/F) of niraparib was 16.2 L/h in cancer patients. Following administration of single oral 300mg dose of [^{14}C]-niraparib, 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 (8.8% as parent and 23% as M1) and 31.6% of the dose was recovered in the faeces primarily as unchanged niraparib (18.7%).

Special Populations and Conditions

- **Pediatrics:** Health Canada has not authorized an indication for pediatric use. No studies have been conducted to investigate the pharmacokinetics of niraparib in pediatric patients.

- **Geriatrics:** Population pharmacokinetic analyses suggested that age had no significant impact on the pharmacokinetics of niraparib.
- **Ethnic Origin:** Analyses suggested that race/ethnicity had no clinically significant effect on the pharmacokinetics of niraparib.
- **Hepatic Insufficiency:** Mild hepatic impairment had no clinically significant effect on the pharmacokinetics 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 4.2 Recommended Dose and Dosage Adjustment, Hepatic Insufficiency). Moderate hepatic impairment did not have an effect on niraparib C_{max} or on niraparib protein binding. The effect of severe hepatic impairment on the pharmacokinetics of niraparib is unknown.
- **Renal Insufficiency:** Analyses suggested that mild to moderate renal impairment had no clinically significant effect on the pharmacokinetics of niraparib. The effect of severe renal impairment or end-stage renal disease undergoing hemodialysis on the pharmacokinetics of niraparib is unknown.
- **Obesity:** The effect of obesity on the pharmacokinetics of niraparib is not studied.

11 STORAGE, STABILITY AND DISPOSAL

Store ZEJULA capsules up to 25°C.

Store ZEJULA tablets between 15°C and 30°C in the original container.

Keep out of reach and sight of children.

Health professionals should recommend that their patients return all unused medications to a pharmacy for proper disposal.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special requirements for use or handling of this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

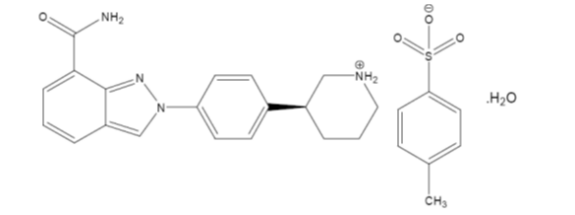
Drug Substance

Common name: niraparib tosylate

Chemical name: The chemical name for niraparib tosylate monohydrate is 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1).

Molecular formula and molecular mass: The molecular formula is $C_{19}H_{20}N_4O \bullet C_7H_8O_3S \bullet H_2O$ and it has a molecular weight of 510.61 amu (320.4 amu for niraparib free base).

Structural formula:



Physicochemical properties: Niraparib tosylate monohydrate is a white to off-white, non-hygroscopic crystalline solid. Niraparib solubility is pH independent below the pKa of 9.95, with an aqueous free base solubility of 0.7 mg/mL to 1.1 mg/mL across the physiological pH range.

Each ZEJULA capsule contains 159.4 mg niraparib tosylate monohydrate equivalent to 100 mg niraparib free base as the active ingredient.

Each ZEJULA tablet contains 159.3 mg niraparib tosylate monohydrate equivalent to 100 mg niraparib free base as the active ingredient.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

First-Line Maintenance Treatment of Advanced Ovarian Cancer

Table 12 – Summary of Patient Demographics for Clinical Trials in First-Line Maintenance Treatment of Advanced Ovarian Cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PRIMA/PR-30-5017-C	Double-blind, 2:1 randomized, placebo-controlled	200 mg or 300 mg niraparib orally once daily in continuous 28-day cycles Matching placebo orally once daily	733	ZEJULA: 61.1 years (32 – 85 years) Placebo: 61.3 years (33 – 88 years)	Females

PRIMA was a double-blind, placebo-controlled study in which patients (n=733) in complete or partial response to first-line platinum-based chemotherapy were randomized 2:1 to ZEJULA or matched placebo. The study was initiated with a starting dose of 300 mg QD in continuous 28-day cycles regardless of baseline body weight or platelet count (henceforth referred to as a fixed starting dose). 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/µL were administered ZEJULA 300 mg (3×100 mg capsules) or placebo (3 capsules) daily and patients with a baseline body weight <77 kg or baseline platelet count <150,000/µL were administered ZEJULA 200 mg (2×100 mg capsules) or placebo (2 capsules) daily (henceforth referred to as an individualized starting dose).

Patients were randomized post completion of first-line platinum-based chemotherapy plus/minus surgery. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no residual disease. Randomization 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 vs negative or not determined]. Testing for HRD was performed using the HRD test (myChoice CDx assay) on tumour tissue obtained at the time of initial diagnosis. HRD positive status included either tumor BRCA mutant (tBRCAm) or a genomic instability score (GIS) ≥ 42.

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).

Overall, the median dose intensity in subjects who received ZEJULA was 181.3 mg/day and the median relative dose intensity was 63% in subjects who received ZEJULA. In patients who received the

individualized starting dose (n = 169; which is 35% of the patients), the median dose intensity was 178.6 mg/day and the median relative dose intensity was 66%. Among these patients, 122 patients received a starting dose of 200 mg. In patients who received the fixed starting dose, the median dose intensity was 181.8 mg/day and the median relative dose intensity was 61%.

