PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ZEJULA™

niraparib capsules

Capsule, 100 mg niraparib (as niraparib tosylate), oral

Antineoplastic agent

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZEJULA™ (niraparib capsules) is indicated 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 Dosage Forms, Strengths, Composition and Packaging.

- Breast-feeding (see WARNINGS AND PRECAUTIONS, Special Populations, Breast-feeding)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with ZEJULA should be initiated and supervised by a physician 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 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).
- ZEJULA can cause bone marrow suppression (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Table 3).
- Hypertension, including hypertensive crisis, has been reported with the use of ZEJULA (see WARNINGS AND PRECAUTIONS, Cardiovascular, and Monitoring and Laboratory Tests).
- ZEJULA can cause foetal harm when administered to a pregnant woman (see WARNINGS AND PRECAUTIONS, Sexual Health and Special Populations, Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients with low body weight: Approximately 25% of patients in the Phase III Trial (ENGOT-OV16/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.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dosage

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

Patients should start treatment with ZEJULA no later than 8 weeks after their most recent platinum-containing regimen. Patients should have recovered from prior haematologic toxicities prior to starting ZEJULA (≤ Grade 1) (see WARNINGS AND PRECAUTIONS, Haematologic and Monitoring and Laboratory Tests, Haematologic Testing).

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

Health Canada has not authorized an indication for pediatric use (see WARNINGS AND PRECAUTIONS, Special Populations).

Dose Adjustments for Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment. The safety of ZEJULA in patients with moderate to severe hepatic impairment is unknown.

Dose Adjustments for Renal Impairment

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.

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 Tables 1, 2 and 3.

Table 1: Recommended dose modifications for adverse reactions	
Starting dose	300 mg/day (three 100 mg capsules)
First dose reduction	200 mg/day (two 100 mg capsules)
Second dose reduction	100 mg/day* (one 100 mg capsule)

*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 where prophylaxis is not considered feasible or adverse reaction persists despite treatment	• Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction. • Resume ZEJULA at a reduced dose per Table 1. Up to 2 dose reductions are permitted for the starting dose of 300 mg dose; only 1 dose reduction is permitted for the starting dose of 200 mg.
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

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 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

Table 3: Dose modifications for haematologic adverse reactions	
	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	• For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors 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 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

4.3 Administration

Instruct patients to take their dose of ZEJULA at approximately the same time each day. Each capsule 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, healthcare practitioners 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

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, gelatin, lactose monohydrate, magnesium stearate, pharmaceutical grade printing ink, and titanium dioxide.

ZEJULA capsules are packaged as unit dose blister in cartons of 28 × 1, 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.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Carcinogenesis and Mutagenesis

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received ZEJULA. In the Phase III NOVA trial (ENGOT-OV16/NOVA), MDS/AML occurred in 5 out of 367 (1.4%) of patients who received ZEJULA and in 2 out of 179 (1.1%) patients who received placebo. Overall, MDS/AML has been reported in 7 out of 751 (0.9%) patients treated with ZEJULA in clinical studies.

The duration of ZEJULA treatment in patients prior to developing MDS/AML varied from 1 month to >2 years. All patients had received previous chemotherapy with platinum and some had also received other DNA damaging agents and radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Cardiovascular

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA. Grade 3-4 hypertension occurred in 9% of ZEJULA-treated patients compared to 2% of placebo treated patients in ENGOT-OV16/NOVA. Discontinuation due to hypertension occurred in <1% of patients. Monitor blood pressure and heart rate (see Monitoring and Laboratory Tests, Cardiovascular Monitoring).

Driving and Operating Machinery

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

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

Careful monitoring of haematological parameters is required (see DOSAGE AND ADMINISTRATION, Table 3, and WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Haematologic Testing).

Monitoring and Laboratory Tests

Cardiovascular Monitoring: Monitor blood pressure and heart rate 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. Medically manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary (see DOSAGE AND ADMINISTRATION).