The major efficacy outcome measure, PFS, was determined by blinded independent central review (BICR) per RECIST, version 1.1. In some cases, criteria other than RECIST, such as clinical signs and symptoms and increasing CA-125, were also applied. Overall survival (OS) was a key secondary endpoint. PFS testing was performed hierarchically: first in the HR deficient (HRD positive) population, then in the overall population.

The median age was 62 ranged from 32 to 85 years among patients randomized with ZEJULA and 33 to 88 years among patients randomized with placebo. Eighty-nine percent of all patients were white. Sixty-nine percent of patients randomized with ZEJULA and 71% of patients randomized with placebo had an ECOG of 0 at study baseline. Approximately 45% of patients were enrolled in the U.S. or Canada. In the overall population, 65% of patients had stage III disease and 35% had stage IV disease. Sixty-seven percent of the patients received NACT. Sixty-nine percent of the patients had a complete response to the first-line platinum-based chemotherapy. Patients who had received bevacizumab with chemotherapy but could not receive bevacizumab as maintenance therapy were not excluded from the study; 1.2% of patients in the niraparib arm and 0.4% in the placebo arm had prior bevacizumab treatment.

Demographic and baseline characteristics in each cohort and are summarized in Table 13.

Table 13 – Patient Demographics and Baseline Characteristics by Cohort (ITT Population)

Demographic/Baseline Characteristic	HR deficient Population		Overall Population	
	Niraparib (N=247) n (%)	Placebo (N=126) n (%)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Age (years), n				
Median	58.0	58.0	62.0	62.0
Min, Max	32, 83	33, 82	32, 85	33, 88
18 to <65	173 (70.0)	88 (69.8)	297 (61.0)	147 (59.8)
65 to <75	49 (19.8)	32 (25.4)	136 (27.9)	77 (31.3)
≥65	74 (30.0)	38 (30.2)	190 (39.0)	99 (40.2)
≥75	25 (10.1)	6 (4.8)	54 (11.1)	22 (8.9)
Race				
White	218 (88.3)	108 (85.7)	436 (89.5)	219 (89.0)
Black	5 (2.0)	1 (0.8)	10 (2.1)	2 (0.8)
Asian	10 (4.0)	8 (6.3)	14 (2.9)	11 (4.5)
American Indian or Alaska Native	1 (0.4)	0	1 (0.2)	0

Demographic/Baseline Characteristic	HR deficient Population		Overall Population	
	Niraparib (N=247) n (%)	Placebo (N=126) n (%)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)	0
Unknown	5 (2.0)	0	6 (1.2)	1 (0.4)
Not reported	7 (2.8)	9 (7.1)	19 (3.9)	13 (5.3)
Weight (kg)				
Median	65.30	65.10	66.00	65.55
Min, Max	38.0, 137.0	38.5, 136.5	38.0, 137.0	37.8, 146.5
ECOG PS				
0	182 (73.7)	97 (77.0)	337 (69.2)	174 (70.7)
1	65 (26.3)	29 (23.0)	150 (30.8)	72 (29.3)
Geographic Region, n (%)				
US and Canada	ND	ND	218 (44.8)	115 (46.7)
Eastern Europe	ND	ND	61 (12.5)	27 (11.0)
Western Europe	ND	ND	192 (39.4)	96 (39.0)
Primary tumor site				
Ovarian	201 (81.4)	105 (83.3)	388 (79.7)	201 (81.7)
Primary peritoneal	14 (5.7)	8 (6.3)	34 (7.0)	13 (5.3)
Fallopian tube	32 (13.0)	13 (10.3)	65 (13.3)	32 (13.0)
Cancer stage (FIGO) at time of diagnosis				
III, not otherwise specified	7 (2.8)	1 (0.8)	10 (2.1)	4 (1.6)
IIIA	4 (1.6)	1 (0.8)	7 (1.4)	4 (1.6)
IIIB	10 (4.0)	9 (7.1)	16 (3.3)	12 (4.9)
IIIC	140 (56.7)	67 (53.2)	285 (58.5)	138 (56.1)
IV	86 (34.8)	48 (38.1)	169 (34.7)	88 (35.8)

ECOG=Eastern Cooperative Oncology Group; HR deficient=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; Max=maximum; Min=minimum; ND=not determined; PS=performance score; US=United States.

Study Results

PRIMA demonstrated a statistically significant improvement in PFS for patients randomized to ZEJULA as compared with placebo in the HR deficient and overall population (Table 14, Figure 1, and Figure 2).

Table 14 – Efficacy Results for PRIMA (determined by BICR[a])

	HR deficient Population		Overall Population	
	Niraparib (N=247)	**Placebo (N=126)**	**Niraparib (N=487)**	**Placebo (N=246)**
PFS events, n (%)	81 (33)	73 (58)	232 (48)	155 (63)
PFS Median in 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)[b] (95% CI)	0.43 (0.310,0.588)		0.62 (0.502,0.755)	
p-value[c]	<0.0001		<0.0001	

[a] efficacy analysis was based on blinded independent central review (BICR)
[b] based on a stratified Cox proportional hazards model
[c] based on a stratified log-rank test
NE=Not Evaluable

In exploratory subgroup analyses of patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count (individualized starting dose), the hazard ratio for PFS was 0.39 (95% CI [0.22, 0.72]) in the HR deficient population (n=130), and 0.69 (95% CI [0.48, 0.98]) in the overall population (n=258).

In exploratory subgroup analyses the hazard ratios within the HR deficient population (with or without *BRCA* mutation) and within the HR proficient population (HRD negative) were consistent with the primary efficacy analysis of HRD and overall population.

Figure 1 – Kaplan-Meier Plot of Progression-Free Survival by BICR Assessment in Subjects with Homologous Recombination Deficient Tumors (ITT Population, N=373)

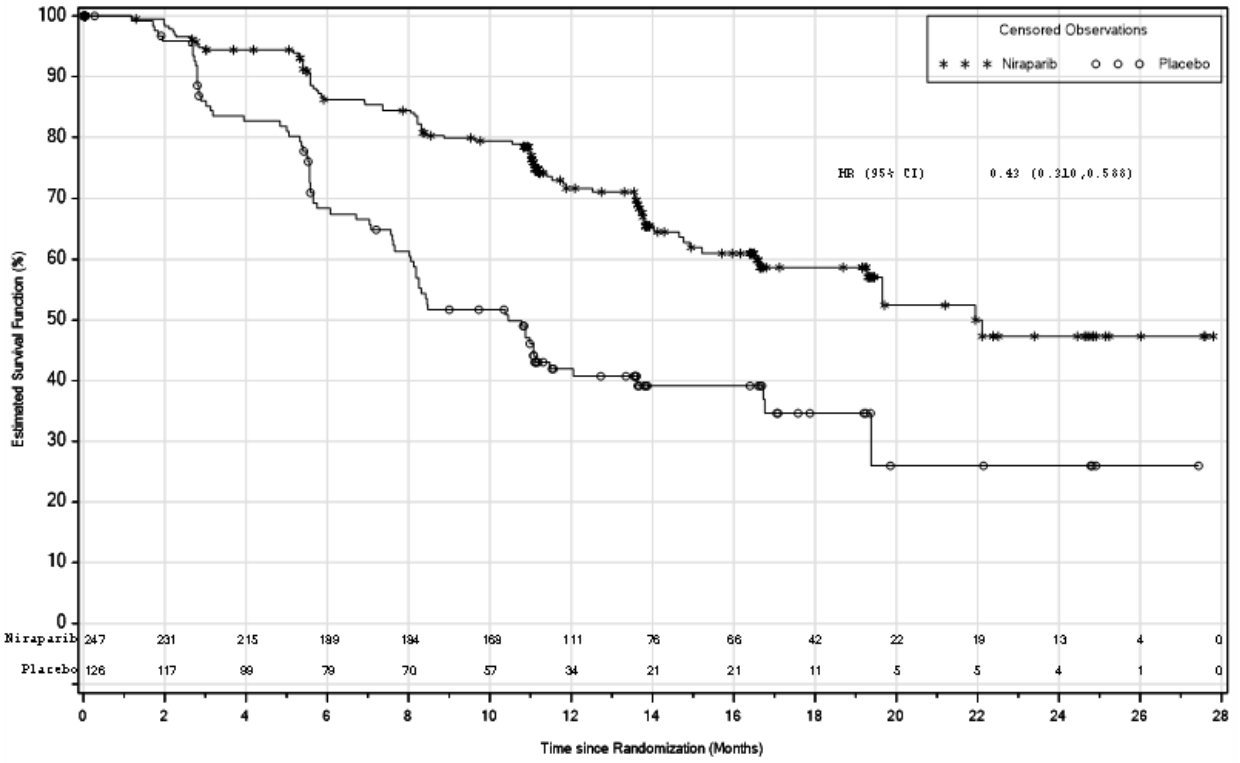
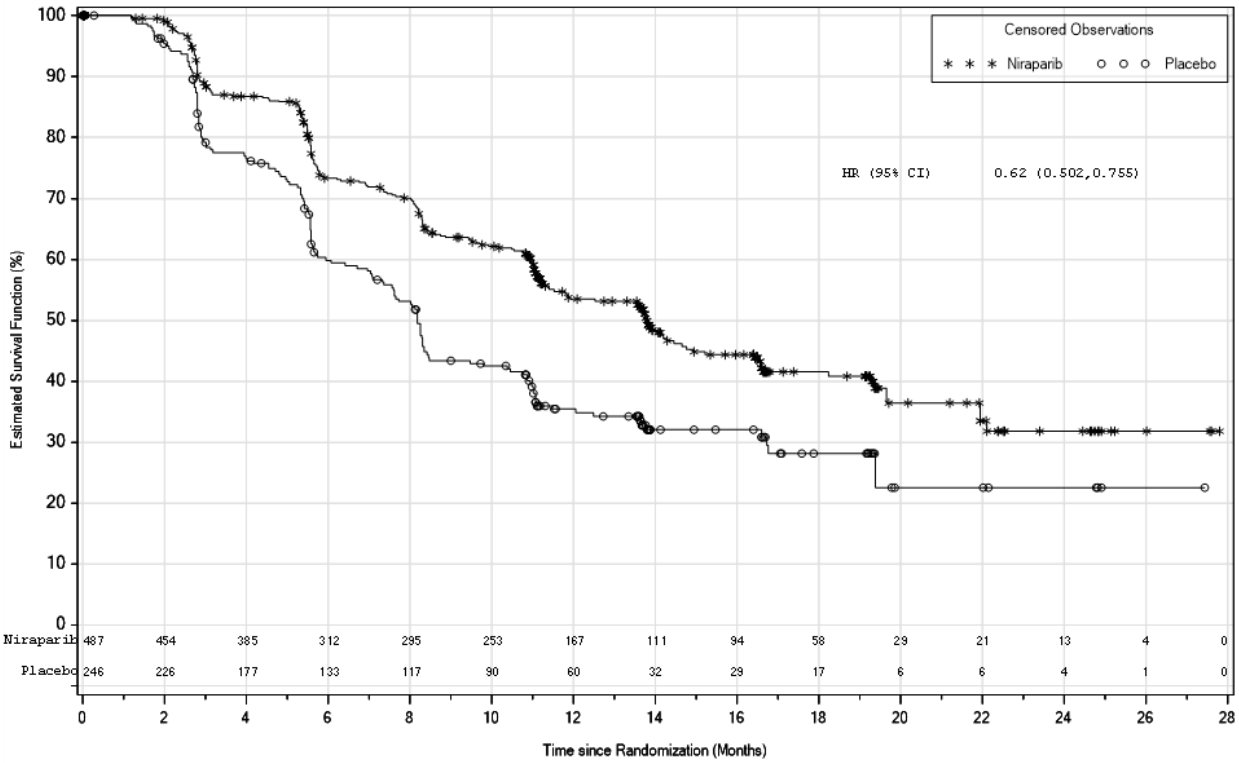