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 DOSAGE AND ADMINISTRATION, Dose Adjustments for Adverse Reactions 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 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Sexual Health

Reproduction
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 effective contraception during therapy and for 1 month 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 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 WARNINGS AND PRECAUTIONS, Sexual Health, ACTION AND CLINICAL PHARMACOLOGY and 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 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): 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

In the Phase III trial (ENGOT-OV16/NOVA) study, adverse reactions (ADRs) occurring in ≥10 % of patients receiving ZEJULA monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anemia, constipation, vomiting, abdominal pain/distention, neutropenia, insomnia, headache, decreased appetite, nasopharyngitis, rash, mucositis/stomatitis, diarrhea, dyspnea, hypertension, myalgia, dyspepsia, back pain, dizziness, leukopenia, cough, urinary tract infection, arthralgia, anxiety, palpitations, dry mouth, AST and ALT elevation, and dysgeusia (see Table 4).

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

Adverse reactions in the NOVA study (where all patients were started at 300 mg) 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.

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.

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation (see Recommended Dose and Dosage Adjustment, Tables 1, 2 and 3).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

The ZEJULA clinical development program has included patients with a variety of other solid tumours receiving monotherapy and combination treatment in dose range of 300 mg to 100 mg once daily. The monotherapy pooled dataset includes 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in a Phase 3 randomized, double-blind, placebo-controlled international trial (ENGOT-OV16/NOVA). The adverse event profile was generally similar in type, frequency and severity for all patients in the 300-mg daily monotherapy pooled dataset. The median total treatment duration in all patients was 250 days in the ZEJULA group and 163 days for placebo.

Table 4 summarizes the common adverse reactions observed in patients treated with ZEJULA.

Table 4: Adverse Reactions reported in ≥10% of Patients Receiving ZEJULA

	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

	Grades 1-4*		Grades 3-4*	
	ZEJULA N=367 (%)	**Placebo N=179 (%)**	**ZEJULA N=367 (%)**	**Placebo N=179 (%)**
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
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 ≥1 to <10% of the 367 patients receiving ZEJULA in the ENGOT-OV16/NOVA trial and not included in the table:

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
Metabolism and nutrition disorders: Hypokalemia
Psychiatric disorders: Depression
Respiratory, thoracic and mediastinal disorders: Bronchitis, epistaxis

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

Table 5 summarizes the abnormal laboratory findings observed in patients treated with ZEJULA.

Table 5: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA

	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

9 DRUG INTERACTIONS

9.2 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 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, or BSEP. 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. 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-Drug Interactions

Interactions with other drugs have not been established.

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.

9.4 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).

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

Photosensitivity has been observed in patients in the NOVA trial when exposed to ZEJULA (0.12 with niraparib vs 0.01 with placebo; adjusted for patient years of exposure). Patients should be counselled to avoid sun exposure when possible while on treatment.

10 ACTION AND 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 homologus 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 NON-CLINICAL TOXICOLOGY).

In the ENGOT-OV16/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 trial 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 trial following the treatment of niraparib 300 mg once daily.

10.3 Pharmacokinetics

Niraparib exhibits linear pharmacokinetics. Following a single-dose administration of 300 mg niraparib, the mean (±SD) peak plasma concentration (C_{max}) was 804 (± 403) ng/mL. 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, a value consistent with an approximate terminal half-life of 48 hours.

Absorption: The absolute bioavailability of niraparib is approximately 73%. Following oral administration of 300 mg of niraparib, peak plasma concentration, C_{max}, is reached in approximately 3 hours.

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. 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 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. The effect of moderate or 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 at 20° to 25°C

Keep out of reach and sight of children

Healthcare 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

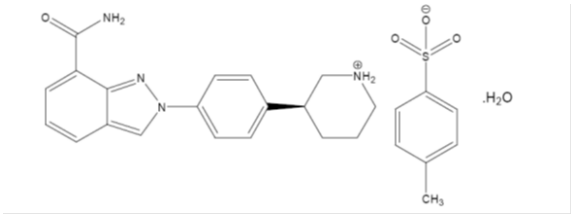
Drug Substance

Proper /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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The Phase III trial is summarized in Table 6.

Table 6: Characteristics of the Phase III trial ENGOT-OV16/NOVA

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ENGOT-OV16/ NOVA	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 trial (ENGOT-OV16/NOVA) 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 ENGOT-OV16/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 7. 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 7: 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)

14.2 Study Results

The trial 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 8, and Figures 1 and 2).