Figure 2 – Kaplan-Meier Plot of Progression-Free Survival by BICR Assessment in the Overall Population (ITT Population, N=733)



At the time of the PFS analysis, overall survival data were immature with 11% deaths in the overall population.

Health related outcomes were assessed for FOSI, EQ-5D-5L, EORTC-QLQ-C30 and EORTC-QLQ-OV28. Treatment with ZEJULA did not negatively impact most patient reported outcomes or health related quality of life measures; however, gastrointestinal related domains (constipation, nausea/vomiting), appetite loss and dyspnea from EORTC-QLQ-C30 appeared to be negatively impacted in the ZEJULA treated patients while diarrhea appeared worse in the placebo treated patients.

Maintenance Treatment of Recurrent Ovarian Cancer

Table 15 – Summary of Patient Demographics for Clinical Trials in Maintenance Treatment of Recurrent Ovarian Cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
NOVA /PR-30-5011-C	Double-blind, 2:1 randomized, placebo-controlled	300 mg orally daily or placebo in continuous 28-day cycles for a median duration of 250 days.	553	ZEJULA: 60.3 years (33 – 84 years) Placebo: 59.8 years (34 – 82 years)	Females

The Phase III NOVA study was a double-blind, placebo-controlled trial in which female patients (n=553) with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer were randomized 2:1 to ZEJULA 300 mg orally daily or matched placebo within 8 weeks of the last therapy. All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen.

Randomization was stratified by time to progression after the penultimate platinum therapy (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 most recent platinum regimen (complete response and partial response). Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx. Patients with deleterious or suspected deleterious germline *BRCA* mutations (g*BRCA*m) were assigned to the germline *BRCA* mutated (g*BRCA*mut) cohort (n=203), and those without germline *BRCA* mutations were assigned to the non-g*BRCA*mut cohort (n=350).

The most commonly used dose after dose modification in niraparib-treated patients in the NOVA study was 200 mg.

The major efficacy outcome measure, PFS (progression-free survival), was determined primarily by central independent assessment per RECIST (Response Evaluation Criteria in Solid Tumors, version 1.1). In some cases, criteria other than RECIST, such as clinical signs and symptoms and increasing CA-125, were also applied.

Demographic and baseline characteristics were well balanced in each cohort and are summarized in Table 16. The ages of patients ranged from 33 to 84 years among patients treated with ZEJULA and 34 and 82 years among patients treated with placebo. Eighty-six percent of all patients were white. Sixty-seven percent of patients receiving ZEJULA and 69% of patients receiving placebo had an ECOG of 0 at study baseline. Approximately 40% of patients were enrolled in the U.S. or Canada and 51% of all patients were in complete response to most recent platinum-based regimen, with 39% on both arms

with an interval of 6-12 months since the penultimate platinum regimen. Twenty-six percent of those treated with ZEJULA and 31% treated with placebo had received prior bevacizumab therapy. Of those patients previously treated with bevacizumab, 16% received ZEJULA as switch maintenance after receiving bevacizumab with their last platinum therapy. Approximately 40% of patients had 3 or more lines of treatment.

Table 16 – Patient Demographics and Baseline Characteristics by Cohort (ITT Population)

	g*BRCA*mut Cohort (N=203)		Non-g*BRCA*mut Cohort (N=350)	
Demographic/Baseline Characteristic	**Niraparib (N=138)**	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**
Age (years), n	138	65	234	116
Mean (SD)	56.9 (9.25)	57.2 (9.24)	62.3 (9.25)	61.3 (9.52)
Median	57.0	58.0	63.0	60.5
Min, Max	36, 83	38, 73	33, 84	34, 82
Age (years), n (%)				
18-64	110 (79.7)	49 (75.4)	130 (55.6)	69 (59.5)
65-74	24 (17.4)	16 (24.6)	85 (36.3)	39 (33.6)
≥65	28 (20.3)	16 (24.6)	104 (44.4)	47 (40.5)
≥75	4 (2.9)	0	19 (8.1)	8 (6.9)
Race, n (%)				
White	123 (89.1)	55 (84.6)	201 (85.9)	101 (87.1)
Black	1 (0.7)	1 (1.5)	4 (1.7)	1 (0.9)
Asian	2 (1.4)	3 (4.6)	10 (4.3)	4 (3.4)
American Indian/Alaska Native	1 (0.7)	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0
Unknown	11 (8.0)	6 (9.2)	19 (8.1)	10 (8.6)
BMI (kg/m^2), n	138	64	229	114
Mean (SD)	26.06 (5.749)	26.78 (6.003)	26.29 (5.606)	26.31 (4.859)
Median	24.70	25.50	25.48	25.71
Min, Max	14.0, 44.6	19.0, 50.4	16.8, 45.6	18.1, 45.7

Demographic/Baseline Characteristic	g*BRCA*mut Cohort (N=203)		Non-g*BRCA*mut Cohort (N=350)	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
ECOG PS, n (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
2	0	0	0	0
Geographic Region, n (%)				
US and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)

Study Results

The study demonstrated a statistically significant improvement in PFS for patients randomized to ZEJULA as compared with placebo in the g*BRCA*mut cohort and the non-g*BRCA*mut cohort (Table 17, and Figure 3 and Figure 4).

Table 17 – Efficacy Results - Study 1 (IRC Assessment[a], Intent-To-Treat Population)

	g*BRCA*mut Cohort		non-g*BRCA*mut Cohort	
	ZEJULA (N=138)	Placebo (N=65)	ZEJULA (N=234)	Placebo (N=116)
PFS Median in 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)
Hazard Ratio (HR)[b] (95% CI)	**0.26** (0.17, 0.41)		**0.45** (0.34, 0.61)	
p-value[c]	**<0.0001**		**<0.0001**	

[a] efficacy analysis was based on blinded central independent radiologic and clinical oncology review committee (IRC).
[b] based on a stratified Cox proportional hazards model
[c] based on a stratified log-rank test
NR=Not Reached

Figure 3 – Kaplan-Meier Plot for Progression-Free Survival in the g*BRCA*mut Cohort Based on IRC Assessment (ITT Population, N=203)