Table 8: 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 1: Kaplan-Meier Plot for Progression-Free Survival in the g*BRCA*mut Cohort Based on IRC Assessment (ITT Population, N=203)

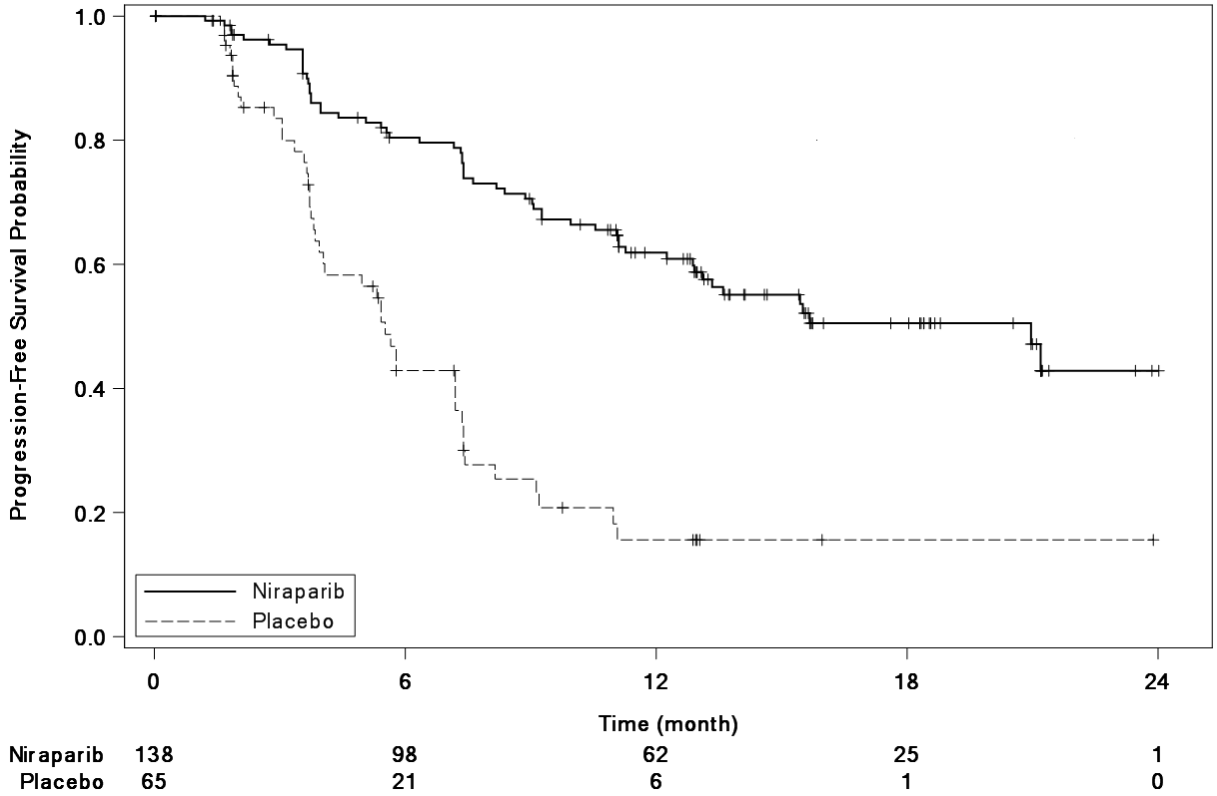
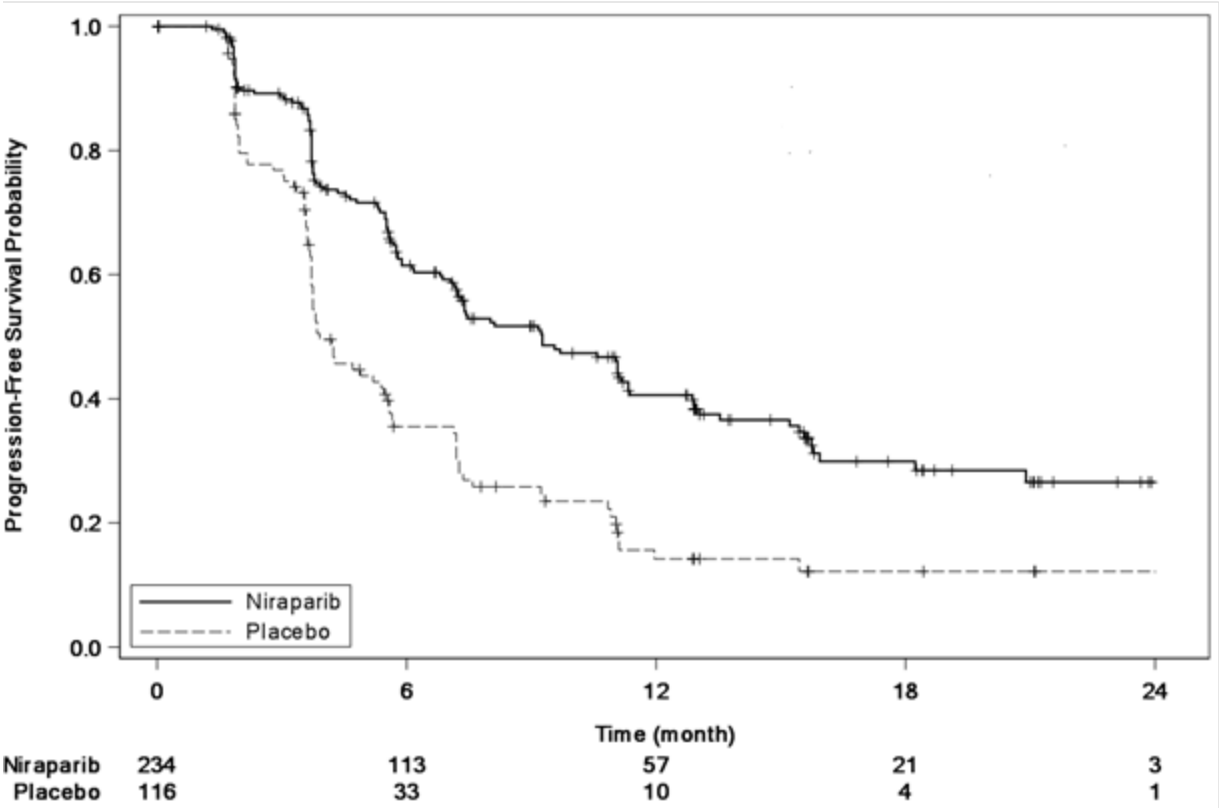