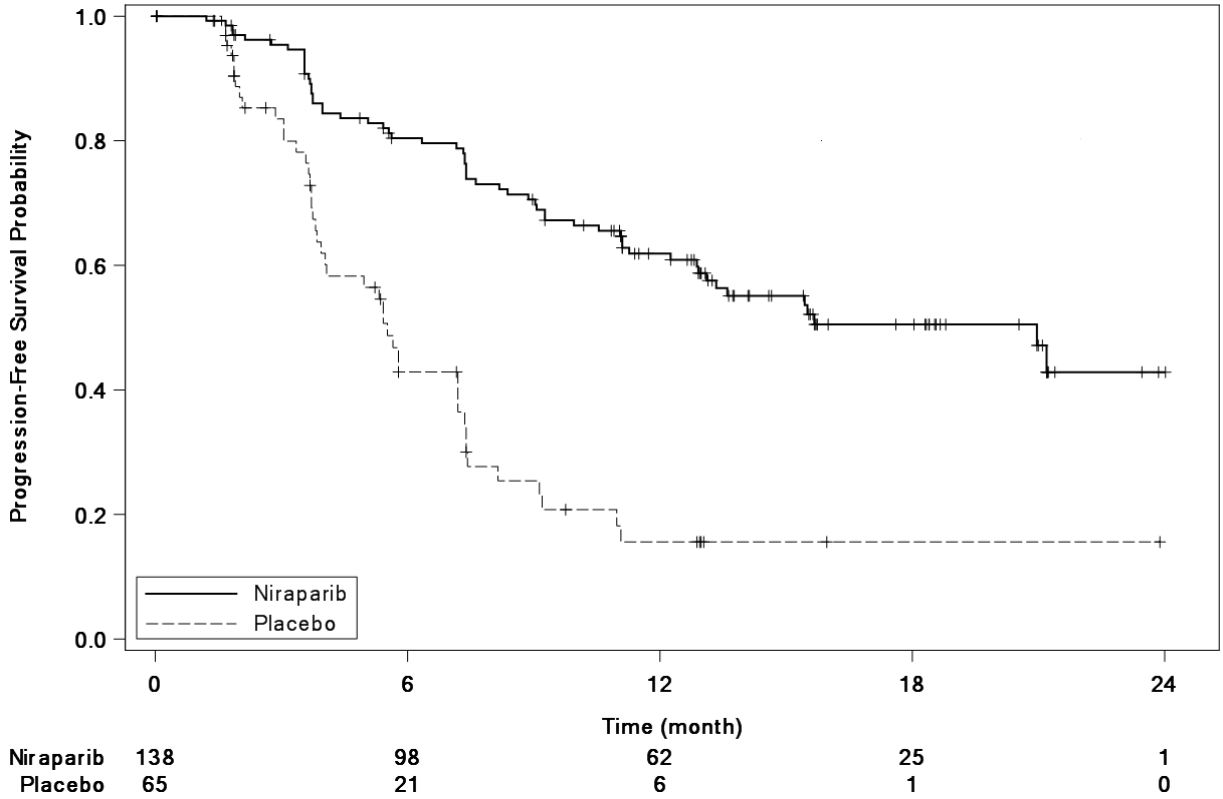
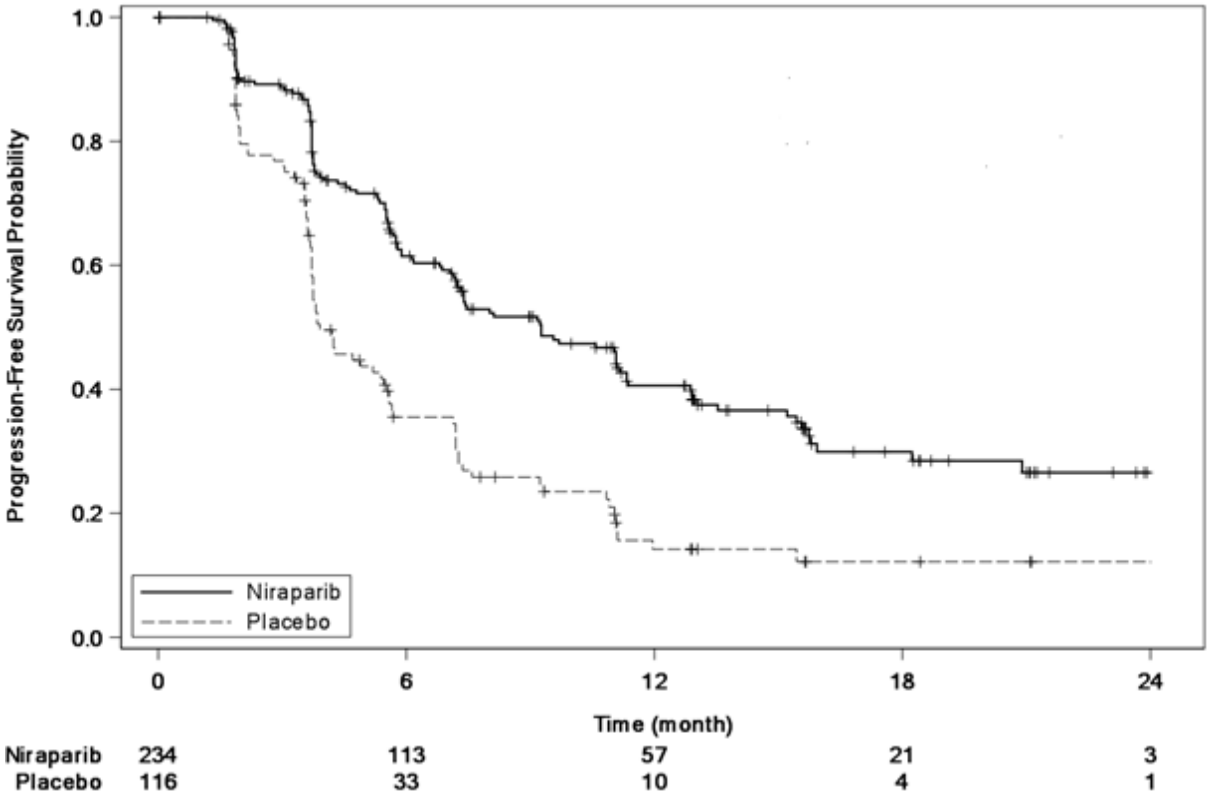


Figure 4 – Kaplan-Meier Plot for Progression-Free Survival in the Non-g*BRCA*mut Cohort Overall Based on IRC Assessment (ITT Population, N=350)



At the time of the PFS analysis, limited overall survival data were available with 17% deaths across the two cohorts.

14.2 Comparative Bioavailability Studies

A randomized, single-crossover study in 108 patients with advanced solid tumors was conducted under fasted conditions to evaluate if the tablet dosage form (1 × 300 mg) of niraparib was bioequivalent to the capsule dosage form (3 × 100 mg).

Results:

One niraparib 300 mg tablet was bioequivalent to three niraparib 100 mg capsules. The results are presented below:

Niraparib 1 x 300 mg From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test**	**Reference**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_T (hr•ng/mL)	17,020	17,740	0.9594	90% CI (0.9199, 1.0006)
AUC_I (hr•ng/mL)	17,620	18,420	0.9566	90% CI (0.9164, 0.9986)
C_{max} (ng/mL)	518.1	538.6	0.9619	90% CI (0.9124, 1.0140)
T_{max} (h), median	5.00 (1.55, 8.00)	4.97 (0.970, 23.8)	Not applicable	Not applicable
$T_{½}$ (h)	49.64 (28.2)	51.88 (27.1)	Not applicable	Not applicable

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In vitro, niraparib bound to the dopamine transporter (DAT), norepinephrine transporter (NET) and serotonin transporter (SERT) and inhibited uptake of norepinephrine and dopamine in cells with IC50 values that were lower than the C_{min} at steady-state in patients receiving the recommended dose. In mice, a single dose of niraparib increased intracellular levels of dopamine and metabolites in the cortex. Niraparib has the potential to cause effects in patients related to inhibition of these transporters (e.g., cardiovascular or CNS).

In safety pharmacology studies, intravenous administration of niraparib to vagotomized dogs over 30 minutes at 1, 3 and 10 mg/kg resulted in an increased range of arterial pressures of 13-20, 18-27 and 19-25% and increased range of heart rates of 2-11, 4-17 and 12-21% above pre-dose levels, respectively. The unbound plasma concentrations of niraparib in dogs at these dose levels were approximately 0.7, 2 and 8 times the unbound C_{max} at steady-state in patients receiving the recommended dose. Reduced locomotor activity was seen in one of two single dose studies in mice.

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 reversible within 4 weeks of cessation of dosing.

Carcinogenicity: Carcinogenicity studies have not been conducted with niraparib.

Genotoxicity: 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 and Developmental Toxicology: While no direct fertility studies were conducted in animals, repeat dose toxicity studies in rats and dogs showed a reduction in spermatogenesis, small testes and germ cell depletion in the testes and epididymides at niraparib doses of 20 mg/kg/day and 6 mg/kg/day respectively (0.74- and 0.05-times clinical exposure based on AUC, respectively). There was a trend towards reversibility of these findings 4 weeks after dosing was stopped.

Special Toxicology: Non-clinical experiments concluded that no direct phototoxicity was seen in rats. Potential niraparib related photosensitivity in humans cannot be excluded.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] ZEJULA

Niraparib Capsules and Tablets

Read this carefully before you start taking ZEJULA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ZEJULA.

Serious Warnings and Precautions

- Only a doctor who has experience treating cancer should treat you with this drug.
- **Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML)** is a problem with the bone marrow. You may have low red, white or platelet cell counts. This is serious and can lead to death.
- ZEJULA can cause bone marrow problems.
- ZEJULA can cause high blood pressure, which in some cases, can be severe.
- ZEJULA can harm your unborn baby if you take it while you are pregnant.

What is ZEJULA used for?

ZEJULA is used in adult women for:

• the maintenance treatment of ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (the membrane that lines the inside of the abdomen).

• the maintenance treatment of ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that has come back (reoccurred).

In both cases ZEJULA is used after your cancer responds to platinum-based chemotherapy. ZEJULA helps to keep or maintain that response.

How does ZEJULA work?

ZEJULA is a type of drug called a PARP inhibitor. PARP inhibitors block a protein called poly [adenosine diphosphate-ribose] polymerase (PARP). This protein helps cells to repair their damaged DNA. Blocking PARP activity prevents the repair of damaged DNA in cancer cells leading to cell death.

What are the ingredients in ZEJULA?

Medicinal ingredients: niraparib, as niraparib tosylate

Non-medicinal ingredients (capsules): FD&C Blue #1, FD&C Red #3, FD&C Yellow #5 (tartrazine), gelatin, lactose monohydrate, magnesium stearate, pharmaceutical grade printing ink, and titanium dioxide

Non-medicinal ingredients (tablets): Crospovidone, ferrosoferric oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, silicon dioxide, talc, titanium dioxide

ZEJULA comes in the following dosage forms:

Capsules, 100 mg niraparib
Tablets, 100 mg niraparib

Do not use ZEJULA if:

- you are allergic to niraparib tosylate or to any of the other ingredients of ZEJULA.
- **you are breast-feeding or plan to breastfeed**. It is not known if ZEJULA passes into breast milk. You and your doctor should decide if you will take ZEJULA or breastfeed. You should not do both. Do not breastfeed for 1 month after taking your last dose of ZEJULA. Talk to your doctor about the best way to feed your baby while you are being treated with ZEJULA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZEJULA. Talk about any health conditions or problems you may have, including if you:

- have or have had high blood pressure or heart problems.
- have or have had liver or kidney problems.
- are pregnant or plan to become pregnant**.**
- have an allergy to lactose. This is because ZEJULA contains lactose.
- have an allergy to a yellow dye called tartrazine (FD&C Yellow #5). This is because ZEJULA contains tartrazine.
- are over 65 years of age.

Other warnings you should know about:

Posterior Reversible Encephalopathy Syndrome (PRES):

- Cases of PRES have been reported with ZEJULA use. PRES is a rare neurological disorder. Contact your doctor immediately if you develop the following symptoms: headaches, confusion, speech and vision loss, vision changes, seizures, with or without high blood pressure.

Pregnancy and fertility:

- If you are pregnant or still able to get pregnant, there are specific risks you must discuss with your healthcare professional.
- Avoid becoming pregnant while taking ZEJULA. It may harm your unborn child or make you lose the pregnancy. Use highly effective methods of birth control while taking ZEJULA. Keep using birth control for 6 months after taking your last dose of ZEJULA. If you do become pregnant while taking ZEJULA, tell your doctor right away. Talk to your doctor about birth control methods that may be right for you.
- **For women who can get pregnant:** a pregnancy test should be done before you start to take ZEJULA; regularly while you are taking it; and one month after taking your last dose.
- ZEJULA may affect your fertility.

Children and adolescents:

- ZEJULA is not for use in patients under the age of 18 years.

Sensitivity to sunlight:

- While taking ZEJULA, your skin may be more sensitive to the sun. You may burn more easily during treatment with ZEJULA. Avoid sun exposure. When in the sunlight, wear a sunscreen with a high protection factor of at least SPF 15 and protective clothing.