Figure 2: Kaplan-Meier Plot for Progression-Free Survival in the Non-g*BRCA*mut Cohort Overall Based on IRC Assessment (ITT Population, N=350)



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

15 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 Studies

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

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrZEJULA™

Niraparib Capsules

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 to treat the following types of cancer in adult women whose cancer has come back:
  - ovarian cancer,
  - fallopian tube cancer, and
  - primary peritoneal cancer (the membrane that lines the inside of the abdomen)
- ZEJULA is used after the cancer has responded to chemotherapy treatment with a platinum medicine. It helps to keep 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: gelatin, lactose monohydrate, magnesium stearate, pharmaceutical grade printing ink, and titanium dioxide.

ZEJULA comes in the following dosage forms:
Capsules, 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**.**
- are over 65 years of age.

Other warnings you should know about:

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 effective methods of birth control while taking ZEJULA. Keep using birth control for 1 month 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 should not be given to 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, 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 has told you. Check with your doctor, pharmacist or nurse if you are not sure.
- Your doctor will tell you how many capsules of ZEJULA to take. It is important that you take the recommended daily dose.
- Do not change your dose or stop taking ZEJULA without first talking with your doctor.
- Start taking ZEJULA within 8 weeks of your last dose of chemotherapy.
- Take with or without food at approximately the same time every day.
- Take ZEJULA at bedtime if it upsets your stomach. This may help you to manage nausea.
- Swallow capsules 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:
300 mg: Take three 100 mg capsules by mouth once a day.

Your doctor may change your dose of ZEJULA or tell you to stop taking it. This may happen if you have certain side effects while taking ZEJULA.

Reduced Daily Adult Dose:
200 mg: Take two 100 mg capsules by mouth once a day
100 mg: Take one 100 mg capsule by mouth once a day

Overdose:

If you think you have taken too much ZEJULA, contact your 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 feel when taking ZEJULA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

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

- inflammation of the nose and throat
- shortness of breath
- cough
- rash
- constipation

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.

Your healthcare professional will tell you if your test results are abnormal. ZEJULA may lower your blood cell counts and affect certain liver enzyme levels in your blood. Your doctor may adjust your treatment to correct these side effects and run additional tests.

Your health care 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		
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		
UNCOMMON			
Allergic Reactions: 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

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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 at 20° to 25°C.
- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.gsk.ca or by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.

 <Item #>

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