Driving and using machines:

- Before you do tasks, which may require special attention, wait until you know how you respond to ZEJULA. If you feel dizzy, weak, unfocused or tired, do not drive or use tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ZEJULA:

- Take ZEJULA exactly as your healthcare professional tells you. Check with your doctor, pharmacist or nurse if you are not sure.
- Do not change your dose or stop taking ZEJULA without first talking with your doctor.
- Your doctor will tell you when to start ZEJULA after you finish your chemotherapy treatment.
- Take with or without food at about the same time each day.
- Take ZEJULA at bedtime if it upsets your stomach. This may help you to manage nausea.
- Swallow capsules or tablets whole.
- If you vomit after taking your dose, do NOT take another one. Take your next dose at your regular time.

Usual dose:

Usual Daily Adult Dose:

The recommended dose is different for different patients. Your doctor will determine the right dose for you. **Be sure to take the dose prescribed to you by your doctor.** Your doctor will decide how long you stay on ZEJULA treatment.

For the maintenance therapy of ovarian cancer, fallopian tube cancer or primary peritoneal cancer:

- **The recommended dose is:**

  200 mg (two 100 mg capsules or tablets) by mouth once a day

  OR

  300 mg (three 100 mg capsules or tablets) by mouth once a day.

  The dose prescribed will depend on your body weight and platelet count.

For the maintenance therapy of ovarian cancer, fallopian tube cancer or primary peritoneal cancer that has come back (reoccurred):

- **The recommended dose is 300 mg** (three 100 mg capsules or tablets) by mouth once a day. If you have a low body weight, your doctor may prescribe a dose of 200 mg (two 100 mg capsules or tablets) by mouth once a day.

Your doctor may change (reduce) or interrupt your dose or tell you to stop taking it. This may happen if you have:

- certain side effects while taking ZEJULA
- liver problems

Reduced Daily Adult Doses:

- **200 mg** (two 100 mg capsules or tablets) by mouth once a day
- **100 mg** (one 100 mg capsule or tablet) by mouth once a day

Overdose:

If you think you, or a person you are caring for, have taken too much ZEJULA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of ZEJULA, take your next dose at your regular time. Do not take an extra dose to make up for a missed dose.

What are possible side effects from using ZEJULA?

These are not all the possible side effects you may have when taking ZEJULA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- pain in the stomach area
- indigestion or heartburn
- dry mouth
- feeling tired or weak
- loss of appetite
- loss of weight
- pain in your joints, muscles and back
- headache
- feeling dizzy
- changes in the way food tastes
- trouble sleeping
- anxiety and depression

- inflammation of the nose and throat
- shortness of breath
- cough
- rash
- constipation
- hot flashes
- nose bleeds
- pink eye
- swelling
- increased sensitivity to the sun, sunburn

Your healthcare professional will test your blood:

- before you start on ZEJULA
- every week for the first month, and
- once a month for the next eleven months and periodically thereafter.

ZEJULA can cause abnormal blood test results. This includes low blood cell counts and increased creatinine and liver enzyme levels in your blood. Your doctor may adjust your treatment to correct these side effects and run additional tests.

Your healthcare professional will check your blood pressure and heart rate regularly throughout your treatment. Your doctor may adjust your treatment and give you medicine to treat your high blood pressure.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (low red blood cells): Being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, or weakness.		**X**	
Diarrhea: Severe, at least 3 loose or liquid bowel movements in a day.	**X**		
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations.	**X**		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Nausea and Vomiting: Feeling sick. Being sick or throwing up.	**X**		
Neutropenia or Leukopenia (low white blood cells: neutrophils and leukocytes): Fever or infection, fatigue, aches and pains, and flu-like symptoms.		**X**	
Stomatitis (mouth sores, inflammation of the mouth) or **Mucosal Inflammation** (inflammation of the moist body surfaces): Red, sore or swollen mouth, lips, gums, nose or eyes, and ulcers.	**X**		
Thrombocytopenia (low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		X	
Urinary Tract Infection (UTI) (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine.	**X**		
COMMON			
Allergic Reactions, including Anaphylaxis: Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			**X**
Myelodysplastic Syndrome or Acute Myeloid Leukemia (a group of diseases in which the body produces large numbers of abnormal blood cells): Fever, infection, bruising or bleeding easily, breathlessness, blood in urine or stool.			**X**

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Kidney Disorder/Problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma).		**X**	
Psychiatric Disorders: seeing or hearing things that are not really there, confusion or difficulty concentrating/thinking, bad memory.		**X**	
Bronchitis/Pneumonitis (inflammation in the lungs): persistent cough with or without mucous, fatigue, trouble breathing, shortness of breath.		**X**	
Palpitation/Tachycardia (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly.	**X**		
Posterior Reversible Encephalopathy Syndrome, PRES – also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS (a rare neurological disorder): headaches, seizures, confusion, speech and visual loss, visual changes, with or without high blood pressure.		**X**	
RARE			
Hypertensive Crisis: a sudden increase in blood pressure, which may be a medical emergency that could lead to organ damage or can be life-threatening.			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store ZEJULA capsules up to 25°C.
- Store ZEJULA tablets between 15°C and 30°C, in the original container.
- Do not use after the expiry date stated on the carton and blister pack. The expiry day refers to the last day of that month.
- Do not throw away any medicines via wastewater or household waste. Ask your healthcare provider or pharmacist about the right way to throw away outdated or unused ZEJULA. These measures will help protect the environment.
- **Keep out of reach and sight of children**.

If you want more information about ZEJULA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.gsk.ca, or by calling 1-800-387-7374.

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